Cost-effectiveness of oral anticoagulants versus aspirin in patients after infrainguinal bypass grafting surgery

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Purpose: **Several antithrombotic therapies are available for the treatment of patients with peripheral vascular diseases. It is unknown how quality of life and costs of treatment are influenced by different therapies. This study assessed the cost-effectiveness of oral anticoagulants versus aspirin in patients after infrainguinal bypass grafting surgery.**
Methods: **Clinical outcome events and event-free survival were collected from 2650 patients in 77 centers who participated in the Dutch Bypass Oral anticoagulants or Aspirin trial. Approximately half the patients had critical ischemia; 60% received vein grafts, and 20% had femorocrural bypass grafts. A model that was primarily driven by clinical outcome events was used as a means of determining quality of life (EuroQol EQ-5D) and costs for each patient. The main outcome measure was the incremental health care costs in relation to the additional number of quality-adjusted life years and the additional number of event-free years.**
Results: **The mean costs during the 21 months of follow-up were € 6875 per patient in the oral anticoagulants group versus € 7072 in the aspirin group (difference, 197; 95% CI, –746 to 343). The event-free survival was 1.10 years in the group treated with oral anticoagulants versus 1.09 years in the group treated with aspirin (difference, 0.01; 95% CI, –0.07 to 0.08), whereas the corresponding quality-adjusted life years were 1.06 and 1.05, respectively (difference, 0.01; 95% CI, –0.03 to 0.06).**
Conclusion: **Health care costs, event-free survival, and quality-adjusted life years in patients after infrainguinal bypass surgery were not different in patients treated with aspirin and patients treated with oral anticoagulants. The extra costs of monitoring patients treated with oral anticoagulants were limited and play no role in the decision for treatment. (J Vasc Surg 2001;34:254-62.)**

Until recently, it was not clear whether oral anticoagulants or aspirin was the optimal treatment after infrainguinal bypass surgery. The choice of treatment was made on the basis of a few trials that compared antithrombotic therapies and indirect evidence from studies in patients with other manifestations of atherosclerotic disease.[1] Recently, the Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study found no overall difference in treatment effect between oral anticoagulants and aspirin.[2] Oral anticoagulants were found to be the optimal treatment for preventing autologous vein graft occlusion and were more effective than aspirin in reducing ischemic events. Aspirin was the optimal treatment for preventing nonvenous graft occlusion and was associated with fewer cases of bleeding. Apart from the clinical effects, it is unknown how treatment with oral anticoagulants and aspirin after infrainguinal bypass grafting surgery leads to different results in the quality of life of patients and the costs of treatment. Treatment with oral anticoagulants is associated with higher costs and more inconvenience for the patients than aspirin treatment, because of the necessity of monitoring and adjusting the anticoagulant dose in each patient. However, the extra costs and adverse effects of oral anticoagulant treatment should be considered in relation to the total costs and beneficial effects of the entire treatment path.

The objective of this study, which was part of the Dutch BOA Study, was to compare quality of life and costs after infrainguinal bypass surgery in patients treated with either oral anticoagulants or aspirin. Because of the opposite effects of the two treatments in patients with autologous vein grafts and nonvenous grafts, an additional subgroup analysis was performed for these groups of patients.

METHODS

Patients. The Dutch BOA Study was a multicenter randomized trial designed to compare the effectiveness of oral anticoagulants and aspirin in preventing occlusions of infrainguinal bypass grafts and the composite event of vascular death, myocardial infarction, stroke, or amputation.

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Competition of interest: nil.
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The background, design, and results of the trial have been reported elsewhere.[2] In brief, all patients who required an infrainguinal bypass graft for obstructive arterial disease were eligible for inclusion, with only a limited number of exclusion criteria. Between April 1995 and March 1998, 2650 patients from 77 centers were randomized to receive either oral anticoagulants (n = 1326) or 80 mg of aspirin daily. Oral anticoagulant treatment consisted of phenprocoumon or acenocoumarol, depending on the surgeons' preference, with a target international normalized ratio of 3.0 to 4.5. All patients gave written informed consent.

The model. A model was designed that enabled the incorporation of data from all 2650 patients in the cost-effectiveness analysis, whereas costs and quality of life values were measured in two samples of these patients. The model was entirely driven by the clinical outcome events of graft occlusion, vascular intervention, amputation, (nonfatal) myocardial infarction, (nonfatal) stroke, major hemorrhage, and (vascular) death. According to the event(s) patients experienced, they were assigned to a certain "health state." All patients started in the health state of "no additional event after the initial bypass surgery." Patients remained in this state until they experienced a clinical outcome event. Patients then moved to the health state associated with this event, for instance, the health state "after myocardial infarction." Each health state was associated with fixed estimates of quality of life and costs per day. During the time a patient remained in a certain health state, the patient was assigned the costs and quality of life corresponding with that particular state. If a patient experienced more events, the patient moved to the health state corresponding with the last event only when the last event was more severe (ie, when it was associated with higher costs and lower quality of life than any of the earlier events). If the last event was less severe, the patient remained in the original health state.

Data collection. The model-input consisted of the clinical outcome events, the time until the first event, and the quality of life and costs associated with each health state. Clinical outcome events as defined and the time until the first event were collected for all patients in the study. Costs and quality of life were not measured in all patients, but estimates of costs and quality of life associated with each health state were collected from two samples of patients. The first sample consisted of the first 409 consecutive patients with patent grafts who entered the trial as of November 1995. These patients received a mailed questionnaire at 3 months and subsequently every 6 months until the end of the study, 30 months after randomization. The second sample consisted of 609 patients who experienced a clinical event and who were not already part of the first sample. From the moment the event was reported, these patients received a questionnaire on the same schedule as the first group. Incomplete questionnaires were returned to the patients for completion. Any answers still missing after the questionnaire had been returned to the trial office were completed by means of a telephone call. Data of patients were included only when complete resource use and quality of life data of at least 1 month were available.

Health outcomes. Health outcomes were measured for event-free survival and quality-adjusted life-years (QALYs). Event-free survival was defined as the mean time a patient remained in the study without experiencing a clinical outcome event. QALYs were calculated by multiplying the time a patient remained in a certain health state by the quality of life value associated with that particular state and subsequent summing over all health states. Quality of life values only depended on the preceding events and were independent from treatment group. Quality of life values associated with each health state were derived from the two samples of patients described. The first sample yielded quality of life estimates of the health state in which patients experienced no clinical outcome event other than the initial bypass grafting procedure. Both samples were used as a means of obtaining quality of life values of the health states after any of the other clinical outcome events. Quality of life values were measured with the EuroQol questionnaire (EQ-5D). The EQ-5D results in a single numeric value that represents health status. A value of 1 represents normal health, whereas 0 represents death.[3] The analysis of the quality of life data was published in detail in this journal.[4,5]

Costs. In calculating the costs per patient, a distinction was made in three categories: "health state-related costs," "event-related costs," and the costs of study medication. Health state-related costs reflected the costs of health care resource use in the period after an event. These costs were assigned to a patient for each month the patient remained in a certain health state. Estimates of the costs per month for each health state were based on resource use of the two samples defined. In each questionnaire, we asked for the number of days in the hospital, nursing home, rehabilitation center, or other inpatient setting, the number of outpatient visits to the consultant, general practitioner, and physiotherapist, and the number of hours of home-care in the last month. The mean resource use was multiplied with fixed unit costs, as described in Appendix II. This data collection resulted in estimates of the monthly costs associated with each health state after an event, including the health state in which patients had experienced no other clinical event after the initial bypass surgery.

Health care costs at the time of an event were higher than in the months after an event. To incorporate these higher costs at the time of an event in the model, we distinguished a second cost category: the event-related costs. Event-related costs contained the costs of hospitalization directly after an event and, when applicable, the costs of the (surgical) intervention. These event-related costs were assigned to a patient each time the patient experienced an event, irrespective of the number or severity of earlier events. Because all patients underwent an initial bypass grafting procedure, the costs of the first intervention at randomization were not included. Like quality of life values, similar estimates of the health state- and event-related

Table I. Baseline characteristics according to treatment allocation

Characteristic	*Oral anticoagulants (n = 1326)*	*Aspirin (n = 1324)*
Mean age (y)	69	69
Male sex	859 (65%)	839 (63%)
Indication		
Intermittent claudication	665 (50%)	690 (52%)
Critical ischemia	661 (50%)	634 (21%)
Type of bypass		
Femoropopliteal	1070 (81%)	1049 (79%)
Femorocrural/pedal	256 (19%)	275 (21%)
Graft material		
Venous	784 (59%)	762 (58%)
Nonvenous	542 (41%)	562 (42%)

costs were used in both treatment groups. In cases of limited data, cost estimates were complemented with data from earlier publications.[6,7]

Costs of study medication, aspirin or oral anticoagulants, were based on 1996 list prices and enlarged with the pharmacists' fee. The costs of monitoring patients with oral anticoagulant treatment were determined by means of a costing study in three anticoagulation clinics.[8] The extra costs of monitoring in the anticoagulant group consisted of 25 visits to the anticoagulation clinic per year, with a mean cost of € 8 per visit. Costs of aspirin included the prescription costs of the general practitioner, consisting of four telephone consultations per year. All costs were calculated in Dutch guilders and converted to Euros (fl.2.20 = € 1.00 = US $ 0.93).

Analysis. Costs and health outcomes were presented as the mean outcomes per patient. Incremental cost-effectiveness ratios (CE-ratios) were defined as the difference in costs divided by the difference in event-free survival and QALYs. In accordance with earlier publications, ratios were calculated only in cases of a significant difference in costs or effects between treatment groups.[9] Bootstrapping was used as a means of determining the 95% CIs around the means of these ratios. The bootstrap method is a means of estimating the sampling distribution of a statistic (in this case, the CE-ratio) through a large number of simulations, on the basis of sampling with replacement from the original data.[10,11] A further explanation of bootstrapping is presented in Appendix III. In this study, we performed a bootstrap with 1000 replications. To express the uncertainty around the CE-ratio, we plotted the results of the bootstrap analysis in a cost-effectiveness plane (CE-plane).[12] Every dot in the CE-plane represented one bootstrap replicate. The CE-plane consisted of four quadrants. A dot on the right of the vertical axis meant that oral anticoagulants were more effective, whereas a dot on the left side meant that aspirin was more effective. Likewise, a dot above the horizontal axis meant the costs of oral anticoagulants were higher, whereas a dot below the horizontal axis implied the costs of aspirin were higher.

Because of the different effects of oral anticoagulants and aspirin in patients with autologous vein grafts and nonvenous grafts, a subgroup analysis was performed by means of graft conduit.

RESULTS

Patients. The mean length of follow-up was 21 months, with a range from 0 to 45 months. Baseline characteristics and risk factors were well balanced between the treatment groups (Table I). The demographics of the patients in the two samples were comparable with those of the entire population in the Dutch BOA Study. The first sample of patients from whom data were collected on quality of life and resource use included 409 patients. Of these patients, 379 had complete data for at least 1 month. The proportion of patients with complete data was 100% at month 3 and declined to 87% at month 18 and to 57% at month 30. The number of patients with an event included in the second sample was 609. The percentage of patients with complete data was 65% at month 3, 86% at month 12, and declined to 64% at month 30. The number of clinical outcome events in patients who no longer filled in the questionnaires was approximately 20% higher than in patients who completed all questionnaires.

Health outcomes. The number and types of events in both treatment groups are presented in Table II. The mean number of events was 1.22 (SD, 1.62) in the anticoagulant group and 1.27 (SD, 1.69) in the aspirin group; the mean difference was 0.05 (95% CI, –0.08 to 0.18). Event-free survival and QALYs were almost the same in both treatment groups. In patients with vein grafts, event-free survival and QALYs were higher in the anticoagulant group. In patients with nonvenous grafts, QALYs were higher in the anticoagulant group, whereas the event-free survival was higher in the aspirin group. However, the differences were small, and none of the differences were statistically significant.

Costs. The cost estimates associated with each event and each health state after an event are presented in Table III. These estimates were used as a means of calculating the health care costs of all patients (Table IV). Mean costs per patient were € 6875 per patient in the anticoagulant group and € 7072 in the aspirin group. None of the differences shown in Table IV were statistically significant. Health state-related costs made-up 62% of the total costs. Costs of medication in the aspirin group consisted of 1.5% of the total costs, whereas costs of medication and monitoring in the anticoagulant group were 3.6% of the total costs.

Cost-effectiveness. Because the differences in health outcomes or costs were not statistically significant, the CE-ratios were not calculated. The relationship between costs and health outcomes and the uncertainty surrounding these estimates are shown in the CE-planes in the Figure. The proportion of dots in each quadrant is reported in the tables. In the Figure, *a* and *b* (event-free survival and quality of life of all patients) show that almost half of the replicates were in the right lower quadrant,

Table II. Quality of life scores, events, event-free survival, and quality of life

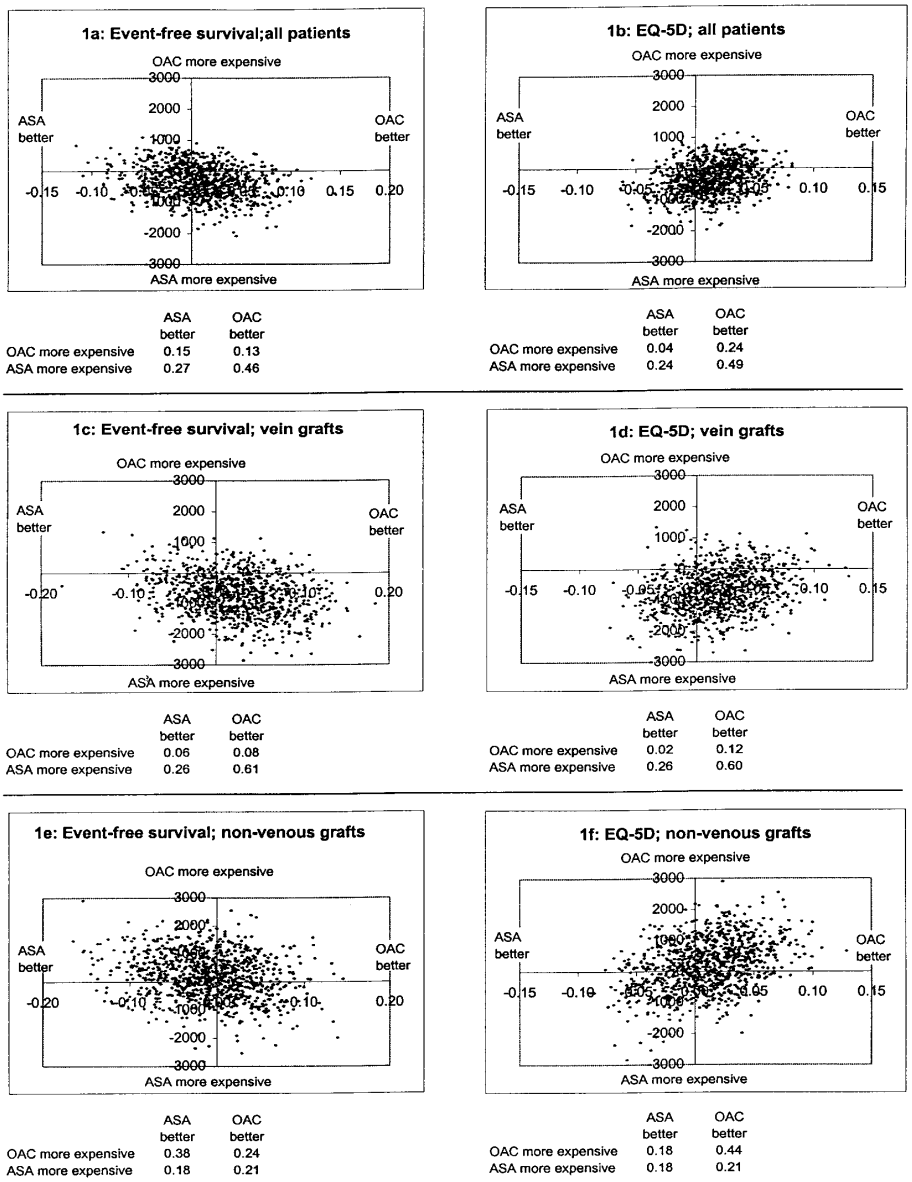
Health state after	*EQ-5D* score*	*No. of events*					
		All patients		*Vein graft*		*Nonvenous graft*	
		AC† (N = 1326)	*Aspirin (N = 1324)*	*AC (N = 784)*	*Aspirin (N = 762)*	*AC (N = 542)*	*Aspirin (N = 562)*
No event	0.68						
Vascular intervention							
Coronary artery bypass grafting surgery	0.58	16	13	10	9	6	4
Coronary artery angioplasty	0.58	12	10	8	7	4	3
Carotid thromboendarterectomy	0.58	6	10	6	7	0	3
Surgery of the aorta	0.58	11	6	7	4	4	2
Aortoiliac surgery	0.58	25	36	20	15	5	21
Infrainguinal surgery, contralateral leg	0.58	225	286	119	142	106	144
Infrainguinal surgery, ipsilateral leg	0.58	387	396	193	207	194	189
Other vascular surgery	0.58	3	4	1	1	2	3
All vascular interventions		685	761	364	392	321	369
Occlusion	0.58	308	323	112	156	196	167
Amputation	0.43	158	171	83	112	75	59
Hemorrhage	0.58	213	145	132	84	81	61
Stroke	0.45	30	46	20	28	10	18
Myocardial infarction	0.58	19	25	14	15	5	10
Death	0.00	211	205	125	127	86	78
Total		1624	1676	850	914	774	762
Event-free survival (y)*		1.10	1.09	1.15	1.13	1.02	1.03
Difference		0.01		0.02		–0.01	
95% CI		–0.07 to 0.08		–0.08 to 0.11		–0.08 to 0.13	
QALYs†		1.06	1.05	1.09	1.07	1.03	1.02
Difference		0.01		0.02		0.01	
95% CI		–0.03 to 0.06		–0.04 to 0.07		–0.04 to 0.09	

EQ-5D, Euroqol 5D; *AC,* oral anticoagulants; *QALY,* quality-adjusted life years.
*Mean follow-up: 21 months.
†A patient with perfect health who remained in the study for 21 months would have obtained a QALY score of 1.75.

Table III. Costs related to events and health states after an event in Euros

Type of event	*Event-related costs*	*Costs per month of each health state*
No event	0	250
After vascular intervention		
Coronary artery bypass grafting surgery	18,000	450
Coronary artery angioplasty	4,100	450
Carotid thromboendarterectomy	4,100	450
Surgery of the aorta	5,000	450
Aortoiliac surgery	5,000	450
Infrainguinal bypass grafting surgery	4,500	450
Other vascular interventions	4,100	450
After other events		
Occlusion	0	250
Amputation (first 6 mo)	11,500	1800
Amputation (after first 6 mo)	0	900
Hemorrhage	900	450
Stroke	11,500	900
Myocardial infarction	7,700	450
Death	3,200	0

indicating that oral anticoagulants tended to have favorable health outcomes against lower costs in comparison with aspirin. Likewise, *c* and *d* demonstrate that oral anticoagulants tended to be the favorable treatment in patients with venous bypass grafts. However, *e* and *f* demonstrate that aspirin was less expensive and associated with a higher event-free survival in patients with nonvenous grafts, whereas QALYs were higher in patients taking



1a	ASA better	OAC better
OAC more expensive	0.15	0.13
ASA more expensive	0.27	0.46

1b	ASA better	OAC better
OAC more expensive	0.04	0.24
ASA more expensive	0.24	0.49

1c	ASA better	OAC better
OAC more expensive	0.06	0.08
ASA more expensive	0.26	0.61

1d	ASA better	OAC better
OAC more expensive	0.02	0.12
ASA more expensive	0.26	0.60

1e	ASA better	OAC better
OAC more expensive	0.38	0.24
ASA more expensive	0.18	0.21

1f	ASA better	OAC better
OAC more expensive	0.18	0.44
ASA more expensive	0.18	0.21

CE-planes of oral anticoagulants versus aspirin (all costs in Euros).

Table IV. Mean costs per patient per year in Euros

	All patients		*Vein graft*		*Nonvenous graft*	
	AC	*Aspirin*	*AC*	*Aspirin*	*AC*	*Aspirin*
Event-related costs	2322	2631	2115	2550	2621	2757
Health state-related costs	4304	4331	4255	4380	4380	4255
Drugs and monitoring	250	109	250	109	250	109
Total costs	6875	7072	6619	7039	7251	7121
Difference	–196		–419		131	
95% CI	–746 to 343		–1166 to 289		–1111 to 774	

AC, Oral anticoagulants.

oral anticoagulants. In none of the graphs does the proportion of dots on one side of the vertical or horizontal axis exceed 95%, demonstrating that none of the differences in health outcomes or costs were statistically significant.

DISCUSSION

No differences in costs or effects between patients treated with oral anticoagulants and patients treated with aspirin after infrainguinal bypass surgery were shown by means of the results of this study. Until this study, the cost-effectiveness of these treatments had not been investigated. Economic evaluations were directed toward the comparison of antithrombotic therapies in patients with other manifestations of atherosclerosis, and most of these studies were not made on the basis of trial data.[13-17]

Instead of collecting data throughout the entire study period from all patients, we used a model to incorporate the outcomes of all patients. The strength of this model is that it allows the inclusion of all patients in the analysis, without the need for collecting complete data on all patients. The model makes use of data that were already collected in the clinical study. The crucial additional inputs in the model were the quality of life and costs associated with each health state. The triggered design of the data collection made it possible to base these values on most of the patients with events. In a traditional design, this would only be possible by collecting complete data on all patients.

The design of the data collection resulted in quality of life and cost estimates at different months after randomization. Although the data collection included most patients with events, it appeared to be hard to obtain reliable estimates of subsequent treatment costs of events. Costs did not only differ strongly between patients, the relationship between costs and events was also blurred by the large number of combinations of events, the high costs of patient care before an event, and the varying periods between events. These factors, combined with the availability of only repetitive 1-month data, made it difficult to determine which of the events were particularly related to an increase in resource use and costs. Therefore, only estimates of the event- and health state-related costs could be made, and similar estimates were used in both treatment groups. Considering the impact of an event, we considered it unlikely that we would find any differences in costs and quality of life between treatment groups, independent from events. Also, a test on the difference in costs and effects in the random population of the first sample showed no differences between the two treatment groups. Another consequence of assigning fixed health states and costs to events was that the uncertainty in the model-outcomes only resulted from events, and not from uncertainty around the quality of life or cost estimates. If, in addition to the uncertainty around the events, the uncertainty around these estimates was taken into account, it would have increased the overall uncertainty of the outcomes. Hence, this would have resulted in wider CIs and larger areas of the CE-planes.

Patients in the two samples who no longer filled in the questionnaires had approximately 20% more clinical outcome events than patients who completed all questionnaires. This could have influenced the estimates of quality of life and costs associated with each health state. It should be noted, however, that these estimates were obtained for each health state separately. Even if patients who no longer filled in the questionnaires had lower quality of life or higher costs, the estimates associated with each health state were not necessarily influenced. In addition, because similar estimates were used in both treatment groups, it seems unlikely that the difference in costs or effects has been influenced substantially by the follow-up in the samples.

When we estimated the costs of each health state after an event, we had expected that the occurrence of an event would lead to a higher resource use and a rise in subsequent treatment costs during the months after an event. This expectation was not confirmed by means of the resource use data in this study. Compared with patients without events, patients with events not only had higher costs after an event, but also before an event. This raises questions about the association between costs and events. Patients prone to have an event have higher medical resource use already in the period before the event. Patients who keep pain at rest after femorodistal bypass grafting may illustrate this phenomenon. These patients probably visit their vascular surgeon more often than patients who have undergone successful bypass grafting. Moreover, patients with rest pain probably get more diagnostic examinations, such as angiograms, to visualize the native arteries and the graft, because a reoperation is considered. Because it is common to use event-driven models in cost calculations, the validity of such models is questioned. We should be aware of this phenomenon when using an event-driven model. Rather than only assigning higher treatment costs to patients after an event, attention should also be paid to the treatment costs before an event.

To determine the costs of monitoring patients, we set up a separate costing study for the anticoagulation clinics. We expected that the higher costs of monitoring in the anticoagulant group would be an important factor that could account for the difference in costs between the treatment groups. However, the extra costs of monitoring patients taking anticoagulants were only € 200 per year, which was very limited compared with the mean annual costs of patients, which was € 6970. Even patients without events after the initial operation had yearly costs of € 3000. This implies that the extra costs of monitoring patients taking anticoagulants do not play a decisive role in comparing the cost-effectiveness of anticoagulants versus aspirin after infrainguinal bypass surgery. In patients with other manifestations of atherosclerosis, the additional costs only become relevant when patients have low resource use and costs. In patients with high resource use, these costs will not contribute substantially to differences in costs between treatment groups. Costs of monitoring in this study were made on the basis of the Dutch situation, with a highly effective system of anticoagulation clinics. In

several other countries, the costs of monitoring may be higher. However, even when the costs of monitoring are considerably higher than in the Netherlands, they still make up a small amount of the total treatment costs.

Finally, we should note that our results apply to clinical practice as performed in the Netherlands. Approximately half of our patients had intermittent claudication, a condition not always considered to be an indication for bypass surgery. Moreover, approximately 60% of our patients received venous grafts, whereas this percentage may be different in other settings.

In summary, we conclude that costs, event-free survival, and QALYs in patients after infrainguinal bypass surgery were not different between patients treated with aspirin and patients treated with oral anticoagulants. The extra costs of monitoring patients with oral anticoagulants were very limited and play no role in the decision for treatment with either aspirin or oral anticoagulants.

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APPENDIX I. PARTICIPATING INVESTIGATORS OF THE DUTCH BYPASS ORAL ANTICOAGULANTS OR ASPIRIN (BOA) STUDY GROUP

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Steering Committee: P. J. van Aken, A. Algra, J. H. van Bockel, J. Buth, J. J. A. M. van den Dungen, B. C. Eikelboom, J. A. Lawson, F. L. Moll, J. A. Rauwerda, P. de Smit, M. J. D. Tangelder, H. van Urk, J. de Vries-Goldschmeding (on behalf of the Federation of Dutch Thrombosis Services).

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APPENDIX II. UNIT COSTS

Unit costs of inpatient hospital days, visits to the consultant, infrainguinal bypass grafting surgery, and the monitoring of patients in the oral anticoagulant group were determined by means of detailed costing studies, because these items were expected to have the largest contribution to the incremental and total costs. The unit costs of inpatient days were calculated in two university hospitals and two general hospitals and included the costs of physicians, nursing, additional medication, diagnostic procedures, and buildings, equipment, and overhead. The unit costs of infrainguinal bypass surgery were calculated by means of multiplying the estimated duration of surgery with the cost per minute of the operating theater. The average duration of surgery was made on the basis of the registration system of the operating theaters and on the basis of earlier research.[7] The resulting unit costs are presented in Table V.

Table V. Unit costs in Euros

Type of resource use	*Unit costs*
Vascular surgery	
Coronary artery bypass grafting surgery	8000
Coronary artery angioplasty	2700
Carotid thromboendarterectomy	1250
Surgery of the aorta	2220
Aortoiliac surgery	2150
Infrainguinal bypass surgery	1750
Amputation	720
Inpatient days	
Hospital	250
Nursing home	120
Rehabilitation	270
Elderly home	60
Day care	
Hospital	100
Nursing home	60
Rehabilitation center	140
Outpatient visits	
Physician	50
General practitioner	16
Physiotherapy	16
District nurse	20
Home care (per h)	20
Medication (per y)	
Aspirin	100
Oral anticoagulants	50
Monitoring anticoagulant patients	200

APPENDIX III. BOOTSTRAPPING

Several authors have recommended the use of nonparametric bootstrapping to estimate CIs around the incremental CE-ratios.[9-11] One of the advantages of this method is that it does not depend on parametric assumptions of the underlying sampling distribution. The bootstrap method consists of these steps[10]:

1. Sample with replacement N_A pairs of costs and effects of patients in treatment group A, in which N_A is the number of patients in group A.
2. Calculate the mean costs and effects of this new sample.
3. Repeat these two steps in treatment group B.
4. Calculate the differences in mean costs and effects between the samples drawn from treatment group A and those from group B and calculate the incremental CE-ratio by dividing the difference in costs by the difference in effects.

The four steps reflect one bootstrap replicate. In this study, 1000 bootstrap replicates were obtained. CIs of the CE-ratio were obtained with the percentile method. This method implies that the 1000 replicates are sorted in ascending order and that the 95% CI constitutes of the 25th and 975th observations.