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Asymptomatic peripheral arterial disease: is pharmacological prevention of cardiovascular risk cost-effective?

B Sigvant[1,2], M Henriksson[3], F Lundin[4] and E Wahlberg[1,5]

Abstract

Peripheral arterial disease (PAD) is associated with an increased risk of early death in cardiovascular (CV) disease. The majority of PAD subjects are asymptomatic with a prevalence of 11 per cent among the elderly. Long-term drug prevention aiming to minimize disease progression and CV events in these subjects is probably beneficial, but expensive. The purpose of this analysis was to evaluate the cost-effectiveness of pharmacological risk reduction in subclinical PAD. Long-term costs and quality-adjusted life years (QALYs) were estimated by employing a decision-analytic model for ACE-inhibitor, statin, aspirin and non-aspirin anti-platelet therapy. Rates of CV events without treatment were derived from epidemiological studies and event rate reduction were retrieved from clinical trials. Costs and health-related quality of life estimates were obtained from published sources.

All four drugs reduced CV events. Using ACE-inhibition resulted in a heart rate (HR) of 0.67 (95% CI: 0.55–0.79), statins 0.74 (0.70–0.79), and clopidogrel 0.72 (0.43–1.00). Aspirin had a HR of 0.87 and the 95% CI passed included one (0.72–1.03). ACE-inhibition was associated with the largest reduction in events leading to the highest gain in QALYs (7.95). Furthermore, ACE-inhibitors were associated with the lowest mean cost €40.556.

In conclusion, while all drugs reduced CV events, ACE-inhibition was the most cost-effective. These results suggest that we should consider efforts to identify patients with asymptomatic PAD and, when identified, offer ACE-inhibition.

Keywords

Cost-benefit analysis, peripheral vascular disease, pharmacological prevention

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Introduction

PAD is an indicator of generalized atherosclerosis that is associated with a three to seven times increased risk for early death in cardiovascular disease (CVD).[1,2] The majority of PAD subjects are asymptomatic (APAD)[3] and even though the disease is subclinical it is associated with CV morbidity similar to symptomatic PAD stages and ischaemic heart disease.[2,4] In a recent published review, the pooled relative risk for CV mortality was 3.34 for APAD subjects.[4]

Current guidelines differ in their recommendations regarding treatment of APAD patients. One recommends that all APAD subjects should be offered anti-platelet therapy for CV risk prevention,[5] while others state that only APAD with other CV manifestations should be treated and then preferably with aspirin.[6,7] A consequence of this inconsistency is that few patients are treated and diagnosing APAD is a low priority.[8–10]

Since APAD is common – about 11 per cent of the elderly population in the West are affected – implementation of risk reducing drug programmes would require considerable health care resources.[3,11–12] Accordingly, the benefits of such strategies is ambiguous and the lack of information supporting or opposing prevention prevents potentially beneficial diagnostic efforts

[1]Inst of Molecular Med and Surgery, Karolinska Institutet, Stockholm, Sweden.
[2]Department of Surgery, Karstad Hospital, Sweden.
[3]Center for Technology Assessment, Department of Medicine and Health Sciences, Linköping University, Sweden.
[4]Medical Research Center, Karlstad Hospital, Sweden.
[5]The Heart Centre, Linköping University Hospital, Sweden.

Corresponding author:
Birgitta Sigvant, Department of Surgery, 650 81 Karlstad Hospital, Sweden
Email: birgitta.sigvant@liv.se

and prescription.[13] Besides being a prerequisite for considerations of preventive programmes, it is important to evaluate the cost- effectiveness of different treatment options for APAD to ensure sensible use of scarce health-care resources.[12]

The purpose of this study was to evaluate the cost-effectiveness of treating APAD with CV-event reducing medication. The study employs a decision-analytic model to address the impact of preventive treatment strategies for APAD on disease progression and health-care resources.

Methods

Patients and treatment strategies

This study focused on APAD only, which was defined as an ankle brachial blood pressure index (ABI) of <0.9 without leg symptoms.[6] Health outcomes of five treatment strategies were evaluated for primary prevention – one of no active treatment (usual clinical practice) and four active drug treatments: (1) low-dose aspirin; (2) angiotensin converting enzyme inhibition (ACE-i); (3) non-aspirin anti-platelet therapy; and (4) lipid-lowering therapy with statins. These four drugs were selected because they have scientific support for use in PAD. Dosages were the same as those used in the main clinical trials.

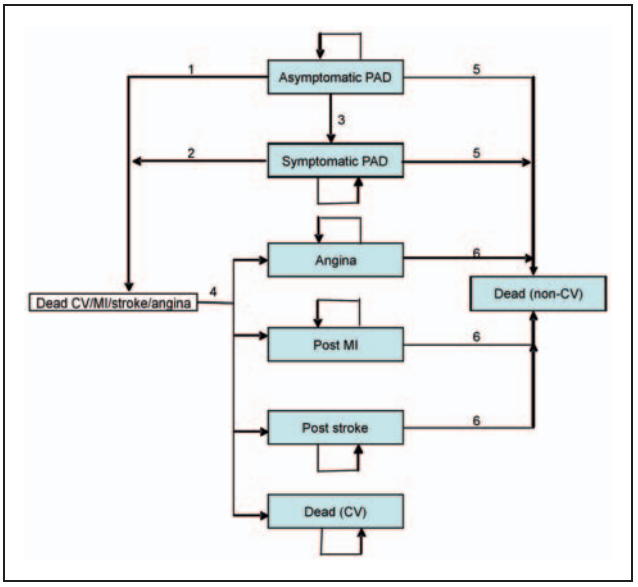

Figure 1. Model structure and transitions. 1. Risk of composite endpoint of CV death, MI, stroke or angina with asymptomatic PAD 2. Risk of composite endpoint of CV death, MI, stroke or angina with symptomatic PAD 3. Risk of developing symptomatic PAD 4. Conditional risk of a composite endpoint being CV death, MI, stroke or angina 5. Risk of non-CV death with PAD 6. Mortality risk after a composite endpoint (PAD, peripheral artery disease; CV, cardiovascular; MI, myocardial infarction).

Cost-effectiveness model

The analysis was undertaken from a health-service perspective and costs were expressed in Euros (€) at 2009 prices. Health outcomes were estimated in terms of quality-adjusted life years (QALYs). Costs and QALYs were discounted by 3 per cent per annum.[14] A Markov model[15] was developed in order to model disease progression and estimate costs and QALYs over a lifetime horizon. In a Markov structure, hypothetical individuals reside in one of a set of mutually exclusive health states at particular points in time.[15] During discrete time intervals of equal length (normally referred to as Markov cycles), individuals can either remain in a particular health state or move to a separate health state (e.g. the patient experiences a clinical event). The likelihood that an individual remains in a particular health state, or moves to a separate one, is estimated by transition probabilities. The costs and health outcomes from each Markov cycle were accumulated and summarized for the cohort of hypothetical individuals at the termination of the analysis. Annual Markov cycles were employed.

The model used the following health states: APAD, symptomatic PAD, angina pectoris (AP), post myocardial infarction (MI), post stroke, CV death and non-CV death (Figure 1). All subjects started in the APAD state. Each year patients face a risk of a composite endpoint (Transition 1 in Figure 1). This risk differs between treatment strategies and is determined using epidemiological data (clinical practice strategy) and data from randomized trials (all active treatments). If a composite endpoint occurs, a conditional risk (Transition 4) determines whether the event is fatal, a non-fatal MI, a non-fatal stroke or AP. Patients with non-fatal events made a transition to the relevant state (post MI, post stroke or AP), whereas patients with a fatal event transit to the dead state. In each cycle (year) patients were also at risk of developing symptomatic PAD (Transition 3). In this state patients were at risk of a composite endpoint although this risk is elevated compared with the APAD state (Transition 2). Both APAD and symptomatic PAD patients were at risk of dying from non-CV causes each year (Transition 5). An elevated mortality risk was applied to patients having suffered a non-fatal event (Transition 6). Furthermore, costs and health-related quality of life post non-fatal events were estimated to capture the possibility of further events. Hence, second and subsequent events were not explicitly modelled.

Input Parameters

Event Rates. An overview of the clinical data, its associated uncertainty and literature sources are presented in Table 1. Baseline risk for initial events (i.e. AP, MI, stroke, symptomatic PAD, CV death and non-CV death) were retrieved from epidemiological cohort studies carried out in the 1980s and early 1990s.[1,16] The reason for using older studies was that they covered subjects rarely using preventive drugs and could thus be considered relevant for estimating event rates in the untreated group (clinical practice strategy).

The event rates used are crude estimates not taking background variables (such as age, smoking, diabetes mellitus ((DM), CAD or stroke) into account. The crude estimates result in more robust data than adjusted ones and are more in concordance with our study population. Incidence rates were calculated using the person-year method. Further event rates for subjects in post-event states were estimated from Swedish patient-based registers.[17–18] Age-dependent non-CV mortality rates by gender were estimated from life tables.[19]

The risk reductions of CV events associated with the drugs under investigation was derived from clinical trials[20–24] and is presented in Table 1. Intervention effects were assumed to be independent from one another.

The estimated hazard ratios were multiplied by the baseline risk in order to determine the risk of a composite event with each of the active treatment strategies. Data for symptomatic PAD was used for clopidogrel and statins, despite the fact that APAD was the population of interest. The reason was lack of data for these two drugs. It use was supported by the assumption that effects of intervention only differ marginally between the PAD stages[25] and that we were able to adjust for this difference by using data in the literature.[16,26] We also assumed treatment effectiveness in terms of relative risks was constant across all ages and

Table 1. Baseline event rates and treatment efficacy for patients with peripheral arterial disease

Parameter in model	Mean estimate	Distribution	Source (References published supplementary)
Rate (per 100 patient years) of composite enpoint of angina pectoris, myocardial infarction, stroke or CV death*			
Asymptomatic patients	4.9	Gamma (178, 0,0003)	Hooi 2004, Leng 1996
Symptomatic patients	11.9	Gamma (101, 0,0011)	Hooi 2004, Leng 1996, Newman 1999
Relative risk (hazard ratios) of composite enpoint with different treatment strategies**			
Statins	0.74	Lognormal (−0.3011, 0.02)	HPS 2002(21)
Aspirin	0.87	Lognormal (−0.1393, 0.075)	Belch 2008, Catalano 2007
Non aspirin anti-platelet therapy	0.72	Lognormal (−0.3285, 0.24)	Caprie 1996(20)
ACE-inhibitors	0.67	Lognormal (−0.4005, 0.06)	Ostergren 2004
Conditional probability of composite endpoint being angina pectoris, non-fatal myocardial infarction, non-fatal stroke or CV death***			
Asymptomatic patients			
Angina pectoris	0.29		Hooi 2004, Leng 1996
Non-fatal myocardial infarction	0.34		Hooi 2004, Leng 1996, Lee 2004
Non-fatal stroke	0.32	Dirichlet (52,61,56,9)	Hooi 2004, Abott 2001
CV death	0.05		Vogt 1993
Symptomatic patients			
Angina pectoris	0.15		Caro 2005
Non-fatal myocardial infarction	0.55		Caro 2005
Non-fatal stroke	0.15	Dirichlet (1555,1563,1589,5693)	Caro 2005
CV death	0.15		Caro 2005
Rate per (100 patient years) of asymptomatic PAD turning symptomatic****	8.6	Gamma (160, 0.0005)	Newman 1999, Hooi 2004, Leng 1996

*Baseline event rates were converted to annual probabilities and implemented for the clinical practise strategy in the model (transitions 1 and 2).
**Hazard ratios were multiplied by baseline event rate and converted to annual probabilities of a composite endpoint with each active treatment strategy (transitions 1 and 2).
***Transition 4 in the model.
****Rates were converted to annual probabilities and implemented in the model (transition 3).

between sexes. Age- and sex-specific data are lacking and we considered this a reasonable postulation for our model. A separate investigation looked into the effect of a lifetime's duration of treatment.

Health outcome. QALYs were calculated by multiplying the time a person remained in a certain health state by a quality-adjustment weight associated with that particular health state. The quality-adjustment weights were derived from published sources and presented in Table 2. [27–29] Decrements associated with health states in the model were applied to quality-adjustment weights of the normal population (adjusted for age and gender).[30] Hence, in patients with APAD the general population quality-adjustment weight was applied.

Cost. Medication costs were calculated as an annual cost and are based on the current price list from Pharmaceutical Specialities in Sweden[31] (Table 2). Two scenarios were tested in the sensitivity analyses, in the first; patients were assumed to stay on medication for five years and in the second they were treated lifelong. Costs associated with the health states in the model were estimated using a large Swedish hospital based register (Cost Per Patient) that collects detailed costs of administration, hospitalization, diagnostic work-up, intervention and rehabilitation for each diagnosis on a national level. Costs for nursing home care are not included in the registry. We did not include indirect costs since the population is retired.

Analysis

Life-years, QALYs and costs are presented as mean outcomes per patient. Relevant decision rules were applied when calculating incremental cost-effectiveness ratios (defined as differences in costs divided by differences in QALYs) for relevant comparators.[32] A cohort of 65-year-old APAD patients was analysed in the model. Separate analyses were performed for men and women. In separate studies, 55- and 75-year-old cohorts were analysed.

Uncertainty in cost-effectiveness was evaluated using probabilistic sensitivity analysis. In the probabilistic analysis, second-order Monte Carlo simulation was used to propagate the uncertainty in single-model inputs through the model. This meant that the uncertainty in the cost-effectiveness results indicated the uncertainty in the decision to implement a treatment strategy rather than the uncertainty surrounding single-model inputs. Cost-effectiveness acceptability (CEA) curves were drawn to show the probability of

Table 2. Costs and health-related quality of life parameters

Parameter in model	Mean estimate	Distribution	Source (references published supplementary)
Quality-of-life weights (utilities)			
Asymptomatic PAD 60–69 year olds*	0.78	Beta (53, 15)	Burström 2007
Decrement symptomatic PAD	0.27	Gamma (7.3, 0.04)	Letterstal 2008
Decrement myocardial infarction	0.10	Gamma (4, 0.03)	Xie 2008
Decrement stroke	0.26	Gamma (6.8, 0.04)	Xie 2006, Haacke 2006
Decrement angina	0.18	Gamma (12.5, 0.01)	Longworth 2005
Costs			
Annual cost of aspirin	19.92	Deterministic	Pharm list
Annual cost of statins	26.48	Deterministic	Pharm list
Annual cost of non-aspirin antiplatelet therapy**	545.76	Deterministic	Pharm list(47)
Annual cost of ACE-inhibitors	24.44	Deterministic	Pharm list
Annual cost first year with symptomatic PAD	19288	Gamma(103,187)	Swed Ass
Annual cost second and subsequent years with symptomatic PAD	5764	Gamma(133, 43)	Swed Ass
Annual cost first year with myocardial infarction	15457	Gamma(106,146)	Swed Ass (48)
Annual cost second and subsequent years after myocardial infarction	4119	Gamma(17, 243)	Swed Ass
Annual cost first year with stroke	12812	Gamma(114, 112)	Swed Ass
Annual cost second and subsequent years after stroke	3462	Gamma(48, 72)	Swed Ass
Annual cost first year with angina	14066	Gamma(101, 139)	Swed Ass
Annual cost second and subsequent years with angina	4200	Gamma(71, 60)	Swed Ass

*For 70–79 year old males (females) this utility was lowered by 2.5 (0) percent. Corresponding figurer for patients 80 years or older was 11 (5) percent.
**Cost of branded Plavix (clopidogrel), in a sensitivity scenario generic clopidogrel was assumed and cost was lowered by 80 percent.

the CEA strategy being cost-effective at different levels of willingness to pay for a QALY. Several analyses were also performed to assess uncertainty in the cost-effectiveness results related to model assumptions. The model was programmed and analysed using Microsoft Excel (Microsoft, Redmond, Washington, USA).

Results

Statin, aspirin, non-aspirin anti-platelet therapy and ACE-i treatment yielded a 26 per cent, 13 per cent, 28 per cent and 33 per cent reduction in composite endpoint, respectively (Table 3). Applying these treatment effects for five years' duration resulted in an increased life expectancy compared with clinical practice. The largest improvement was seen for treatment with ACE-i (from 11.40 years to 11.48 and 12.83 years to 12.89 for men and women, respectively).

Non-aspirin anti-platelet therapy was most expensive, costing €545/year. The other treatments had a much lower yearly price. For example ACE-i cost €24/year and statins, and €26/year. Predicted mean costs differed 13 per cent between men and women for all treatment strategies as an effect of the shorter life expectancy of men (Table 3).

ACE-i treatment resulted in the highest mean QALYs (7.44 and 8.45 for men and women respectively). For the other treatment strategies, the mean QALYs ranged from 7.36 to 7.43 for men and 8.38 to 8.44 for women. The gain was small for aspirin treatment (Table 3).

ACE-i was the most effective treatment for both men and women in the model and it was associated with the lowest mean cost (Table 3). Accordingly, as apparent in the CEA curves, ACE-i was more cost-effective than the other treatments (Figure 2).

Sensitivity analyses

The results of sensitivity investigations are presented in Table 4. Extending the duration of treatment to a lifetime, lowering the cost of non-aspirin anti-platelet therapy due to patent expiry, and running the model for 55- and 75-year-olds did not alter the conclusion that ACE-i is the most cost-effective strategy.

Discussion

Our analysis suggests that medical treatment for prevention of CV events in APAD subjects is cost-effective, and among the treatment strategies evaluated ACE-i

Table 3. Estimated health outcomes and costs with the investigated treatment strategies for 65-year-old APAD subjects

	Clinical practice		Statins		Aspirin		Non-aspirin antiplatelet therapy		ACE inhibitors	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Proportion of cohort suffering angina at 5 years	0.062	0.063	0.048	0.048	0.055	0.056	0.047	0.047	0.044	0.044
Proportion of cohort suffering angina over lifetime	0.143	0.157	0.135	0.150	0.139	0.153	0.135	0.149	0.133	0.148
Proportion of cohort suffering a stroke at 5 years	0.067	0.067	0.051	0.052	0.059	0.060	0.050	0.050	0.047	0.047
Proportion of cohort suffering a stroke over lifetime	0.151	0.165	0.142	0.157	0.147	0.162	0.142	0.157	0.140	0.155
Proportion of cohort suffering a myocardial infarction at 5 years	0.071	0.072	0.055	0.055	0.063	0.064	0.053	0.054	0.050	0.051
Proportion of cohort suffering a myocardial infarction over lifetime	0.159	0.173	0.149	0.164	0.154	0.169	0.148	0.164	0.146	0.162
Proportion of cohort dying from cardiovascular causes at 5 years	0.047	0.048	0.037	0.038	0.042	0.043	0.036	0.037	0.034	0.034
Proportion of cohort dying from cardiovascular causes over lifetime	0.218	0.249	0.222	0.255	0.220	0.252	0.222	0.256	0.223	0.257
Mean life years	11.4002	12.8293	11.4634	12.8798	11.4307	12.8533	11.4640	12.8807	11.4815	12.8945
Mean quality-adjusted life years	7.3674	8.3809	7.4269	8.4350	7.3965	8.4070	7.4276	8.4360	7.4436	8.4500
Mean costs	37979	43758	37776	43521	37904	43667	39808	45566	37688	43425

Clinical practice, non-aspirin antiplatelet therapy and ASA were all dominated (lower QALYs and higher costs) by statins or ACE-inhibitors.
The incremental cost-effectiveness ratio comparing ACE-inhibitors and statins was 1,484 and 1,259 for men and women respectively.

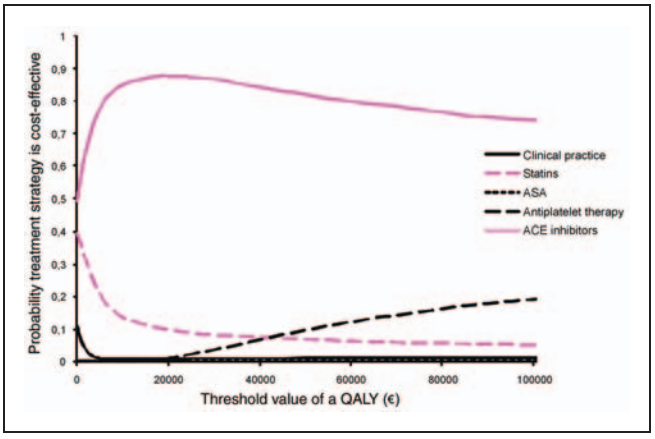

Figure 2. Cost-effectiveness acceptability curves The cost-effectiveness acceptability curves are for the analysis of 65-year-old males. However, the analysis of 65-year old women showed almost identical cost-effectiveness acceptability curves. QALY: quality-adjusted life year.

was the most cost-effective. Another observation is that aspirin treatment was not cost-effective. These findings challenge the few guideline recommendations that are available.[5–7]

ACE-i was most cost-effective in the model, and it can be considered cost-effective in general. Even for conventional thresholds of cost-effectiveness (proposed by NICE to be €32.000/QALY gained) the probability that CV prevention with ACE-i is cost-effective is high (85 per cent to a cost of €20.000/QALY gained.[33] Despite its pleiotropic beneficial effects, ACE-i is not recommended as a first-line anti-HTN agent in PAD subjects.[34] Considering the cost-effectiveness of ACE-i treatment in APAD, these prescribing recommendations must be questioned and its use as a first-line agent in PAD should probably be re-evaluated.[35]

The finding that aspirin is not cost-effective is surprising. Despite its very low costs the poor event reduction causes a low QALY gain and regardless of willingness to pay, this treatment is not cost-effective in APAD. Moreover, despite the lack of clinical evidence for use in PAD subjects in general, aspirin is widely recommended in guidelines and in review articles.[36–38] There appears to be a consensus of the benefits of primary CV prevention in a broader high CV risk population[7,39] and the American Heart Association,[40] for instance, calls for prevention after the first episode of CAD, stroke, diagnosis of an aortic aneurysm or PAD. Health economic analyses of such primary CV prevention strategies have favoured aspirin treatment.[41] Pigone et al.,[42] for example, observed that aspirin prevented only MI out of all CV events in a healthy elderly population. Information on cost-effectiveness of lipid-lowering treatment is variable for high CV risk populations. Ward et al.[43] found that cost-effectiveness

Table 4. Results of Sensitivity Analyses

Scenario investigated and reported outcome	Clinical practice		Statins		Aspirin		Non-aspirin antiplatelet therapy		ACE inhibitors		Incremental Cost Effectiveness Ratio	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Treatment effect for lifetime duration												
Mean quality-adjusted life years	7.3674	8.3809	7.5237	8.5550	7.4361	8.4572	7.5336	8.5706	7.5739	8.6142		Statins vs. clin pract: 5141
Mean costs	37979	43758	38656	44692	38306	44204	42085	48350	38868	45001	ACE-i vs. clin pract: 4218	ACE-i vs. statins: 5220
*Generic price of antiplatelet therapy**												
Mean quality-adjusted life years	7.3674	8.3809	7.4269	8.4350	7.3965	8.4070	7.4276	8.4360	7.4436	8.4500	ACE-i dominates all	ACE-i dominates all
Mean costs	37979	43758	37776	43521	37904	43667	38106	43831	37688	43425	other strategies	other strategies
75-year-old patients												
Mean quality-adjusted life years	5.0392	6.0757	5.0964	6.1370	5.0668	6.1058	5.0985	6.1373	5.1124	6.1542	ACE-i dominates all	ACE-i dominates all
Mean costs	24311	29345	24130	29150	24248	29273	26046	31137	24048	29063	other strategies	other strategies
55-year-old patients												
Mean quality-adjusted life years	9.4127	10.2242	9.4541	10.2539	9.4329	10.2384	9.4548	10.2552	9.4659	10.2623	ACE-i dominates all	ACE-i dominates all
Mean costs	50956	55912	50663	55558	50837	55764	52729	57624	50549	55428	other strategies	other strategies

*Assuming an 80 percent reduction of current price.

ratios were dependent on the level of CV risk and age, whereas Pilot et al.[44] concluded that statins were cost-effective regardless of lipid levels for a high proportion of this population. Cost-effectiveness analyses of ACE-i in high risk patients were found to be cost-neutral or cost saving.[45]

Using relevant input data is essential for modelling analyses of this kind. By using 'older' studies for the event rates for best clinical practice, we avoided comparison with existing cohorts on preventive medication. The drugs used in the model are the ones evaluated in large clinical trails enrolling PAD patients and therefore recommended in guidelines and of acceptable quality.[5–7] HOPE, CAPRIE and HPS are all large, well-known, outcome trials.[20–21,24] It was more difficult to find trials evaluating aspirin treatment. The CLIPS study[23] enrolled few patients and terminated early and the POPADAD trial,[22] was of sufficient size but included only subjects with diabetes.

One limitation of this analysis is the deficiency of source data for APAD. This forced us to use data for symptomatic patients for statins and clopidogrel.[20–21] At least for clopidigrel this approach has support in the literature and is acceptable according to our sensitivity analysis. The HOPE trial[24] addressed the target population but has its limitation since it is a post-hoc subgroup analysis Another limitation is the variability in background medication and concomitant diseases in the clinical trials used as source data. Efficacy estimates of treatment effects, however, did not threaten the validity of results in sensitivity analysis. We did not model poor adherence for drug intake although we used efficacy estimates from trials that used intention to treat analyses. Other modelling issues such as length of treatment and changes in cost were evaluated by sensitivity analyses and did not alter the results of the base-case analysis to a large extent.

Sweden is a unique country in terms of its efforts to register all citizens, including their use of health care.[46] The health authority registries gathering costs are very robust and reliable.

This study supports the notion that it is cost-effective to prevent CV events in APAD. ACE-i treatment was associated with the largest reduction in CV events leading to the highest quality-adjusted survival compared to the other drugs. Aspirin treatment was associated with a low mean cost but a small event reduction. These findings are in direct contrast to the recommendations in prevention guidelines that support the use of aspirin and rarely mention ACE-i for this group of patients.

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