



Cost-effectiveness of a European preventive cardiology programme in primary care: A Markov Modelling Approach

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-001029
Article Type:	Research
Date Submitted by the Author:	16-Feb-2012
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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	HEALTH ECONOMICS, CARDIOLOGY, PRIMARY CARE

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Cost-effectiveness of a European preventive cardiology programme in primary care

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and on behalf of the EUROACTION study group

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3 **Abstract (word count 300)**
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6 **Objective:** To investigate the longer-term cost-effectiveness of a nurse-coordinated
7 preventive cardiology programme for primary prevention of cardiovascular disease
8 compared to routine practice from a health service perspective.
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14 **Design:** A matched, paired cluster-randomised controlled trial.
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19 **Setting:** Six pairs of general practices in six countries.
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23 **Participants:** 1,019 patients were randomised to the EUROACTION intervention
24 programme and 1,005 patients to usual care.
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29 **Outcome measures:** Evidence on health outcomes and costs were based on patient level
30 data from the study, which had a one-year follow-up period. Future risk of cardiovascular
31 (CVD) events was modelled, using published risk models based on patient characteristics.
32 An individual level Markov model for each patient was used to extrapolate beyond the end of
33 the trial, which was populated with data from published sources. We used an 11-year time
34 horizon and investigated the impact on cost-effectiveness of varying the duration of the
35 effect of the intervention beyond the end of the trial. Results are expressed as incremental
36 cost per quality-adjusted life year gained.
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47 **Results:** Unadjusted results found the intervention to be more costly and also more effective
48 than usual care. However, after adjusting for differences in age, gender, country and
49 baseline risk factors, the intervention was dominated by usual care, but this analysis was not
50 able to take into account of lifestyle changes in terms of diet and physical activity.
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3 **Conclusions:** Although the EUROACTION study achieved healthier lifestyle changes and
4 improvements in management of blood pressure and lipids for patients at high risk of CVD,
5 compared to usual care, it was not possible to show, using available risk equations which do
6 not incorporate diet and physical activity, that the intervention reduced longer-term
7 cardiovascular risk cost-effectively. Whether or not an intervention such as that offered by
8 EUROACTION is cost-effective requires a longer term trial with major cardiovascular events
9 as the outcome.
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Article summary

Article focus

- To investigate the longer-term cost-effectiveness of a nurse-coordinated preventive cardiology programme for primary prevention of cardiovascular disease compared to routine practice.

Key messages

- The EUROACTION study achieved healthier lifestyle changes and improvements in management of blood pressure and lipids for patients at high risk of CVD, compared to usual care.
- The unadjusted results of the cost effectiveness analysis found the intervention to be more effective than usual care but also more costly. However, the adjusted results showed that the intervention was dominated by usual care.
- The published cardiovascular risk equations do not take account of lifestyle changes in terms of diet and physical activity and therefore may be inadequate for the evaluation of whether or not a lifestyle intervention to prevent cardiovascular disease is cost-effective.

Strengths and limitations of the study

- This is the first study assessing the cost-effectiveness of the EUROACTION programme.
- The available cardiovascular risk modelling is based on a limited number of risk factors, which do not include measures of diet or physical activity, and a healthier lifestyle was the most important outcome of the EUROACTION trial.

Trial Registration number: ISRCTN 71715857

Keywords: Multi-centre studies; cardiovascular prevention programme; cost-effectiveness; Markov model; QALYs.

Text word Count: 3,064

Introduction

Evidence has shown that individuals with increased risk of cardiovascular disease (CVD) can reduce their risk of cardiovascular morbidity and mortality by stopping smoking, changing their diet, engaging in physical activity, achieving a healthy body weight, and controlling their blood pressure, cholesterol and diabetes.[1] However, not all patients at high risk of developing CVD manage to achieve these recommended lifestyle and risk factor goals and there remains considerable potential to reduce CVD risk in these patients.[2] The EUROACTION study was designed to address the need for preventive cardiology care in everyday clinical practice.[3]

The EUROACTION study was a matched, paired cluster-randomised controlled trial, across eight countries and 24 hospitals and general practices. The project evaluated the impact of a nurse-coordinated, multidisciplinary preventive cardiology programme for coronary patients in hospital and high risk individuals in general practice. It aimed to help all these high risk patients and their families to achieve recommended lifestyle and risk factor targets for CVD prevention in everyday clinical practice over one year. The principal results concluded that the EUROACTION programme achieved healthier lifestyle changes and improvements in risk factor management for patients with coronary heart disease (CHD) and those at high risk of CVD, together with their partners, compared to usual care.[4]

While there is evidence that the EUROACTION programme is effective in terms of modifying lifestyle and some CVD risk factors, there is no evidence as to its cost-effectiveness.

Therefore, this paper aims to model the long-term cost-effectiveness of the EUROACTION programme in comparison with usual care within the primary care setting.

Methods

Patients

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2 The EUROACTION primary care study took place in Denmark, Italy, Netherlands, Poland,
3 Spain and UK, where a matched pair of general practices was identified, and then
4 randomised to either the EUROACTION programme or to usual care (UC). GPs
5 prospectively identified the study population. The comparison was restricted to patients and
6 did not include partners. Eligibility criteria for patients has previously been published.[4]
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13 All intervention patients were assessed at baseline and one-year. These assessments
14 focussed on smoking habits, diet and physical activity, measurement of body mass index,
15 blood pressure, cholesterol and glucose levels, and cardiac medications were also recorded.
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17 The programme was delivered by specialist nurses, working with GPs, and supported by
18 software programmes (HEARTSCORE), educational materials and group workshops to
19 achieve individual goals. Each person was given a personal record card to record lifestyle
20 and risk factor goals, medications and appointments. To avoid the possibility that
21 undergoing baseline assessments might affect outcomes, only a random sub-sample
22 (~25%) of UC patients were seen at baseline and then all UC patients were invited for
23 assessment at one-year. In the UC arm, patients did not receive any form of special care.
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37 ***Model structure***

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39 We adopted a health service perspective to measure costs and outcomes. Each cycle in the
40 model is of one year's duration. All patients were CVD-free on entering the model. In each
41 subsequent cycle patients may remain CVD-event free, they may have a fatal or non-fatal
42 CVD event, or they may die from non-CVD causes. Once the patient has had an initial CVD
43 event, then in subsequent cycles they move to the post CVD-event states and they may
44 move between different CVD states and/or die from CVD or non-CVD causes.
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53 The CVD event states are: non-fatal myocardial infarction (MI), stable angina, unstable
54 angina, CHD death, transient ischaemic attack (TIA), stroke, CVD death and non-CVD
55 death.
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Measuring initial CVD risk

To estimate the risk of an initial CVD event in a subsequent year we used the D'Agostino et al [5] CVD risk function, derived from the Framingham Heart Study. This calculates individual sex-specific risks for future cardiovascular events (in patients initially free of CVD). These CVD risk equations incorporate as risk factors the natural logarithms of age, total and HDL cholesterol, systolic blood pressure (SBP) if treated with or without anti-hypertensive medications, smoking and diabetes. We used the published calibration factors to focus on the CHD and stroke event states.

Ten-year risks were estimated from the equations and adjusted to one-year values.[6] One-year CVD risk beyond the end of the trial was calculated based on both a) baseline patient characteristics (adjusted for age) for intervention patients only; and b) one-year follow-up characteristics for both groups, in order to evaluate any changes to CVD risk factors as a result of the EUROACTION programme.

Validating the appropriateness of the risk functions of the model

We tested the validity of applying the D'Agostino et al [5] risk equations to the study population, by comparing the observed number of CHD cases with the number predicted at one-year. Because stroke and TIA incidence data was not collected in the study we converted the CVD risk equations to CHD risks using the recommended calibration factors.[5] We present the results of the comparison for both groups.

Transition probabilities

We disaggregated the overall risk of a CVD event into rates for specific events by age and gender, using UK relative incidence rates based on published literature [7-9] and expert opinion, as previously used in Ward et al [10]. These event rates were applied to individual annual CVD risks to calculate individual transition probabilities for moving from the CVD-free

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2 state to the initial CVD-event states. Also, individual patients could die from non-vascular
3 causes, depending on their age and gender. The non-CVD death transition probabilities
4 were taken from Briggs et al.[11] Transition probabilities for moving from primary event
5 health states to subsequent non-fatal health states are taken from Ward et al.[10]
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10 11 12 **Measuring cost**

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14 Data on resources used during the trial and staff contacts were recorded in case record
15 forms and then converted into electronic format. To determine the total one-year costs for
16 each group, we obtained unit costs for all relevant items of resources used in the trial:
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22 *1. Costs relating to EUROACTION programme and other contacts in primary care were*
23 *obtained from the programme facilitators and included the EUROACTION nurses costs,*
24 *training costs, production of patient educational materials and any other costs*
25 *associated with implementing the programme. The average time spent by staff for all*
26 *patient contacts at baseline and one-year was provided by each centre. Hourly wage*
27 *rates of the staff salaries and training were calculated and then applied to these various*
28 *patient contacts. We costed the EUROACTION family information packs, a pocket-*
29 *sized personal record card, questionnaires and group sessions that each patient in the*
30 *intervention group received as part of their prevention programme.*
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44 Costs were applied to other contacts with health care professionals, such as GPs,
45 outside of the intervention programme for both arms and these costs were based on
46 national estimates of the staff salaries involved and estimates of the average time spent
47 with the patient provided by the trial co-ordinators.
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53 *2. Cardiac-related drug costs.* Data was collected on patient-specific cardiac-related
54 medications including the drug name and dose at baseline and one-year. This gave
55 point of time information, but no start or end dates. So for each patient it was assumed
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2 that they would remain on the same medication at a constant dose for the entire
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4 duration e.g. from baseline to one-year. National cost estimates for the drugs were
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6 provided by trial co-ordinators from each country and were applied accordingly to the
7
8 relevant dose and length of time on a patient-specific basis.
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12 *3. Cardiac-related procedures and tests.* During the trial, patients within both groups
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14 may have required inpatient or outpatient admissions for cardiac-related procedures, or
15
16 undertaken any cardiac-related tests. The procedures were costed according to HRG
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18 episodes for each country and the other tests or bed days as simple unit costs.
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20 National unit cost estimates for cardiac-related procedures and tests for each country
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22 were obtained from a database held by United BioSource Corporation (Erwin De Cock,
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24 personal communication, May 2007) for all countries, except Denmark and Poland. For
25
26 these two countries, national unit cost estimates were provided from contacts within the
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28 Centre for Applied Health Services Research and Technology in Denmark (Jan
29
30 Sørensen, personal communication, January 2007) and from the Ministry of Health in
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32 Poland (Andrzej Pająk, personal communication, June 2007).
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37 As the study was based in six countries, a costing algorithm was developed to calculate a
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39 total cost per patient for each country. The costs of the programme were valued in local
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41 currencies and then converted to 2006/2007 £ (GBP) using purchasing power parities.[12]
42
43 Table 1 presents the total one-year costs by group and country.
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47 Subsequent costs relating to health states occupied within the model were based on UK
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49 estimates (see Appendix). It was assumed that patients in a CVD-free state would continue
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51 to receive the cardiac-related medications and primary care contacts (outside of the
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53 intervention programme) that they received during the trial. The mean cost of these
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55 medications and contacts for all patients across both arms was applied to each individual
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57 patient within the model who remained in the event-free health state for subsequent years.
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Health state utilities

To estimate quality-adjusted life years (QALYs) the model requires utility values for each state adjusted by age. For patients who were event-free, the utility values were based on UK general population norms [13]; utilities for events/states were taken from Ward et al [10] which were all were based on UK studies and were obtained using the EQ-5D (see Appendix).

Measuring the impact of the intervention

The study provided results only for a one-year follow-up. We estimated results for a range of possible durations of effect, assuming that the CVD risk reduction experienced by the intervention patients persisted for 0 through to 10 additional years (11-year time horizon), after which they reverted to their individual CVD risk factor levels at the start of the study (adjusted for age). For UC patients, it was assumed that patients would remain at their one-year CVD risk (adjusted annually by age) throughout the model.

Measuring cost-effectiveness

Using the Markov model we calculated for each patient their expected quality-adjusted survival (based on their likelihood of surviving each cycle and their expected health state utility value) and their expected costs. Cost-effectiveness was measured in terms of the incremental cost per QALY gained (ICER). Future costs and benefits were discounted at 3.5%. [14]

Statistical analyses

All statistical analyses were performed in Stata version 10 [15] or Microsoft Excel and a p-value ≤ 0.05 was considered to be statistically significant. We present unadjusted and adjusted cost-effectiveness results. The adjusted results controlled for group allocation, age, gender, age*gender interactions, country, and baseline risk factors using OLS regressions.

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2 As only a random sub-sample of UC patients were seen at baseline, regression analyses
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4 were used to predict baseline values for those patients who had missing values. For total
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6 and HDL cholesterol and SBP, OLS regression was used to predict values in those patients
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8 with missing values, as a function of age, gender and country. For the three binary variables
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10 (medications, smoking and diabetes), logistic regression models were used to predict the
11
12 probability of each binary outcome. Predicted values ≥ 0.5 were categorised to a value of 1
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14 and values < 0.5 were categorised as 0. In the adjusted models we also included an
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16 indicator for whether or not each control variable was missing.
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21 Bootstrapping was undertaken on both unadjusted and adjusted costs and effects using
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23 10,000 replications to provide 95% confidence intervals around the mean. Probabilistic
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25 sensitivity analyses were conducted to obtain cost-effectiveness acceptability curves
26
27 (CEACs).
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30 31 ***Sensitivity analysis***

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33 The main analysis modelling was limited to ten years, in the absence of robust longer-term
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35 risk models. As a sensitivity analysis, we used a simplified longer-term model to check
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37 whether the conclusions of the main analysis would have been likely to be different if a
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39 longer-term perspective had been adopted e.g. 25 years. This model essentially assumed
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41 no further effect of the intervention but modelled out fully the possible QALY gains from the
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43 medium-term (11 year) differences in mortality and event rates.
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46 47 **Results**

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49 We modelled 1,019 patients in the intervention arm and 1,005 patients in the UC arm who
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51 were assessed at one-year.[4] The intervention group had fewer males than the UC group:
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53 49.8% vs. 57.4% male ($p=0.001$), and was significantly younger (mean age at one-year:
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55 intervention: 61.5 years vs. usual care: 62.3 years, $p=0.011$).
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When testing the validity of the Framingham risk equations to the study population we found that 8 intervention patients and 1 UC sub-sample patient experienced a CHD-event. The risk equations produced a close match, predicting 8.5 patients with a first CHD-event in the intervention group and 2.0 in the UC sub-sample.

In terms of the unadjusted results, the incremental costs of the intervention are £362-£419 depending on the duration of the effect of the intervention and the incremental QALYs are 0.076-0.085 (see Table 2). As expected, the incremental costs fall and the incremental QALYs rise as the duration of the effect of the intervention beyond the end of the trial increases. The incremental cost per QALY gained range from £5,539 (95% CI £2,625-£29,627) to £4,266 (95% CI £2,059-£15,945). The unadjusted CEACs under each scenario are in Figure 1a and highlights the results in Table 2 that in all scenarios over 95% of the bootstrapped replications are less than £20,000.

After controlling for differences in age, gender, country and baseline risk factors, the intervention is associated with higher costs and lower QALYs than the UC arm in every scenario. As a result, the intervention is dominated by UC. The adjusted CEACs are in Figure 1b (additional adjusted CEACs, controlling for age, gender and country only are in the Appendix). At a cost-effectiveness threshold of £20,000 the EUROACTION intervention will be cost-effective in under 6% of cases.

The sensitivity analysis produced predictable results that in no way changed the conclusions of the analysis. Using the unadjusted data, the cost-effectiveness of the intervention was further enhanced, and using the adjusted data the domination of UC over the intervention remained.

Discussion

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2 Although this large European trial demonstrated that a nurse-coordinated preventive
3 cardiology programme in primary care helped more high risk patients to achieve the lifestyle
4 and risk factor targets in comparison with UC this does not appear to be cost-effective.
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6 However, these cost-effectiveness analyses require careful qualification because they are
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8 subject to a number of uncertainties which are a consequence of the study design and
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10 important limitations in the statistical model used.
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16 The differences in the adjusted and unadjusted results emphasise that the study design,
17 based on matching pairs of general practices in each country, did not eliminate baseline
18 differences between the two groups in cardiovascular risk factors. These differences meant
19 that the two groups had different levels of baseline risk, higher in intervention than usual
20 care, but the economic results have adjusted for these baseline differences. Though these
21 differences were small in absolute terms they have a substantial effect on the estimates of
22 absolute risk of future cardiovascular events, and therefore on the difference in effectiveness
23 between intervention and UC. Additionally, the study recorded its primary endpoints at
24 baseline and one-year, and to avoid 'contamination' by recording risk factor levels in UC,
25 baseline measurements were only made in a sub-sample of UC patients. Thus, we do not
26 have before and after measurements for 75% of the UC patients.
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41 Our estimates of the risk of future CVD-events are based on published risk equations.[5]
42 These are derived from a large, well characterised cohort (8491 participants) and predict
43 CVD risk as opposed to CHD risk alone. The C statistic for the model ranges from 0.76
44 (men) to 0.79 (women) suggesting that additional risk factors could potentially improve the
45 model's discriminatory power. Other risk models have included risk factors such as family
46 history of CVD, social deprivation and biomarkers e.g. hs-CRP [16-17] although these
47 models also have their own limitations.
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However, to date lifestyle factors such as dietary habits and physical inactivity although important in the aetiology of CHD [18] and independent of the other major risk factors, have not been included in such risk scores, because they are difficult to accurately quantify. The omission of these important lifestyle factors in the Framingham risk equations may be particularly relevant in our study as the cornerstone of the EUROACTION programme was lifestyle change which was clearly evident in the study's most striking achievements in this area including significantly higher fruit and vegetable consumption ($p = 0.005$); physical activity levels ($p = 0.01$); and weight loss ($p = 0.005$).

It is thus possible that our estimates of relative differences in absolute risk between the groups may understate the full effects of the intervention on long-term CVD risk. However, we showed that the risk equations are able to predict CHD events in the study population in the one-year follow-up period, but the accuracy of the risk equations over the ten-year period of our study remains untested.

Our modelling also requires an assumption about how long any differential effect of the intervention persists. Nothing is known about the longer-term effects of EUROACTION, and there are few studies that have looked at longer-term changes. The longest follow-up to a relevant life-style change appears to be the OXCHECK study which showed that the benefits of health checks were sustained over three years.[19-20] However, whatever the duration of effect beyond the trial, and even when a 25-year model was used, the policy conclusions remain the same.

Finally, our model uses a regression analysis approach so that a UK specific estimate can be drawn from the complete multinational EUROACTION dataset on net resource use, costs and net effects of the intervention. The epidemiological, utilities and cost data for the longer-term modelling of risk and events is based on UK data alone. Thus, the results are applicable to the UK and not specifically to the other EUROACTION countries. Whilst formal

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2 analysis would be needed to confirm this, the coefficients on the country parameters in the
3 regression analyses of both costs and outcomes suggest that the cost-effectiveness would
4 be broadly similar in the other countries.
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10 **Conclusion**

11 Although the EUROACTION study demonstrated in high risk patients in primary care
12 significant improvements in lifestyle and CVD risk factors, it is not possible to show, using
13 the best available risk equations, that the intervention was cost-effective. The available risk
14 modelling is based on a limited number of risk factors, which do not include diet or physical
15 activity, and a healthier lifestyle was the most important outcome of this trial. Therefore,
16 whether or not an intervention such as that offered by EUROACTION is cost-effective
17 remains an open question that could be answered by a longer term trial with major adverse
18 cardiovascular events as the primary endpoint.
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Acknowledgements

EUROACTION Steering Group

A scientific steering group approved the protocol and the design for this matched pair cluster-randomised controlled trial, and is responsible for the scientific integrity of the study.

The steering group has the following membership: D Wood (London, UK, Chairman), G De Backer (Ghent, Belgium), D De Bacquer (Ghent, Belgium), M Buxton (Uxbridge, UK), I Graham (Dublin, Ireland), A Howard (Nice, France), K Kotseva (London, UK), S Logstrup (Brussels, Belgium), H McGee (Dublin, Ireland), M Mioulet (Nice, France), K Smith (Dundee, UK), D Thompson (York, UK), T Thomsen (Glostrup, Denmark), T van der Weijden (Maastricht, the Netherlands).

National co-ordinators

The national co-ordinators for each country are also members of the steering committee.

They are responsible for identifying and recruiting general practices, obtaining ethics committee approval, appointing and supervising staff in the centres and contributing scientifically to the publication of results. The EUROACTION National Co-ordinators and Primary care leaders are as follows:

Denmark: T Thomsen, K Brockelmann; Italy: P Fioretti, A Desideri, S Brusaferrò; Poland: A Pajak, K. Kawecka-Jaszcz, P Jankowski, T Grodzicki; Spain: J De Velasco, A Maiques; Netherlands: T van der Weijden; United Kingdom: D Wood, J Morrell.

Co-ordinating and Data Management Centre

The Co-ordinating and Data Management Centre is the Department of Cardiovascular Medicine, National Heart and Lung Institute at Charing Cross Campus, Imperial College, London, UK (Head Professor David Wood). The following staff have specific responsibilities as described: K Kotseva, Senior Clinical Research Fellow; S Connolly, Research Fellow; C Jennings, Study Nurse Co-ordinator; A Mead, Chief Dietician; J Jones, Superintendent

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Physiotherapist; A Holden, Physical activity Co-ordinator; T Collier, Statistician; M Alston, D Charlesworth, P Homewood, K Pandya, M Somaia, IT specialists/Data managers; S Graves, Research Administrator; W Leacock, D Xenikaki, Administrative Assistants. The following experts advised the Co-ordinating Centre on dietary and physical activity assessment: Professor Gary Frost, Professor Barry Margetts, Dr Mike Nelson and Dr Charlie Foster.

Central Laboratory

Central Laboratory analysis of total cholesterol, HDL cholesterol, triglycerides, glucose and HbA1c are undertaken by A McLelland, R Birrell and G Beastall in the Department of Pathological Biochemistry, Royal Infirmary, Glasgow (Head of Department J Shepherd).

Statistical Centres

The statistical analyses for the primary endpoints were undertaken by D De Bacquer, Statistician, from the Department of Public Health (Head of Department G De Backer), Ghent University, Belgium, and supplementary analyses by T Collier, Statistician, Department of Medical Statistics, London School of Hygiene and Tropical Medicine, University of London, UK.

Health Economics Centre

Martin J Buxton, Professor of Health Economics and Director: Health Economics Research Group, Brunel University, UK; Hema Mistry and Matthew Dyer, Research Fellows in Health Economics, Brunel University.

Primary Care Centres

Denmark

Intervention Centre: Sundhedscenteret Skanderborg. Dr Lisbeth Rosborg, GP/ Practice Manager; Susanne Holck Mogensen, Nurse.

Usual Care Centre: Gasvej 5, 8700 Horsens. Dr Henrik Zanoni, GP; Lene Henriksen, Nurse.

Italy

Intervention Centre: Rive dai Stimatinis 12, 33013 Gemona del Friuli. Dr Beppino Colle, Primary Care Intervention Coordinator; Dr Massimiliano Rugolo, Principal Investigator/GP; Tilla Gurisatti, Nurse.

Usual Care Centre: Via S. Valentino 20, 33100 Udine. Dr Mario Casini, Italy Usual Care Coordinator. Dr Fabrizio Gangi, Italy Usual Care PI/GP. Daniela Gurisatti and Loredana Trevisani, Nurses.

Netherlands

Intervention Centre: Gezondheidscentrum Hoensbroek-Noord. Dr Martijn van Nunen and Dr Bem Bruls, GPs; Jasja Janssen, Nurse; Mrs Mathil Sanders, Practice Manager.

Usual Care Centre: Dr Mieke Winten-Huisman and Dr Marc Eyck, GPs; Rene van den Heuvel and Claudia Gessing, Nurses.

Poland

Intervention Centre: Centrum Medycyny Profilaktycznej w Krakowie. Dr Krystyna Pająk, Principal Investigator; Lidia Dwojak, Practice Manager; Joanna Śladek-Ratajewicz, GP; Barbara Waligóra and Irena Smarzyńska, Nurses.

Usual Care Centre: Podstawowa Opieka Zdrowotna - Szpital Uniwersytecki w Krakowie. Dr Maria Fornal, Principal Investigator; Dr Jolanta Walczewska, GP; Barbara Wojtanis and Helena Kamińska, Nurses.

Spain

Intervention Centre: Centro de Salud Salvador Pau, Valencia. Dr Jorge Navarro, Principal Investigator; Gemma Méndez Pérez, Nurse; Dr. Maria Jose Donat, Dr. Raquel Prieto, Dr. Rosario Gonzalez, Dr. Teresa Almela, Dr. Amaparo Garcia and Dr. Francisco Cortes, GPs.

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2 Usual Care Centre: Centro de Salud de Manises, Valencia. Dr Lorenzo Pascual, Principal
3 Investigador; Rocio Marco, Nurse; Dr Juan Manuel García, Practice Manager; Dr Antonia
4 Ibañez, Dr. Cecilia Ruiz, Dr. Santos Plaza, Dr. Amparo Moreno and Dr. Carmen Lloret, GPs.
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10 *UK*

11
12 Intervention Centre: Seaside Medical Centre, Eastbourne. Dr Tim Gietzen, Principal
13 Investigator; Sjouke Ashton, Nurse; George Bordoli, Associate Nurse; Daniel Brookbank and
14 Angela Hughes, Practice Managers.
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17
18 Usual Care Centre: Green Street Clinic, Eastbourne. Dr Ian McNaughton, Principal
19 Investigator; Shirley Colvin, Nurse; Heather King, Practice Manager.
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24
25 *Acknowledgement:* EUROACTION is an initiative of the European Society of Cardiology
26 which highlights its commitment to improve the quality of life of the European population by
27 reducing the impact of cardiovascular diseases. The study protocol conforms to the ethical
28 guidelines of the 1995 Declaration of Helsinki with ethics committee approval in all countries
29 and for every centre. Written informed consent was obtained from every subject.
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34 *Competing interest statement:* All authors declare that the answer to the questions on your
35 competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore
36 have nothing to declare.
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38
39

40 *Funding:* Sponsored solely by AstraZeneca through the provision of an unconditional
41 educational grant.
42
43
44

45 *Author contributions:* DW and MB are part of the steering committee and approved the
46 protocol and the design for this matched paired cluster-randomised trial. DW was
47 responsible for the overall direction of the project. HM and MD conducted the economic
48 analysis under the supervision of SM and MB and with guidance from DW. KK was
49 responsible for local data collection. HM drafted the manuscript with input from all authors;
50 all authors have approved the final manuscript and were involved in the interpretation of the
51 results.
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Table 1: Observed 1-year costs for EUROACTION study (in £ GBP)

2006/2007 prices	Denmark	Italy	Netherlands	Poland	Spain	UK	Total
Intervention							
N	104	165	191	234	199	126	1,019
Mean (SD)	£589 (£379)	£595 (£366)	£756 (£466)	£515 (£179)	£588 (£269)	£625 (£181)	£608 (£329)
Median	£541	£562	£704	£463	£550	£594	£560
IQR	£473 to £614	£451 to £680	£546 to £862	£374 to £616	£420 to £714	£530 to £729	£449 to £714
Range	£268 to £4,054	£179 to £3,733	£166 to £5,064	£282 to £1,578	£139 to £1,669	£163 to £1,206	£139 to £5,064
Usual Care							
N	154	194	123	160	193	181	1,005
Mean (SD)	£295 (£490)	£201 (£365)	£246 (£307)	£159 (£167)	£138 (£207)	£307 (£563)	£221 (£384)
Median	£193	£146	£125	£105	£68	£196	£142
IQR	£152 to £275	£104 to £198	£84 to £250	£84 to £159	£56 to £122	£140 to £303	£90 to £225
Range	£98 to £3,364	£70 to £4,455	£65 to £2,806	£60 to £1,255	£40 to £2,173	£73 to £6,500	£40 to £6,500

Table 2: Results from cost-effectiveness model

	Duration of effect of intervention beyond the end of the trial (model time horizon = 11* years in all cases)			
	0 years	2 years	5 years	10 years
Unadjusted costs and QALYs				
Usual care mean cost (SD)	£2,727 (£29)	£2,727 (£29)	£2,727 (£29)	£2,727 (£29)
Intervention mean cost (SD)	£3,146 (£33)	£3,126 (£31)	£3,105 (£31)	£3,089 (£31)
Usual care mean QALYs (SD)	6.755 (0.021)	6.755 (0.021)	6.755 (0.021)	6.755 (0.021)
Intervention mean QALYs (SD)	6.831 (0.021)	6.835 (0.021)	6.838 (0.021)	6.840 (0.021)
Incremental costs (95% CI)	£419 (£332 to £505)	£399 (£315 to £483)	£378 (£294 to £462)	£362 (£278 to £447)
Incremental QALYs (95% CI)	0.076 (0.017 to 0.135)	0.079 (0.020 to 0.138)	0.083 (0.024 to 0.142)	0.085 (0.026 to 0.144)
ICER	£5,539	£5,031	£4,561	£4,266
95% CI	£2,625 to £29,627	£2,412 to £22,520	£2,202 to £18,155	£2,059 to £15,945
% of bootstrapped ICERs < £20k	95.7%	97.0%	97.9%	98.4%
% of bootstrapped ICERs < £30k	97.6%	98.4%	99.0%	99.2%
Adjusted costs and QALYs†				
Incremental costs (95% CI)	£474 (£368 to £580)	£463 (£358 to £568)	£450 (£343 to £557)	£441 (£331 to £550)
Incremental QALYs (95% CI)	-0.009 (-0.041 to 0.023)	-0.007 (-0.038 to 0.025)	-0.005 (-0.036 to 0.027)	-0.003 (-0.035 to 0.029)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£21,695 to dominated†	£18,495 to dominated†	£15,908 to dominated†	£14,485 to dominated†

% of bootstrapped ICERs <£20k	1.97%	3.16%	4.57%	5.76%
% of bootstrapped ICERs <£30k	5.05%	6.98%	9.42%	11.54%

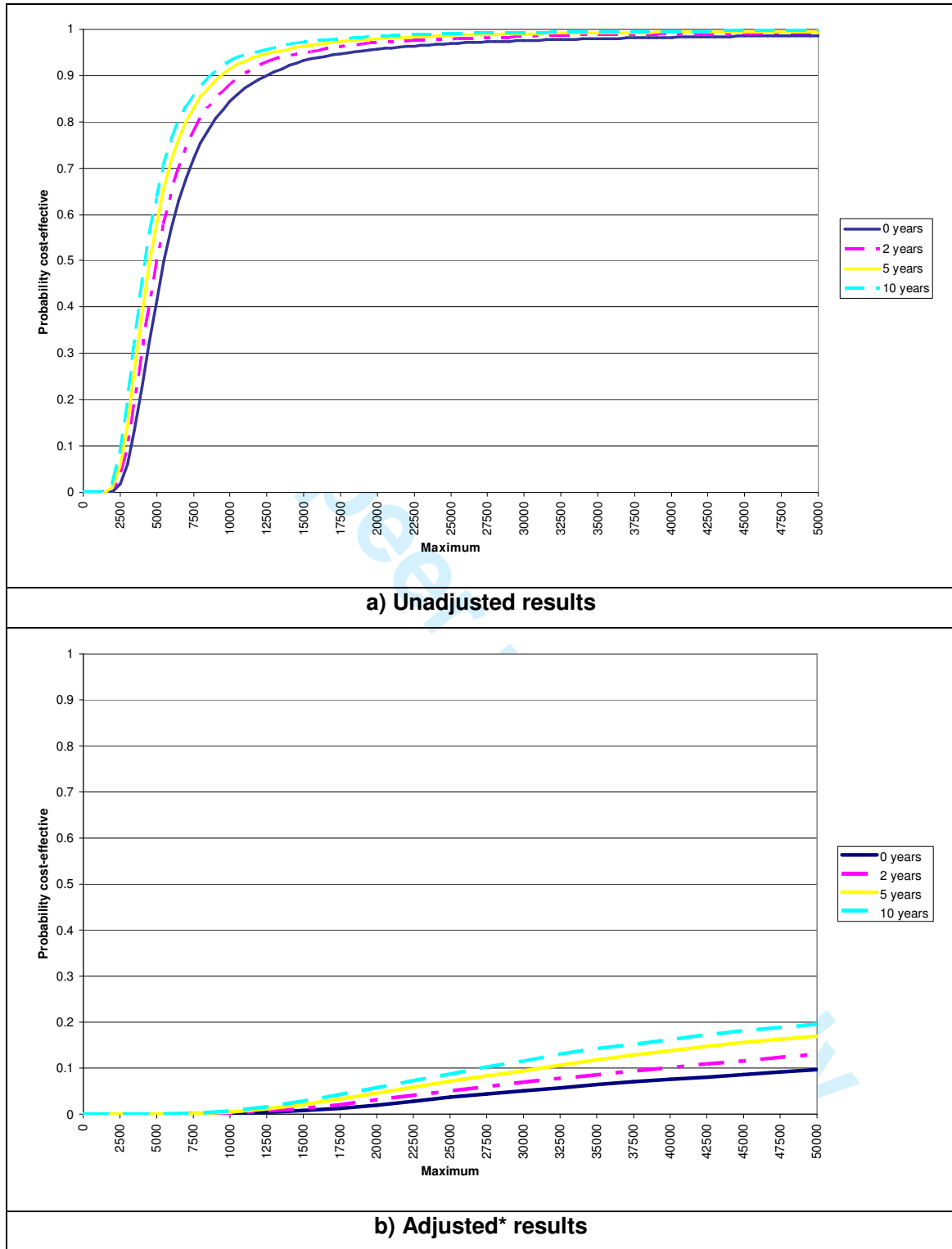
SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

‡ Adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.

Figure 1: Cost-effectiveness acceptability curves



* Adjusted for differences between groups by age, gender, country and baseline risk factors

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Appendix
Table A1: Costs of health states in cost-effectiveness model

Health State	Cost (2006 prices)	Assumption/Source	Source
Event-Free	£197	Based on a mean cost of cardiac-related medication and health care contacts (outside of EUROACTION programme) incurred by all patients during one year follow-up	Trial data
Stable Angina	£383	Based on 3 times 15 minutes' GP contact plus medication (plus cost of event-free)	Ward et al, 2007 [10]
Post-stable angina	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
Unstable angina	£674	Based on 3 times 15 minutes' GP contact plus medication plus 60% of patients are also prescribed clopidogrel (plus cost of event-free)	Ward et al, 2007 [10]
Post-unstable angina	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
MI	£5,020	Based on data from Nottingham Heart Attack Register include revascularisation for a proportion of patients, plus primary care and medication costs as unstable angina (plus cost of event-free)	Palmer et al, 2002 [21]
Post-MI	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
Fatal CHD event	£1,462	Based on costs of a fatal MI (plus cost of event-free)	Clarke et al, 2003 [22]
TIA	£1,351	Based on medication costs plus costs of test and surgery for appropriate patients (plus cost of event-free)	Ward et al, 2007 [10]
Post-TIA	£483	Based on medication costs only (plus cost of event-free)	Ward et al, 2007 [10]

Stroke	£8,922	Based on cost of acute events (mild, moderate and severe stroke) and weighted by distribution of severity of strokes (plus cost of event-free)	Youman et al, 2003 [23]
Post-Stroke	£2,543	Based on cost of acute events (mild, moderate and severe stroke) and weighted by distribution of severity of strokes (plus cost of event-free)	Youman et al, 2003 [23]
Fatal CVD event	£7,832	Based on cost of fatal stroke (plus cost of event-free)	Youman et al, 2003 [23]

Table A2: Utility values for health states used in the model

Utility value	Event free	Stable angina	Unstable angina	MI	TIA	Stroke
45 - 49	0.869	0.702	0.669	0.660	0.869	0.547
50 - 54	0.848	0.685	0.653	0.644	0.848	0.533
55 - 59	0.826	0.667	0.636	0.628	0.826	0.520
60 - 64	0.805	0.650	0.620	0.612	0.805	0.506
65 - 69	0.784	0.633	0.604	0.596	0.784	0.493
70 - 74	0.763	0.617	0.588	0.580	0.763	0.480
75 - 79	0.741	0.599	0.571	0.563	0.741	0.466
80 - 84	0.720	0.582	0.544	0.547	0.720	0.453
85 - 89	0.699	0.565	0.538	0.531	0.699	0.440
90 - 94	0.678	0.548	0.522	0.515	0.678	0.426
95 - 99	0.656	0.530	0.505	0.499	0.656	0.413
100 +	0.635	0.513	0.489	0.483	0.635	0.399

Sources: Event free (Kind et al, 1998) [13]; Stable angina (Meslop et al, 2003) [24]; Unstable angina and MI (Goodacre et al, 2004) [25]; TIA (Kind et al, 1998) [13]; Stroke (Tengs et al, 2003) [26]

Table A3: Additional results from the cost-effectiveness model

	Duration of effect of intervention beyond the end of the trial (model time horizon = 11 [#] years in all cases)			
	0 years	2 years	5 years	10 years
Adjusted costs and QALYs				
<i>Controlling for age and gender only</i>				
Incremental costs (95% CI)	£512 (£438 to £589)	£491 (£418 to £563)	£468 (£396 to £541)	£452 (£378 to £525)
Incremental QALYs (95% CI)	-0.016 (-0.036 to 0.004)	-0.012 (-0.032 to 0.008)	-0.008 (-0.028 to 0.012)	-0.006 (-0.026 to 0.014)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£105,653 to dominated†	£54,307 to dominated†	£34,845 to dominated†	£27,907 to dominated†
% of bootstrapped ICERs <£20k	0.01%	0.10%	0.34%	0.71%
% of bootstrapped ICERs <£30k	0.19%	0.52%	1.69%	3.11%
<i>Controlling for age, gender and country</i>				
Incremental costs (95% CI)	£497 (£424 to £571)	£476 (£404 to £548)	£453 (£381 to £526)	£436 (£364 to £509)
Incremental QALYs (95% CI)	-0.011 (-0.031 to 0.009)	-0.007 (-0.027 to 0.013)	-0.003 (-0.023 to 0.017)	-0.001 (-0.021 to 0.019)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£49,903 to dominated†	£33,290 to dominated†	£24,001 to dominated†	£20,342 to dominated†
% of bootstrapped ICERs <£20k	0.07%	0.34%	1.11%	2.32%
% of bootstrapped ICERs <£30k	0.61%	1.81%	4.78%	7.76%

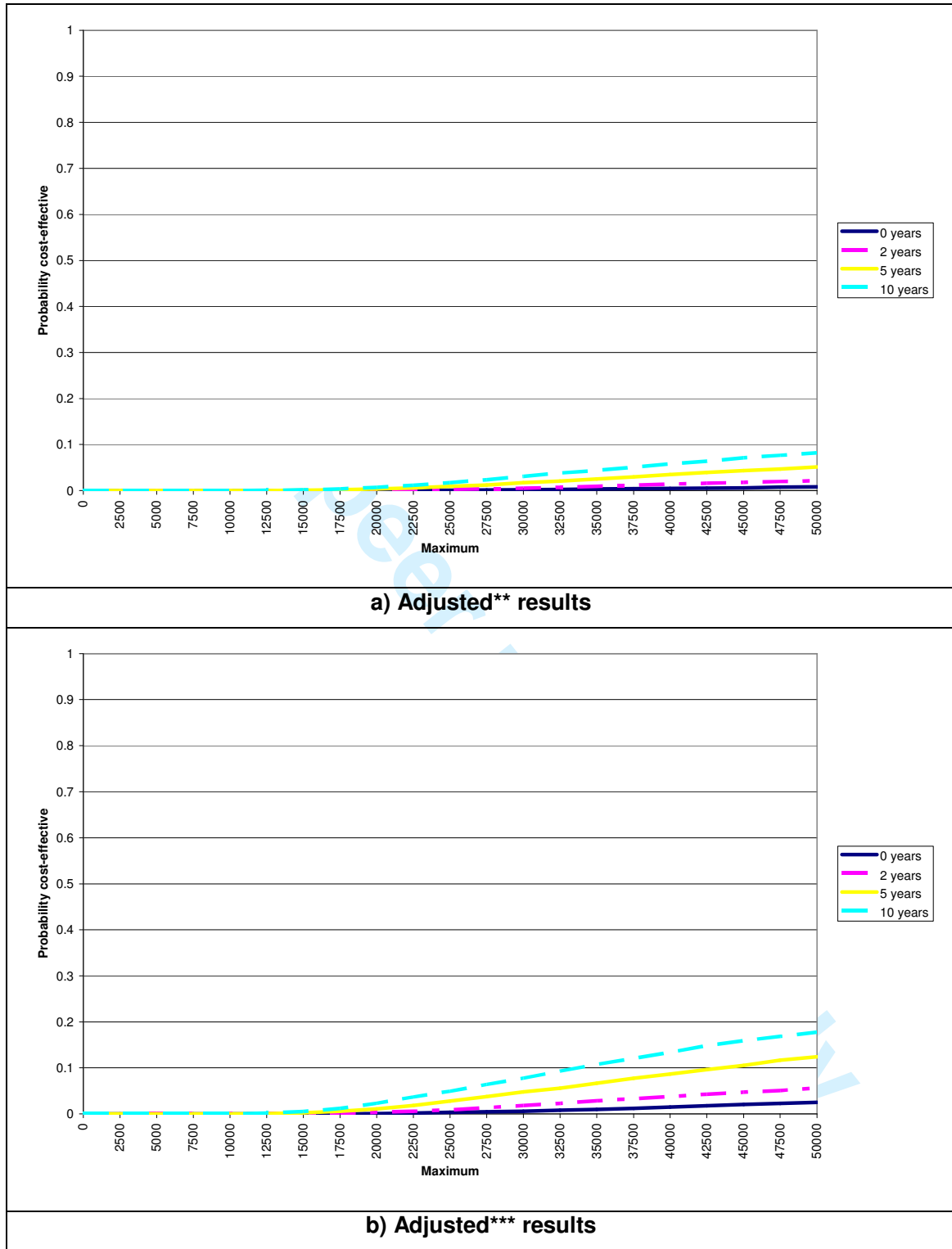
SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

[#] 1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

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Figure A1: Adjusted cost-effectiveness results



** Adjusted for differences between groups by age and gender

*** Adjusted for differences between groups by age, gender and country

Additional References for Appendix

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Cost-effectiveness of a European preventive cardiology programme in primary care

Hema Mistry, Stephen Morris, Matthew Dyer, Kornelia Kotseva, David Wood, Martin Buxton
and on behalf of the EUROACTION study group

Health economics checklist

Requirement	Manuscript page
Study design	
(1) The research question is stated	2, 4
(2) The economic importance of the research question is stated	2, 4
(3) The viewpoint(s) of the analysis are clearly stated and justified	2,5
(4) The rationale for choosing the alternative programmes or interventions compared is stated	4
(5) The alternatives being compared are clearly described	5
(6) The form of economic evaluation used is stated	4,9
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	9
Data collection	
(8) The source(s) of effectiveness estimates used are stated	9
(9) Details of the design and results of effectiveness study are given	9, 11
(10) Method of synthesis/meta-analysis of estimates are given	NA
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	2, 9
(12) Methods to value health states and other benefits are stated	9
(13) Details of the subjects from whom valuations were obtained are given	9
(14) Productivity changes (if included) are reported separately	NA
(15) The relevance of productivity changes to question is discussed	NA
(16) Quantities of resources are reported separately from their unit costs	7-9, 26-27
(17) Methods for the estimation of quantities and unit costs are described	7-9
(18) Currency and price data are recorded	8
(19) Details of currency of price adjustments for inflation or currency conversion are given	8
(20) Details of any model used are given	5-10
(21) The choice of model used and the key parameters are justified	5-10
Analysis and interpretation of results	
(22) Time horizon of costs and benefits is stated	9
(23) The discount rate(s) is stated	9
(24) The choice of rate(s) is justified	9
(25) An explanation is given if costs or benefits are not discounted	NA
(26) Details of statistical tests and confidence intervals are given for stochastic data	9-10
(27) The approach to sensitivity analysis is given	10
(28) The choice of variables for sensitivity analysis is justified	10
(29) The ranges over which the variables are varied are stated	10
(30) Relevant alternatives are compared	11-12
(31) Incremental analysis is reported	11-12
(32) Major outcomes are presented in a disaggregated as well as aggregated form	11-12, 20-21
(33) The answer to the study question is given	12, 14
(34) Conclusions follow from the data reported	12-14
(35) Conclusions are accompanied by the appropriate caveats	12-14



Cost-effectiveness of a European preventive cardiology programme in primary care: A Markov Modelling Approach

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-001029.R1
Article Type:	Research
Date Submitted by the Author:	06-Jun-2012
Complete List of Authors:	Mistry, Hema; University of Birmingham, Health Economics Unit Morris, Stephen; University College London, Department of Applied Health Research Dyer, Matthew; National Institute for Health and Clinical Excellence, Kotseva, Kornelia; Imperial College London, Department of Cardiovascular Medicine Wood, David; Imperial College London, Department of Cardiovascular Medicine Buxton, Martin; Brunel University, Health Economics Research Group
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	HEALTH ECONOMICS, CARDIOLOGY, PRIMARY CARE

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Cost-effectiveness of a European preventive cardiology programme in primary care

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1
2
3 **Abstract (word count 300)**
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6 **Objective:** To investigate the longer-term cost-effectiveness of a nurse-coordinated
7 preventive cardiology programme for primary prevention of cardiovascular disease
8 compared to routine practice from a health service perspective.
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14 **Design:** A matched, paired cluster-randomised controlled trial.
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19 **Setting:** Six pairs of general practices in six countries.
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23 **Participants:** 1,019 patients were randomised to the EUROACTION intervention
24 programme and 1,005 patients to usual care.
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29 **Outcome measures:** Evidence on health outcomes and costs were based on patient level
30 data from the study, which had a one-year follow-up period. Future risk of cardiovascular
31 (CVD) events was modelled, using published risk models based on patient characteristics.
32 An individual level Markov model for each patient was used to extrapolate beyond the end of
33 the trial, which was populated with data from published sources. We used an 11-year time
34 horizon and investigated the impact on cost-effectiveness of varying the duration of the
35 effect of the intervention beyond the end of the trial. Results are expressed as incremental
36 cost per quality-adjusted life year gained.
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47 **Results:** Unadjusted results found the intervention to be more costly and also more effective
48 than usual care. However, after adjusting for differences in age, gender, country and
49 baseline risk factors, the intervention was dominated by usual care, but this analysis was not
50 able to take into account of lifestyle changes in terms of diet and physical activity.
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3 **Conclusions:** Although the EUROACTION study achieved healthier lifestyle changes and
4 improvements in management of blood pressure and lipids for patients at high risk of CVD,
5 compared to usual care, it was not possible to show, using available risk equations which do
6 not incorporate diet and physical activity, that the intervention reduced longer-term
7 cardiovascular risk cost-effectively. Whether or not an intervention such as that offered by
8 EUROACTION is cost-effective requires a longer term trial with major cardiovascular events
9 as the outcome.
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Article summary

Article focus

- To investigate the longer-term cost-effectiveness of a nurse-coordinated preventive cardiology programme for primary prevention of cardiovascular disease compared to routine practice.

Key messages

- The EUROACTION study achieved healthier lifestyle changes and improvements in management of blood pressure and lipids for patients at high risk of CVD, compared to usual care.
- The unadjusted results of the cost effectiveness analysis found the intervention to be more effective than usual care but also more costly. However, the adjusted results showed that the intervention was dominated by usual care.
- The published cardiovascular risk equations do not take account of lifestyle changes in terms of diet and physical activity and therefore may be inadequate for the evaluation of whether or not a lifestyle intervention to prevent cardiovascular disease is cost-effective.

Strengths and limitations of the study

- This is the first study assessing the cost-effectiveness of the EUROACTION programme.
- The available cardiovascular risk modelling is based on a limited number of risk factors, which do not include measures of diet or physical activity, and a healthier lifestyle was the most important outcome of the EUROACTION trial.

Trial Registration number: ISRCTN 71715857

Keywords: Multi-centre studies; cardiovascular prevention programme; cost-effectiveness; Markov model; QALYs.

Text word Count: 3,064

Introduction

Evidence has shown that individuals with increased risk of cardiovascular disease (CVD) can reduce their risk of cardiovascular morbidity and mortality by stopping smoking, changing their diet, engaging in physical activity, achieving a healthy body weight, and controlling their blood pressure, cholesterol and diabetes.[1] However, not all patients at high risk of developing CVD manage to achieve these recommended lifestyle and risk factor goals and there remains considerable potential to reduce CVD risk in these patients.[2] The EUROACTION study was designed to address the need for preventive cardiology care in everyday clinical practice.[3]

The EUROACTION study was a matched, paired cluster-randomised controlled trial, across eight countries and 24 hospitals and general practices. The project evaluated the impact of a nurse-coordinated, multidisciplinary preventive cardiology programme for coronary patients in hospital and high risk individuals in general practice. It aimed to help all these high risk patients and their families to achieve recommended lifestyle and risk factor targets for CVD prevention in everyday clinical practice over one year. The principal results concluded that the EUROACTION programme achieved healthier lifestyle changes and improvements in risk factor management for patients with coronary heart disease (CHD) and those at high risk of CVD, together with their partners, compared to usual care.[4]

While there is evidence that the EUROACTION programme is effective in terms of modifying lifestyle and some CVD risk factors, there is no evidence as to its cost-effectiveness.

Therefore, this paper aims to model the long-term cost-effectiveness of the EUROACTION programme in comparison with usual care within the primary care setting.

Methods

Patients

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2 The EUROACTION primary care study took place in Denmark, Italy, Netherlands, Poland,
3 Spain and UK, where a matched pair of general practices was identified, and then
4 randomised to either the EUROACTION programme or to usual care (UC). GPs
5 prospectively identified the study population. The comparison was restricted to patients and
6 did not include partners. Eligibility criteria for patients has previously been published.[4]
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14 All intervention patients were assessed at baseline and one-year. These assessments
15 focussed on smoking habits, diet and physical activity, measurement of body mass index,
16 blood pressure, cholesterol and glucose levels, and cardiac medications were also recorded.
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18 The programme was delivered by specialist nurses, working with GPs, and supported by
19 software programmes (HEARTSCORE), educational materials and group workshops to
20 achieve individual goals. Each person was given a personal record card to record lifestyle
21 and risk factor goals, medications and appointments. To avoid the possibility that
22 undergoing baseline assessments might affect outcomes, only a random sub-sample
23 (~25%) of UC patients were seen at baseline and then all UC patients were invited for
24 assessment at one-year. In the UC arm, patients did not receive any form of special care.
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37 ***Model structure***

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39 We adopted a health service perspective to measure costs and outcomes. Each cycle in the
40 model is of one year's duration. All patients were CVD-free on entering the model. In each
41 subsequent cycle patients may remain CVD-event free, they may have a fatal or non-fatal
42 CVD event, or they may die from non-CVD causes. Once the patient has had an initial CVD
43 event, then in subsequent cycles they move to the post CVD-event states and they may
44 move between different CVD states and/or die from CVD or non-CVD causes.
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53 The CVD event states are: non-fatal myocardial infarction (MI), stable angina, unstable
54 angina, CHD death, transient ischaemic attack (TIA), stroke, CVD death and non-CVD
55 death.
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Measuring initial CVD risk

To estimate the risk of an initial CVD event in a subsequent year we used the D'Agostino et al [5] CVD risk function, derived from the Framingham Heart Study. This calculates individual sex-specific risks for future cardiovascular events (in patients initially free of CVD). These CVD risk equations incorporate as risk factors the natural logarithms of age, total and HDL cholesterol, systolic blood pressure (SBP) if treated with or without anti-hypertensive medications, smoking and diabetes. We used the published calibration factors to focus on the CHD and stroke event states.

Ten-year risks were estimated from the equations and adjusted to one-year values.[6] One-year CVD risk beyond the end of the trial was calculated based on both a) baseline patient characteristics (adjusted for age) for intervention patients only; and b) one-year follow-up characteristics for both groups, in order to evaluate any changes to CVD risk factors as a result of the EUROACTION programme.

Validating the appropriateness of the risk functions of the model

We tested the validity of applying the D'Agostino et al [5] risk equations to the study population, by comparing the observed number of CHD cases with the number predicted at one-year. Because stroke and TIA incidence data was not collected in the study we converted the CVD risk equations to CHD risks using the recommended calibration factors.[5] We present the results of the comparison for both groups.

Transition probabilities

We disaggregated the overall risk of a CVD event into rates for specific events by age and gender, using UK relative incidence rates based on published literature [7-9] and expert opinion, as previously used in Ward et al [10]. These event rates were applied to individual annual CVD risks to calculate individual transition probabilities for moving from the CVD-free

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2 state to the initial CVD-event states. Also, individual patients could die from non-vascular
3 causes, depending on their age and gender. The non-CVD death transition probabilities
4 were taken from Briggs et al.[11] Transition probabilities for moving from primary event
5 health states to subsequent non-fatal health states are taken from Ward et al.[10]
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10 11 12 **Measuring cost**

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14 Data on resources used during the trial and staff contacts were recorded in case record
15 forms and then converted into electronic format. To determine the total one-year costs for
16 each group, we obtained unit costs for all relevant items of resources used in the trial:
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22 *1. Costs relating to EUROACTION programme and other contacts in primary care were*
23 *obtained from the programme facilitators and included the EUROACTION nurses costs,*
24 *training costs, production of patient educational materials and any other costs*
25 *associated with implementing the programme. The average time spent by staff for all*
26 *patient contacts at baseline and one-year was provided by each centre. Hourly wage*
27 *rates of the staff salaries and training were calculated and then applied to these various*
28 *patient contacts. We costed the EUROACTION family information packs, a pocket-*
29 *sized personal record card, questionnaires and group sessions that each patient in the*
30 *intervention group received as part of their prevention programme.*
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44 Costs were applied to other contacts with health care professionals, such as GPs,
45 outside of the intervention programme for both arms and these costs were based on
46 national estimates of the staff salaries involved and estimates of the average time spent
47 with the patient provided by the trial co-ordinators.
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53 *2. Cardiac-related drug costs.* Data was collected on patient-specific cardiac-related
54 medications including the drug name and dose at baseline and one-year. This gave
55 point of time information, but no start or end dates. So for each patient it was assumed
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2 that they would remain on the same medication at a constant dose for the entire
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4 duration e.g. from baseline to one-year. National cost estimates for the drugs were
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6 provided by trial co-ordinators from each country and were applied accordingly to the
7
8 relevant dose and length of time on a patient-specific basis.
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12 *3. Cardiac-related procedures and tests.* During the trial, patients within both groups
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14 may have required inpatient or outpatient admissions for cardiac-related procedures, or
15
16 undertaken any cardiac-related tests. The procedures were costed according to HRG
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18 episodes for each country and the other tests or bed days as simple unit costs.
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20 National unit cost estimates for cardiac-related procedures and tests for each country
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22 were obtained from a database held by United BioSource Corporation (Erwin De Cock,
23
24 personal communication, May 2007) for all countries, except Denmark and Poland. For
25
26 these two countries, national unit cost estimates were provided from contacts within the
27
28 Centre for Applied Health Services Research and Technology in Denmark (Jan
29
30 Sørensen, personal communication, January 2007) and from the Ministry of Health in
31
32 Poland (Andrzej Pająk, personal communication, June 2007).
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37 As the study was based in six countries, a costing algorithm was developed to calculate a
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39 total cost per patient for each country. The costs of the programme were valued in local
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41 currencies and then converted to 2006/2007 £ (GBP) using purchasing power parities.[12]
42
43 Table 1 presents the total one-year costs by group and country.
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47 Subsequent costs relating to health states occupied within the model were based on UK
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49 estimates (see Appendix). It was assumed that patients in a CVD-free state would continue
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51 to receive the cardiac-related medications and primary care contacts (outside of the
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53 intervention programme) that they received during the trial. The mean cost of these
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55 medications and contacts for all patients across both arms was applied to each individual
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57 patient within the model who remained in the event-free health state for subsequent years.
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Health state utilities

To estimate quality-adjusted life years (QALYs) the model requires utility values for each state adjusted by age. For patients who were event-free, the utility values were based on UK general population norms [13]; utilities for events/states were taken from Ward et al [10] which were all were based on UK studies and were obtained using the EQ-5D (see Appendix).

Measuring the impact of the intervention

The study provided results only for a one-year follow-up. We estimated results for a range of possible durations of effect, assuming that the CVD risk reduction experienced by the intervention patients persisted for 0 through to 10 additional years (11-year time horizon), after which they reverted to their individual CVD risk factor levels at the start of the study (adjusted for age). For UC patients, it was assumed that patients would remain at their one-year CVD risk (adjusted annually by age) throughout the model.

Measuring cost-effectiveness

Using the Markov model we calculated for each patient their expected quality-adjusted survival (based on their likelihood of surviving each cycle and their expected health state utility value) and their expected costs. Cost-effectiveness was measured in terms of the incremental cost per QALY gained (ICER). Future costs and benefits were discounted at 3.5%. [14]

Statistical analyses

All statistical analyses were performed in Stata version 10 [15] or Microsoft Excel and a p-value ≤ 0.05 was considered to be statistically significant. We present unadjusted and adjusted cost-effectiveness results. The adjusted results controlled for group allocation, age, gender, age*gender interactions, country, and baseline risk factors using OLS regressions.

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2 As only a random sub-sample of UC patients were seen at baseline, regression analyses
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4 were used to predict baseline values for those patients who had missing values. For total
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6 and HDL cholesterol and SBP, OLS regression was used to predict values in those patients
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8 with missing values, as a function of age, gender and country. For the three binary variables
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10 (medications, smoking and diabetes), logistic regression models were used to predict the
11
12 probability of each binary outcome. Predicted values ≥ 0.5 were categorised to a value of 1
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14 and values < 0.5 were categorised as 0. In the adjusted models we also included an
15
16 indicator for whether or not each control variable was missing.
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21 Bootstrapping was undertaken on both unadjusted and adjusted costs and effects using
22
23 10,000 replications to provide 95% confidence intervals around the mean. Probabilistic
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25 sensitivity analyses were conducted to obtain cost-effectiveness acceptability curves
26
27 (CEACs).
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30 31 **Sensitivity analysis**

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33 The main analysis modelling was limited to ten years, in the absence of robust longer-term
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35 risk models. As a sensitivity analysis, we used a simplified longer-term model to check
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37 whether the conclusions of the main analysis would have been likely to be different if a
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39 longer-term perspective had been adopted e.g. 25 years. This model essentially assumed
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41 no further effect of the intervention but modelled out fully the possible QALY gains from the
42
43 medium-term (11 year) differences in mortality and event rates.
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46 47 **Results**

48
49 We modelled 1,019 patients in the intervention arm and 1,005 patients in the UC arm who
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51 were assessed at one-year.[4] The intervention group had fewer males than the UC group:
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53 49.8% vs. 57.4% male ($p=0.001$), and was significantly younger (mean age at one-year:
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55 intervention: 61.5 years vs. usual care: 62.3 years, $p=0.011$).
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When testing the validity of the Framingham risk equations to the study population we found that 8 intervention patients and 1 UC sub-sample patient experienced a CHD-event. The risk equations produced a close match, predicting 8.5 patients with a first CHD-event in the intervention group and 2.0 in the UC sub-sample.

In terms of the unadjusted results, the incremental costs of the intervention are £362-£419 depending on the duration of the effect of the intervention and the incremental QALYs are 0.076-0.085 (see Table 2). As expected, the incremental costs fall and the incremental QALYs rise as the duration of the effect of the intervention beyond the end of the trial increases. The incremental cost per QALY gained range from £5,539 (95% CI £2,625-£29,627) to £4,266 (95% CI £2,059-£15,945). The unadjusted CEACs under each scenario are in Figure 1a and highlights the results in Table 2 that in all scenarios over 95% of the bootstrapped replications are less than £20,000.

After controlling for differences in age, gender, country and baseline risk factors, the intervention is associated with higher costs and lower QALYs than the UC arm in every scenario. As a result, the intervention is dominated by UC. The adjusted CEACs are in Figure 1b (additional adjusted CEACs, controlling for age, gender and country only are in the Appendix). At a cost-effectiveness threshold of £20,000 the EUROACTION intervention will be cost-effective in under 6% of cases.

The sensitivity analysis produced predictable results that in no way changed the conclusions of the analysis. Using the unadjusted data, the cost-effectiveness of the intervention was further enhanced, and using the adjusted data the domination of UC over the intervention remained.

Discussion

1
2 Although this large European trial demonstrated that a nurse-coordinated preventive
3 cardiology programme in primary care helped more high risk patients to achieve the lifestyle
4 and risk factor targets in comparison with UC this does not appear to be cost-effective.
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6 However, these cost-effectiveness analyses require careful qualification because they are
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8 subject to a number of uncertainties which are a consequence of the study design and
9
10 important limitations in the statistical model used.
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16 The differences in the adjusted and unadjusted results emphasise that the study design,
17 based on matching pairs of general practices in each country, did not eliminate baseline
18 differences between the two groups in cardiovascular risk factors. These differences meant
19 that the two groups had different levels of baseline risk, higher in intervention than usual
20 care, but the economic results have adjusted for these baseline differences. Though these
21 differences were small in absolute terms they have a substantial effect on the estimates of
22 absolute risk of future cardiovascular events, and therefore on the difference in effectiveness
23 between intervention and UC. Additionally, the study recorded its primary endpoints at
24 baseline and one-year, and to avoid 'contamination' by recording risk factor levels in UC,
25 baseline measurements were only made in a sub-sample of UC patients. Thus, we do not
26 have before and after measurements for 75% of the UC patients.
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41 Our estimates of the risk of future CVD-events are based on published risk equations.[5]
42 These are derived from a large, well characterised cohort (8491 participants) and predict
43 CVD risk as opposed to CHD risk alone. The C statistic for the model ranges from 0.76
44 (men) to 0.79 (women) suggesting that additional risk factors could potentially improve the
45 model's discriminatory power. Other risk models have included risk factors such as family
46 history of CVD, social deprivation and biomarkers e.g. hs-CRP [16-17] although these
47 models also have their own limitations.
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However, to date lifestyle factors such as dietary habits and physical inactivity although important in the aetiology of CHD [18] and independent of the other major risk factors, have not been included in such risk scores, because they are difficult to accurately quantify. The omission of these important lifestyle factors in the Framingham risk equations may be particularly relevant in our study as the cornerstone of the EUROACTION programme was lifestyle change which was clearly evident in the study's most striking achievements in this area including significantly higher fruit and vegetable consumption ($p = 0.005$); physical activity levels ($p = 0.01$); and weight loss ($p = 0.005$).

It is thus possible that our estimates of relative differences in absolute risk between the groups may understate the full effects of the intervention on long-term CVD risk. However, we showed that the risk equations are able to predict CHD events in the study population in the one-year follow-up period, but the accuracy of the risk equations over the ten-year period of our study remains untested.

Our modelling also requires an assumption about how long any differential effect of the intervention persists. Nothing is known about the longer-term effects of EUROACTION, and there are few studies that have looked at longer-term changes. The longest follow-up to a relevant life-style change appears to be the OXCHECK study which showed that the benefits of health checks were sustained over three years.[19-20] However, whatever the duration of effect beyond the trial, and even when a 25-year model was used, the policy conclusions remain the same.

Finally, our model uses a regression analysis approach so that a UK specific estimate can be drawn from the complete multinational EUROACTION dataset on net resource use, costs and net effects of the intervention. The epidemiological, utilities and cost data for the longer-term modelling of risk and events is based on UK data alone. Thus, the results are applicable to the UK and not specifically to the other EUROACTION countries. Whilst formal

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2 analysis would be needed to confirm this, the coefficients on the country parameters in the
3
4 regression analyses of both costs and outcomes suggest that the cost-effectiveness would
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6 be broadly similar in the other countries.
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10 **Conclusion**

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12 Although the EUROACTION study demonstrated in high risk patients in primary care
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14 significant improvements in lifestyle and CVD risk factors, it is not possible to show, using
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16 the best available risk equations, that the intervention was cost-effective. The available risk
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18 modelling is based on a limited number of risk factors, which do not include diet or physical
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20 activity, and a healthier lifestyle was the most important outcome of this trial. Therefore,
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22 whether or not an intervention such as that offered by EUROACTION is cost-effective
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24 remains an open question that could be answered by a longer term trial with major adverse
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26 cardiovascular events as the primary endpoint.
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Acknowledgements

EUROACTION Steering Group

A scientific steering group approved the protocol and the design for this matched pair cluster-randomised controlled trial, and is responsible for the scientific integrity of the study.

The steering group has the following membership: D Wood (London, UK, Chairman), G De Backer (Ghent, Belgium), D De Bacquer (Ghent, Belgium), M Buxton (Uxbridge, UK), I Graham (Dublin, Ireland), A Howard (Nice, France), K Kotseva (London, UK), S Logstrup (Brussels, Belgium), H McGee (Dublin, Ireland), M Mioulet (Nice, France), K Smith (Dundee, UK), D Thompson (York, UK), T Thomsen (Glostrup, Denmark), T van der Weijden (Maastricht, the Netherlands).

National co-ordinators

The national co-ordinators for each country are also members of the steering committee.

They are responsible for identifying and recruiting general practices, obtaining ethics committee approval, appointing and supervising staff in the centres and contributing scientifically to the publication of results. The EUROACTION National Co-ordinators and Primary care leaders are as follows:

Denmark: T Thomsen, K Brockelmann; Italy: P Fioretti, A Desideri, S Brusaferrò; Poland: A Pajak, K. Kawecka-Jaszcz, P Jankowski, T Grodzicki; Spain: J De Velasco, A Maiques; Netherlands: T van der Weijden; United Kingdom: D Wood, J Morrell.

Co-ordinating and Data Management Centre

The Co-ordinating and Data Management Centre is the Department of Cardiovascular Medicine, National Heart and Lung Institute at Charing Cross Campus, Imperial College, London, UK (Head Professor David Wood). The following staff have specific responsibilities as described: K Kotseva, Senior Clinical Research Fellow; S Connolly, Research Fellow; C Jennings, Study Nurse Co-ordinator; A Mead, Chief Dietician; J Jones, Superintendent

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Physiotherapist; A Holden, Physical activity Co-ordinator; T Collier, Statistician; M Alston, D Charlesworth, P Homewood, K Pandya, M Somaia, IT specialists/Data managers; S Graves, Research Administrator; W Leacock, D Xenikaki, Administrative Assistants. The following experts advised the Co-ordinating Centre on dietary and physical activity assessment: Professor Gary Frost, Professor Barry Margetts, Dr Mike Nelson and Dr Charlie Foster.

Central Laboratory

Central Laboratory analysis of total cholesterol, HDL cholesterol, triglycerides, glucose and HbA1c are undertaken by A McLelland, R Birrell and G Beastall in the Department of Pathological Biochemistry, Royal Infirmary, Glasgow (Head of Department J Shepherd).

Statistical Centres

The statistical analyses for the primary endpoints were undertaken by D De Bacquer, Statistician, from the Department of Public Health (Head of Department G De Backer), Ghent University, Belgium, and supplementary analyses by T Collier, Statistician, Department of Medical Statistics, London School of Hygiene and Tropical Medicine, University of London, UK.

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Usual Care Centre: Dr Mieke Winten-Huisman and Dr Marc Eyck, GPs; Rene van den Heuvel and Claudia Gessing, Nurses.

Poland

Intervention Centre: Centrum Medycyny Profilaktycznej w Krakowie. Dr Krystyna Pająk, Principal Investigator; Lidia Dwojak, Practice Manager; Joanna Śladek-Ratajewicz, GP; Barbara Waligóra and Irena Smarzyńska, Nurses.

Usual Care Centre: Podstawowa Opieka Zdrowotna - Szpital Uniwersytecki w Krakowie. Dr Maria Fornal, Principal Investigator; Dr Jolanta Walczewska, GP; Barbara Wojtanis and Helena Kamińska, Nurses.

Spain

Intervention Centre: Centro de Salud Salvador Pau, Valencia. Dr Jorge Navarro, Principal Investigator; Gemma Méndez Pérez, Nurse; Dr. Maria Jose Donat, Dr. Raquel Prieto, Dr. Rosario Gonzalez, Dr. Teresa Almela, Dr. Amaparo Garcia and Dr. Francisco Cortes, GPs.

1
2 Usual Care Centre: Centro de Salud de Manises, Valencia. Dr Lorenzo Pascual, Principal
3 Investigador; Rocio Marco, Nurse; Dr Juan Manuel García, Practice Manager; Dr Antonia
4 Ibañez, Dr. Cecilia Ruiz, Dr. Santos Plaza, Dr. Amparo Moreno and Dr. Carmen Lloret, GPs.
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10 *UK*

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12 Intervention Centre: Seaside Medical Centre, Eastbourne. Dr Tim Gietzen, Principal
13 Investigator; Sjouke Ashton, Nurse; George Bordoli, Associate Nurse; Daniel Brookbank and
14 Angela Hughes, Practice Managers.
15
16

17
18 Usual Care Centre: Green Street Clinic, Eastbourne. Dr Ian McNaughton, Principal
19 Investigator; Shirley Colvin, Nurse; Heather King, Practice Manager.
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24
25 *Acknowledgement:* EUROACTION is an initiative of the European Society of Cardiology
26 which highlights its commitment to improve the quality of life of the European population by
27 reducing the impact of cardiovascular diseases. The study protocol conforms to the ethical
28 guidelines of the 1995 Declaration of Helsinki with ethics committee approval in all countries
29 and for every centre. Written informed consent was obtained from every subject.
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34 *Competing interest statement:* All authors declare that the answer to the questions on your
35 competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore
36 have nothing to declare.
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40 *Funding:* Sponsored solely by AstraZeneca through the provision of an unconditional
41 educational grant.
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45 *Author contributions:* DW and MB are part of the steering committee and approved the
46 protocol and the design for this matched paired cluster-randomised trial. DW was
47 responsible for the overall direction of the project. HM and MD conducted the economic
48 analysis under the supervision of SM and MB and with guidance from DW. KK was
49 responsible for local data collection. HM drafted the manuscript with input from all authors;
50 all authors have approved the final manuscript and were involved in the interpretation of the
51 results.
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Table 1: Observed 1-year costs for EUROACTION study (in £ GBP)

2006/2007 prices	Denmark	Italy	Netherlands	Poland	Spain	UK	Total
Intervention							
N	104	165	191	234	199	126	1,019
Mean (SD)	£589 (£379)	£595 (£366)	£756 (£466)	£515 (£179)	£588 (£269)	£625 (£181)	£608 (£329)
Median	£541	£562	£704	£463	£550	£594	£560
IQR	£473 to £614	£451 to £680	£546 to £862	£374 to £616	£420 to £714	£530 to £729	£449 to £714
Range	£268 to £4,054	£179 to £3,733	£166 to £5,064	£282 to £1,578	£139 to £1,669	£163 to £1,206	£139 to £5,064
Usual Care							
N	154	194	123	160	193	181	1,005
Mean (SD)	£295 (£490)	£201 (£365)	£246 (£307)	£159 (£167)	£138 (£207)	£307 (£563)	£221 (£384)
Median	£193	£146	£125	£105	£68	£196	£142
IQR	£152 to £275	£104 to £198	£84 to £250	£84 to £159	£56 to £122	£140 to £303	£90 to £225
Range	£98 to £3,364	£70 to £4,455	£65 to £2,806	£60 to £1,255	£40 to £2,173	£73 to £6,500	£40 to £6,500

Table 2: Results from cost-effectiveness model

	Duration of effect of intervention beyond the end of the trial (model time horizon = 11* years in all cases)			
	0 years	2 years	5 years	10 years
Unadjusted costs and QALYs				
Usual care mean cost (SD)	£2,727 (£29)	£2,727 (£29)	£2,727 (£29)	£2,727 (£29)
Intervention mean cost (SD)	£3,146 (£33)	£3,126 (£31)	£3,105 (£31)	£3,089 (£31)
Usual care mean QALYs (SD)	6.755 (0.021)	6.755 (0.021)	6.755 (0.021)	6.755 (0.021)
Intervention mean QALYs (SD)	6.831 (0.021)	6.835 (0.021)	6.838 (0.021)	6.840 (0.021)
Incremental costs (95% CI)	£419 (£332 to £505)	£399 (£315 to £483)	£378 (£294 to £462)	£362 (£278 to £447)
Incremental QALYs (95% CI)	0.076 (0.017 to 0.135)	0.079 (0.020 to 0.138)	0.083 (0.024 to 0.142)	0.085 (0.026 to 0.144)
ICER	£5,539	£5,031	£4,561	£4,266
95% CI	£2,625 to £29,627	£2,412 to £22,520	£2,202 to £18,155	£2,059 to £15,945
% of bootstrapped ICERs < £20k	95.7%	97.0%	97.9%	98.4%
% of bootstrapped ICERs < £30k	97.6%	98.4%	99.0%	99.2%
Adjusted costs and QALYs†				
Incremental costs (95% CI)	£474 (£368 to £580)	£463 (£358 to £568)	£450 (£343 to £557)	£441 (£331 to £550)
Incremental QALYs (95% CI)	-0.009 (-0.041 to 0.023)	-0.007 (-0.038 to 0.025)	-0.005 (-0.036 to 0.027)	-0.003 (-0.035 to 0.029)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£21,695 to dominated†	£18,495 to dominated†	£15,908 to dominated†	£14,485 to dominated†

% of bootstrapped ICERs <£20k	1.97%	3.16%	4.57%	5.76%
% of bootstrapped ICERs <£30k	5.05%	6.98%	9.42%	11.54%

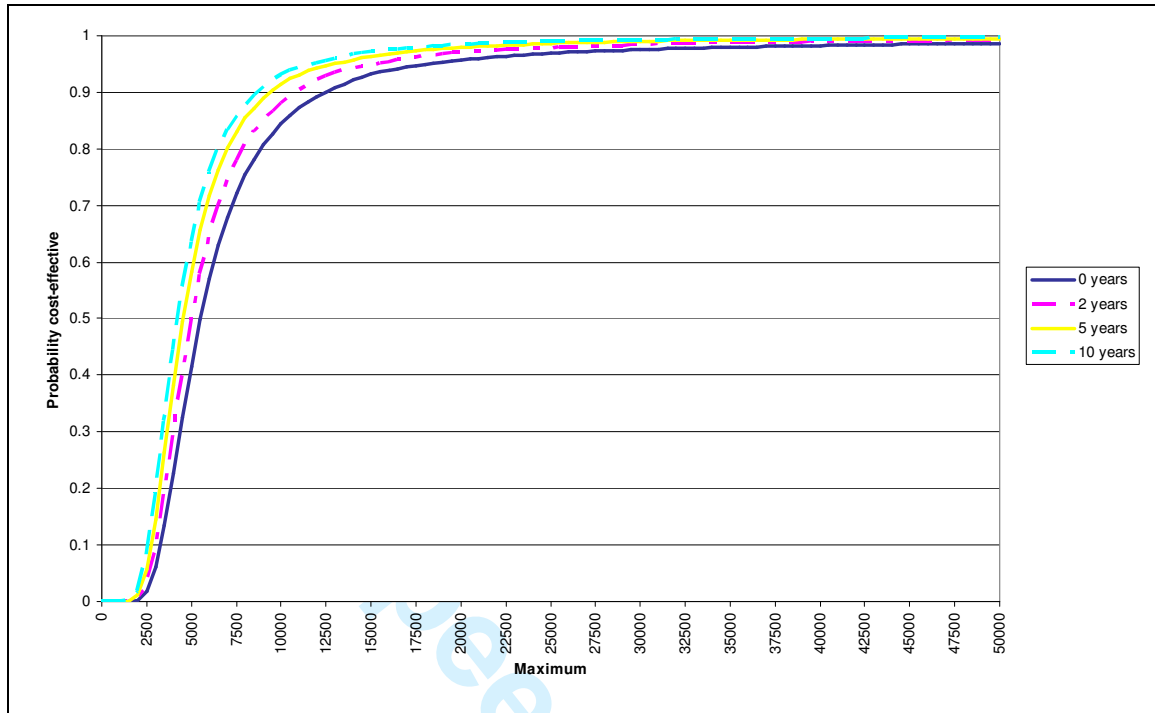
SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

1 year study follow-up period plus a 10 year model

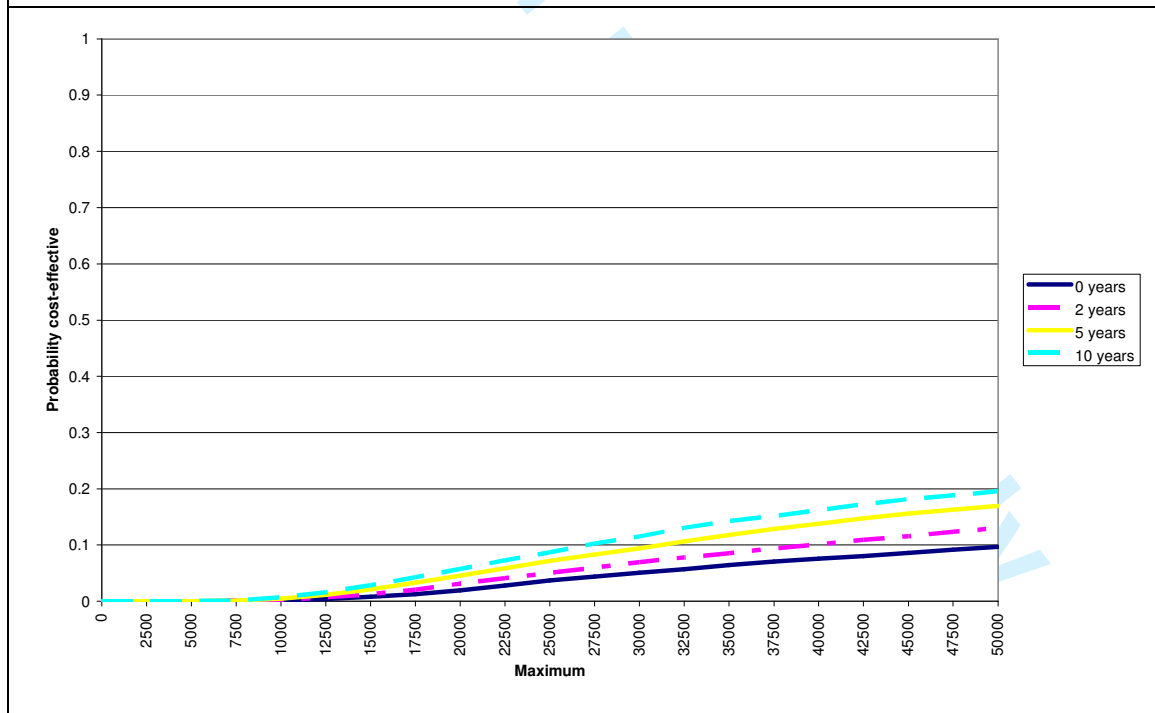
† The intervention is more costly and yield fewer QALYs than usual care

‡ Adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.

Figure 1: Cost-effectiveness acceptability curves



a) Unadjusted results



b) Adjusted* results

* Adjusted for differences between groups by age, gender, country and baseline risk factors

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Appendix
Table A1: Costs of health states in cost-effectiveness model

Health State	Cost (2006 prices)	Assumption/Source	Source
Event-Free	£197	Based on a mean cost of cardiac-related medication and health care contacts (outside of EUROACTION programme) incurred by all patients during one year follow-up	Trial data
Stable Angina	£383	Based on 3 times 15 minutes' GP contact plus medication (plus cost of event-free)	Ward et al, 2007 [10]
Post-stable angina	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
Unstable angina	£674	Based on 3 times 15 minutes' GP contact plus medication plus 60% of patients are also prescribed clopidogrel (plus cost of event-free)	Ward et al, 2007 [10]
Post-unstable angina	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
MI	£5,020	Based on data from Nottingham Heart Attack Register include revascularisation for a proportion of patients, plus primary care and medication costs as unstable angina (plus cost of event-free)	Palmer et al, 2002 [21]
Post-MI	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
Fatal CHD event	£1,462	Based on costs of a fatal MI (plus cost of event-free)	Clarke et al, 2003 [22]
TIA	£1,351	Based on medication costs plus costs of test and surgery for appropriate patients (plus cost of event-free)	Ward et al, 2007 [10]
Post-TIA	£483	Based on medication costs only (plus cost of event-free)	Ward et al, 2007 [10]

Stroke	£8,922	Based on cost of acute events (mild, moderate and severe stroke) and weighted by distribution of severity of strokes (plus cost of event-free)	Youman et al, 2003 [23]
Post-Stroke	£2,543	Based on cost of acute events (mild, moderate and severe stroke) and weighted by distribution of severity of strokes (plus cost of event-free)	Youman et al, 2003 [23]
Fatal CVD event	£7,832	Based on cost of fatal stroke (plus cost of event-free)	Youman et al, 2003 [23]

Table A2: Utility values for health states used in the model

Utility value	Event free	Stable angina	Unstable angina	MI	TIA	Stroke
45 - 49	0.869	0.702	0.669	0.660	0.869	0.547
50 - 54	0.848	0.685	0.653	0.644	0.848	0.533
55 - 59	0.826	0.667	0.636	0.628	0.826	0.520
60 - 64	0.805	0.650	0.620	0.612	0.805	0.506
65 - 69	0.784	0.633	0.604	0.596	0.784	0.493
70 - 74	0.763	0.617	0.588	0.580	0.763	0.480
75 - 79	0.741	0.599	0.571	0.563	0.741	0.466
80 - 84	0.720	0.582	0.544	0.547	0.720	0.453
85 - 89	0.699	0.565	0.538	0.531	0.699	0.440
90 - 94	0.678	0.548	0.522	0.515	0.678	0.426
95 - 99	0.656	0.530	0.505	0.499	0.656	0.413
100 +	0.635	0.513	0.489	0.483	0.635	0.399

Sources: Event free (Kind et al, 1998) [13]; Stable angina (Meslop et al, 2003) [24]; Unstable angina and MI (Goodacre et al, 2004) [25]; TIA (Kind et al, 1998) [13]; Stroke (Tengs et al, 2003) [26]

Table A3: Additional results from the cost-effectiveness model

	Duration of effect of intervention beyond the end of the trial (model time horizon = 11 [#] years in all cases)			
	0 years	2 years	5 years	10 years
Adjusted costs and QALYs				
<i>Controlling for age and gender only</i>				
Incremental costs (95% CI)	£512 (£438 to £589)	£491 (£418 to £563)	£468 (£396 to £541)	£452 (£378 to £525)
Incremental QALYs (95% CI)	-0.016 (-0.036 to 0.004)	-0.012 (-0.032 to 0.008)	-0.008 (-0.028 to 0.012)	-0.006 (-0.026 to 0.014)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£105,653 to dominated†	£54,307 to dominated†	£34,845 to dominated†	£27,907 to dominated†
% of bootstrapped ICERs <£20k	0.01%	0.10%	0.34%	0.71%
% of bootstrapped ICERs <£30k	0.19%	0.52%	1.69%	3.11%
<i>Controlling for age, gender and country</i>				
Incremental costs (95% CI)	£497 (£424 to £571)	£476 (£404 to £548)	£453 (£381 to £526)	£436 (£364 to £509)
Incremental QALYs (95% CI)	-0.011 (-0.031 to 0.009)	-0.007 (-0.027 to 0.013)	-0.003 (-0.023 to 0.017)	-0.001 (-0.021 to 0.019)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£49,903 to dominated†	£33,290 to dominated†	£24,001 to dominated†	£20,342 to dominated†
% of bootstrapped ICERs <£20k	0.07%	0.34%	1.11%	2.32%
% of bootstrapped ICERs <£30k	0.61%	1.81%	4.78%	7.76%

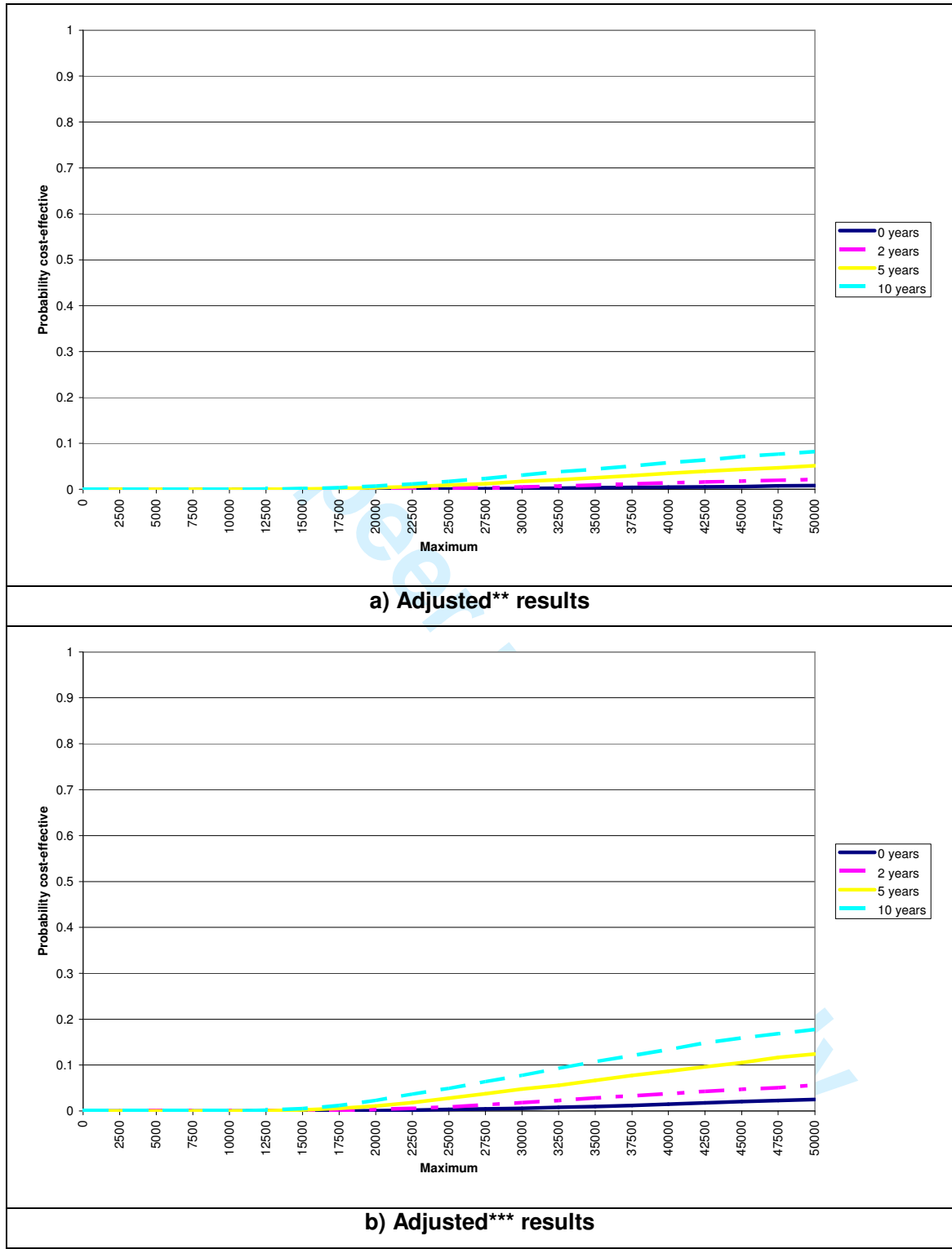
SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

[#] 1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

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Figure A1: Adjusted cost-effectiveness results



** Adjusted for differences between groups by age and gender

*** Adjusted for differences between groups by age, gender and country

Additional References for Appendix

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Cost-effectiveness of a European preventive cardiology programme in primary care

Hema Mistry, Stephen Morris, Matthew Dyer, Kornelia Kotseva, David Wood, Martin Buxton
and on behalf of the EUROACTION study group

Health economics checklist

Requirement	Manuscript page
Study design	
(1) The research question is stated	2, 4
(2) The economic importance of the research question is stated	2, 4
(3) The viewpoint(s) of the analysis are clearly stated and justified	2,5
(4) The rationale for choosing the alternative programmes or interventions compared is stated	4
(5) The alternatives being compared are clearly described	5
(6) The form of economic evaluation used is stated	4,9
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	9
Data collection	
(8) The source(s) of effectiveness estimates used are stated	9
(9) Details of the design and results of effectiveness study are given	9, 11
(10) Method of synthesis/meta-analysis of estimates are given	NA
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	2, 9
(12) Methods to value health states and other benefits are stated	9
(13) Details of the subjects from whom valuations were obtained are given	9
(14) Productivity changes (if included) are reported separately	NA
(15) The relevance of productivity changes to question is discussed	NA
(16) Quantities of resources are reported separately from their unit costs	7-9, 26-27
(17) Methods for the estimation of quantities and unit costs are described	7-9
(18) Currency and price data are recorded	8
(19) Details of currency of price adjustments for inflation or currency conversion are given	8
(20) Details of any model used are given	5-10
(21) The choice of model used and the key parameters are justified	5-10
Analysis and interpretation of results	
(22) Time horizon of costs and benefits is stated	9
(23) The discount rate(s) is stated	9
(24) The choice of rate(s) is justified	9
(25) An explanation is given if costs or benefits are not discounted	NA
(26) Details of statistical tests and confidence intervals are given for stochastic data	9-10
(27) The approach to sensitivity analysis is given	10
(28) The choice of variables for sensitivity analysis is justified	10
(29) The ranges over which the variables are varied are stated	10
(30) Relevant alternatives are compared	11-12
(31) Incremental analysis is reported	11-12
(32) Major outcomes are presented in a disaggregated as well as aggregated form	11-12, 20-21
(33) The answer to the study question is given	12, 14
(34) Conclusions follow from the data reported	12-14
(35) Conclusions are accompanied by the appropriate caveats	12-14

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Cost-effectiveness of a European preventive cardiology programme in primary care: a Markov modelling approach

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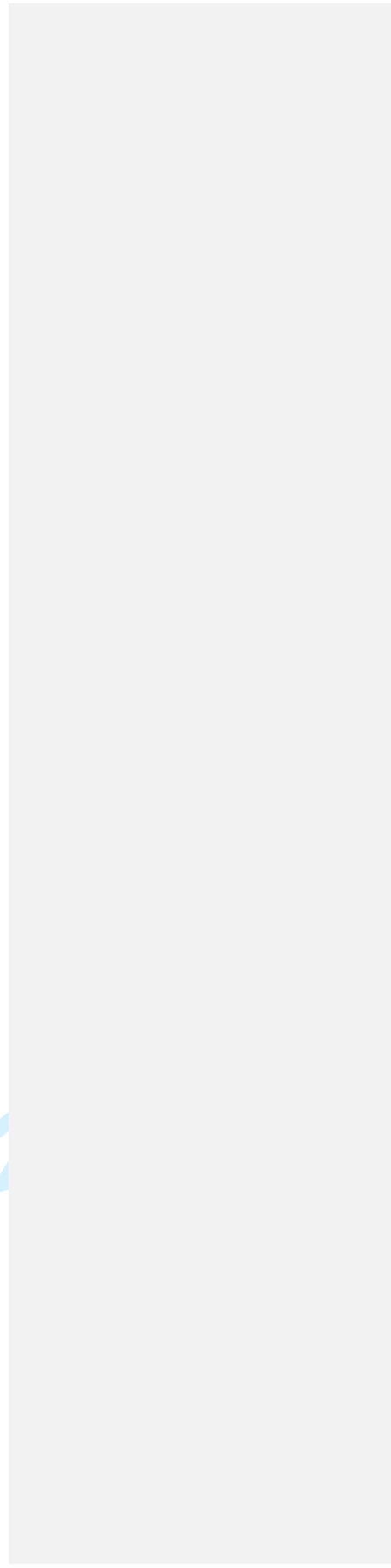
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For peer review only



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6 **Abstract (word count 3096)**
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10 **Objective:** To investigate the longer-term cost-effectiveness of a nurse-coordinated
11 preventive cardiology programme for primary prevention of cardiovascular disease
12 compared to routine practice from a health service perspective.
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17 **Design:** A matched, paired cluster-randomised controlled trial.
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20 **Setting:** Six pairs of general practices in six countries.
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24 **Participants:** 1,019 patients were randomised to the EUROACTION intervention
25 programme and 1,005 patients to usual care and who completed the one-year follow-up-
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29 **Outcome measures:** Evidence on health outcomes and costs were based on patient level
30 data from the study, which had a one-year follow-up period. Future risk of cardiovascular
31 (CVD) events was modelled, using published risk models based on patient characteristics.
32 An individual level Markov model for each patient was used to extrapolate beyond the end of
33 the trial, which was populated with data from published sources. We used an 11-year time
34 horizon and investigated the impact on cost-effectiveness of varying the duration of the
35 effect of the intervention beyond the end of the trial. Results are expressed as incremental
36 cost per quality-adjusted life year gained.
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45 **Results:** Unadjusted results found the intervention to be more costly and also more effective
46 than usual care. However, after adjusting for differences in age, gender, country and
47 baseline risk factors, the intervention was dominated by usual care, but this analysis was not
48 able to take into account of lifestyle changes in terms of diet and physical activity.
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6 **Conclusions:** Although the EUROACTION study achieved healthier lifestyle changes and
7 improvements in management of blood pressure and lipids for patients at high risk of CVD,
8 compared to usual care, it was not possible to show, using available risk equations which do
9 not incorporate diet and physical activity, that the intervention reduced longer-term
10 cardiovascular risk cost-effectively. Whether or not an intervention such as that offered by
11 EUROACTION is cost-effective requires a longer term trial with major cardiovascular events
12 as the outcome.
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Article summary

Article focus

- To investigate the longer-term cost-effectiveness of a nurse-coordinated preventive cardiology programme for primary prevention of cardiovascular disease compared to routine practice.

Key messages

- The EUROACTION study achieved healthier lifestyle changes and improvements in management of blood pressure and lipids for patients at high risk of CVD, compared to usual care.
- The unadjusted results of the cost-effectiveness analysis found the intervention to be more effective than usual care but also more costly. However, the adjusted results showed that the intervention was dominated by usual care.
- The published cardiovascular risk equations do not take account of lifestyle changes in terms of diet and physical activity and therefore may be inadequate for the evaluation of whether or not a lifestyle intervention to prevent cardiovascular disease is cost-effective.

Strengths and limitations of the study

- This is the first study assessing the cost-effectiveness of the EUROACTION programme.
- The available cardiovascular risk modelling is based on a limited number of risk factors, which do not include measures of diet or physical activity, and a healthier lifestyle was the most important outcome of the EUROACTION trial.

Trial Registration number: ISRCTN 71715857

Keywords: Multi-centre studies; cardiovascular prevention programme; cost-effectiveness; Markov model; QALYs.

Text word Count: 3,415064

Introduction

Evidence has shown that individuals with increased risk of cardiovascular disease (CVD) can reduce their risk of cardiovascular morbidity and mortality by stopping smoking, changing their diet, engaging in physical activity, achieving a healthy body weight, and controlling their blood pressure, cholesterol and diabetes.[1] However, not all patients at high risk of developing CVD manage to achieve these recommended lifestyle and risk factor goals and there remains considerable potential to reduce CVD risk in these patients.[2] The EUROACTION study was designed to address the need for preventive cardiology care in everyday clinical practice.[3]

The EUROACTION study was a matched, paired cluster-randomised controlled trial, across eight countries and 24 hospitals and general practices. The project evaluated the impact of a nurse-coordinated, multidisciplinary preventive cardiology programme for coronary patients in hospital and high risk individuals in general practice. It aimed to help all these high risk patients and their families to achieve recommended lifestyle and risk factor targets for CVD prevention in everyday clinical practice over one year. The principal results concluded that the EUROACTION programme achieved healthier lifestyle changes and improvements in risk factor management for patients with coronary heart disease (CHD) and those at high risk of CVD, together with their partners, compared to usual care.[4]

While there is evidence that the EUROACTION programme is effective in terms of modifying lifestyle and some CVD risk factors, there is no evidence as to its cost-effectiveness.

Therefore, this paper aims to model the long-term cost-effectiveness of the EUROACTION programme in comparison with usual care within the primary care setting.

Methods

Patients

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6 The EUROACTION primary care study took place in Denmark, Italy, Netherlands, Poland,
7 Spain and UK, where a matched pair of general practices was identified, and then
8 randomised to either the EUROACTION programme or to usual care (UC). GPs
9 prospectively identified the study population. The comparison was restricted to patients and
10 did not include partners. Eligibility criteria for patients has previously been published.[4]
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16 All intervention patients were assessed at baseline and one-year. These assessments
17 focussed on smoking habits, diet and physical activity, measurement of body mass index,
18 blood pressure, cholesterol and glucose levels, and cardiac medications were also recorded.
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20 The programme was delivered by specialist nurses, working with GPs, and supported by
21 software programmes (HEARTSCORE), educational materials and group workshops to
22 achieve individual goals. Each person was given a personal record card to record lifestyle
23 and risk factor goals, medications and appointments. To avoid the possibility that
24 undergoing baseline assessments might affect outcomes, only a random sub-sample
25 (~25%) of UC patients were seen at baseline and then all UC patients were invited for
26 assessment at one-year. In the UC arm, patients did not receive any form of special care.
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36 **Model structure**

37 We adopted a health service perspective to measure costs and outcomes. Each cycle in the
38 model is of one year's duration. All patients were CVD-free on entering the model. In each
39 subsequent cycle patients may remain CVD-event free, they may have a fatal or non-fatal
40 CVD event, or they may die from non-CVD causes. Once the patient has had an initial CVD
41 event, then in subsequent cycles they move to the post CVD-event states and they may
42 move between different CVD states and/or die from CVD or non-CVD causes.
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50 The CVD event states are: non-fatal myocardial infarction (MI), stable angina, unstable
51 angina, CHD death, transient ischaemic attack (TIA), stroke, CVD death and non-CVD
52 death.
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Measuring initial CVD risk

To estimate the risk of an initial CVD event in a subsequent year we used the D'Agostino et al [5] CVD risk function, derived from the Framingham Heart Study. This calculates individual sex-specific risks for future cardiovascular events (in patients initially free of CVD). These CVD risk equations incorporate as risk factors the natural logarithms of age, total and HDL cholesterol, systolic blood pressure (SBP) if treated with or without anti-hypertensive medications, smoking and diabetes. We used the published calibration factors to focus on the CHD and stroke event states.

Ten-year risks were estimated from the equations and adjusted to one-year values.[6] One-year CVD risk beyond the end of the trial was calculated based on both a) baseline patient characteristics (adjusted for age) for intervention patients only; and b) one-year follow-up characteristics for both groups, in order to evaluate any changes to CVD risk factors as a result of the EUROACTION programme.

Validating the appropriateness of the risk functions of the model

We tested the validity of applying the D'Agostino et al [5] risk equations to the study population, by comparing the observed number of CHD cases with the number predicted at one-year. Because stroke and TIA incidence data was not collected in the study we converted the CVD risk equations to CHD risks using the recommended calibration factors.[5] We present the results of the comparison for both groups.

Transition probabilities

We disaggregated the overall risk of a CVD event into rates for specific events by age and gender, using UK relative incidence rates based on published literature [7-9] and expert opinion, as previously used in Ward et al [10]. These event rates were applied to individual annual CVD risks to calculate individual transition probabilities for moving from the CVD-free

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6 state to the initial CVD-event states. Also, individual patients could die from non-vascular
7 causes, depending on their age and gender. The non-CVD death transition probabilities
8 were taken from Briggs et al.[11] Transition probabilities for moving from primary event
9 health states to subsequent non-fatal health states are taken from Ward et al.[10]
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13 14 **Measuring cost**

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16 Data on resources used during the trial and staff contacts were recorded in case record
17 forms and then converted into electronic format. To determine the total one-year costs for
18 each group, we obtained unit costs for all relevant items of resources used in the trial:
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24 *1. Costs relating to EUROACTION programme and other contacts in primary care were*
25 obtained from the programme facilitators and included the EUROACTION nurses costs,
26 training costs, production of patient educational materials and any other costs
27 associated with implementing the programme. The average time spent by staff for all
28 patient contacts at baseline and one-year was provided by each centre. Hourly wage
29 rates of the staff salaries and training were calculated and then applied to these various
30 patient contacts. We costed the EUROACTION family information packs, a pocket-
31 sized personal record card, questionnaires and group sessions that each patient in the
32 intervention group received as part of their prevention programme.
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41 Costs were applied to other contacts with health care professionals, such as GPs,
42 outside of the intervention programme for both arms and these costs were based on
43 national estimates of the staff salaries involved and estimates of the average time spent
44 with the patient provided by the trial co-ordinators.
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50 *2. Cardiac-related drug costs.* Data was collected on patient-specific cardiac-related
51 medications including the drug name and dose at baseline and one-year. This gave
52 point of time information, but no start or end dates. So for each patient it was assumed
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6 that they would remain on the same medication at a constant dose for the entire
7 duration e.g. from baseline to one-year. National cost estimates for the drugs were
8 provided by trial co-ordinators from each country and were applied accordingly to the
9 relevant dose and length of time on a patient-specific basis.
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15 *3. Cardiac-related procedures and tests.* During the trial, patients within both groups
16 may have required inpatient or outpatient admissions for cardiac-related procedures, or
17 undertaken any cardiac-related tests. The procedures were costed according to HRG
18 episodes for each country and the other tests or bed days as simple unit costs.
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20 National unit cost estimates for cardiac-related procedures and tests for each country
21 were obtained from a database held by United BioSource Corporation (Erwin De Cock,
22 personal communication, May 2007) for all countries, except Denmark and Poland. For
23 these two countries, national unit cost estimates were provided from contacts within the
24 Centre for Applied Health Services Research and Technology in Denmark (Jan
25 Sørensen, personal communication, January 2007) and from the Ministry of Health in
26 Poland (Andrzej Pająk, personal communication, June 2007).
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36 As the study was based in six countries, a costing algorithm was developed to calculate a
37 total cost per patient for each country. The costs of the programme were valued in local
38 currencies and then converted to 2006/2007 £ (GBP) using purchasing power parities.[12]
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41 Table 1 presents the total one-year costs by group and country. Figure 1a shows that the 1-
42 year observed costs (split by type of cost) for the intervention group was significantly more
43 than the usual care group for all countries. This higher cost was explained by the
44 EUROACTION intervention programme costs and contacts with EUROACTION staff, whilst
45 neither arms experienced significantly high cost cardiac interventions or cardiac medications.
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52 Subsequent costs relating to health states occupied within the model were based on UK
53 estimates (see Appendix). It was assumed that patients in a CVD-free state would continue
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6 to receive the cardiac-related medications and primary care contacts (outside of the
7 intervention programme) that they received during the trial. The mean cost of these
8 medications and contacts for all patients across both arms was applied to each individual
9 patient within the model who remained in the event-free health state for subsequent years.
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13 14 15 **Health state utilities**

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17 To estimate quality-adjusted life years (QALYs) the model requires utility values for each
18 state adjusted by age. For patients who were event-free, the utility values were based on
19 UK general population norms [13]; utilities for events/states were taken from Ward et al [10]
20 which were all were based on UK studies and were obtained using the EQ-5D (see
21 Appendix).
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25 26 27 **Measuring the impact of the intervention**

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29 The study provided results only for a one-year follow-up. We estimated results for a range of
30 possible durations of effect, assuming that the CVD risk reduction experienced by the
31 intervention patients persisted for 0 through to 10 additional years (11-year time horizon),
32 after which they reverted to their individual CVD risk factor levels at the start of the study
33 (adjusted for age). For UC patients, it was assumed that patients would remain at their one-
34 year CVD risk (adjusted annually by age) throughout the model.
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41 42 **Measuring cost-effectiveness**

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44 Using the Markov model we calculated for each patient their expected quality-adjusted
45 survival (based on their likelihood of surviving each cycle and their expected health state
46 utility value) and their expected costs. Cost-effectiveness was measured in terms of the
47 incremental cost per QALY gained (ICER). Future costs and benefits were discounted at
48 3.5%. [14]
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53 54 **Statistical analyses**

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6 All statistical analyses were performed in Stata version 10 [15] or Microsoft Excel and a p-
7 value ≤ 0.05 was considered to be statistically significant. We present unadjusted and
8 adjusted cost-effectiveness results. The adjusted results controlled for group allocation, age,
9 gender, age*gender interactions, country, and baseline risk factors using OLS regressions.
10 As only a random sub-sample of UC patients were seen at baseline, regression analyses
11 were used to predict baseline values for those patients who had missing values. For total
12 and HDL cholesterol and SBP, OLS regression was used to predict values in those patients
13 with missing values, as a function of age, gender and country. For the three binary variables
14 (medications, smoking and diabetes), logistic regression models were used to predict the
15 probability of each binary outcome. Predicted values ≥ 0.5 were categorised to a value of 1
16 and values < 0.5 were categorised as 0. In the adjusted models we also included an
17 indicator for whether or not each control variable was missing.
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29 ~~Bootstrapping was undertaken on both unadjusted and adjusted costs and effects using~~
30 ~~10,000 replications to provide 95% confidence intervals around the mean. Probabilistic~~
31 ~~sensitivity analyses were conducted to obtain cost-effectiveness acceptability curves~~
32 ~~(CEACs).~~
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36 We represented uncertainty due to sampling variation in both the unadjusted and adjusted
37 cost-effectiveness ratios using non-parametric bootstrapping. In the unadjusted analyses we
38 sampled individuals in our model with replacement and used their costs and outcomes over
39 the 11-year period to compute replications of the incremental cost per QALY gained. We
40 repeated this approach in the adjusted analyses, also adding the regressions to control for
41 confounding factors. In each case, we generated 10,000 bootstrap replications of the cost-
42 effectiveness ratios and used these to construct 95% confidence intervals around the point
43 estimate of cost-effectiveness.
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50 51 52 **Sensitivity analysis** 53 54 55 56 57 58 59 60

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6 The main analysis modelling was limited to ten years, in the absence of robust longer-term
7 risk models. As a sensitivity analysis, we used a simplified longer-term model to check
8 whether the conclusions of the main analysis would have been likely to be different if a
9 longer-term perspective had been adopted e.g. 25 years. This model essentially assumed
10 no further effect of the intervention but modelled out fully the possible QALY gains from the
11 medium-term (11 year) differences in mortality and event rates.
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18 Results

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20 The baseline characteristics for the intervention group as a whole and the usual care
21 subsample who were seen at baseline are shown in Table 2. There were significant
22 differences in the distribution between countries. Mean total and HDL cholesterol levels
23 were significantly higher for the intervention compared with the UC group. Whilst no
24 statistically significant differences were observed for other baseline characteristics, but the
25 10-year CVD risk at baseline [5] was numerically higher for the UC group than the
26 intervention arm.
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34 We modelled 1,019 patients in the intervention arm and 1,005 patients in the UC arm who
35 were assessed at one-year.[4] The intervention group had fewer males than the UC group:
36 49.8% vs. 57.4% male ($p=0.001$), and was significantly younger (mean age at one-year:
37 intervention: 61.5 years vs. usual care: 62.3 years, $p=0.011$).
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43 When testing the validity of the Framingham risk equations to the study population we found
44 that 8 intervention patients and 1 UC sub-sample patient experienced a CHD-event. The
45 risk equations produced a close match, predicting 8.5 patients with a first CHD-event in the
46 intervention group and 2.0 in the UC sub-sample.
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52 Figure 1b further emphasises that the observed additional costs of the EUROACTION
53 intervention programme and staff costs were not offset by the estimated reduced costs of
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6 cardiac interventions in the subsequent years. In terms of the unadjusted results, the
7 incremental costs of the intervention are £362-£419 depending on the duration of the effect
8 of the intervention and the incremental QALYs are 0.076-0.085 (see Table 32). As
9 expected, the incremental costs fall and the incremental QALYs rise as the duration of the
10 effect of the intervention beyond the end of the trial increases. The incremental cost per
11 QALY gained range from £5,539 (95% CI £2,625-£29,627) to £4,266 (95% CI £2,059-
12 £15,945). The unadjusted CEACs under each scenario are in Figure 24a and highlights the
13 results in Table 32 that in all scenarios over 95% of the bootstrapped replications are less
14 than £20,000.

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24 After controlling for differences in age, gender, country and baseline risk factors, the
25 intervention is associated with higher costs and lower QALYs than the UC arm in every
26 scenario (an example of the various regression models is shown in the Appendix). As a
27 result, the intervention is dominated by UC. Although there is considerable uncertainty
28 around those point estimates with the 95% confidence intervals ranging from acceptably
29 cost-effective to highly dominated, but the probability of being cost-effective are very low, as
30 shown in Figure 4b-2b (additional adjusted CEACs, controlling
31 for age, gender and country only are in the Appendix). At a cost-effectiveness threshold of
32 £20,000 the EUROACTION intervention will be cost-effective in under 6% of cases.

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41 Due to baseline differences, we conducted age-sex matched subgroup analyses and the
42 adjusted results confirmed that the intervention remained dominated, even when an
43 optimistic timeframe was considered (an example of age-sex matched subgroup analysis is
44 shown in the Appendix).

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50 The sensitivity analysis produced predictable results that in no way changed the conclusions
51 of the analysis. Using the unadjusted data, the cost-effectiveness of the intervention was

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6 further enhanced, and using the adjusted data the domination of UC over the intervention
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8 remained.

11 Discussion

13 Although this large European trial demonstrated that a nurse-coordinated preventive
14 cardiology programme in primary care helped more high risk patients to achieve the lifestyle
15 and risk factor targets in comparison with UC this does not appear to be cost-effective.
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18 However, these cost-effectiveness analyses require careful qualification because they are
19 subject to a number of uncertainties which are a consequence of the study design and
20 important limitations in the statistical model used.
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25 The differences in the adjusted and unadjusted results emphasise that the study design,
26 based on matching pairs of general practices in each country, did not eliminate baseline
27 differences between the two groups in cardiovascular risk factors. These differences meant
28 that the two groups had different levels of baseline risk, higher in intervention than usual
29 care, but the economic results have adjusted for these baseline differences. Though these
30 differences were small in absolute terms they have a substantial effect on the estimates of
31 absolute risk of future cardiovascular events, and therefore on the difference in effectiveness
32 between intervention and UC. Additionally, the study recorded its primary endpoints at
33 baseline and one-year, and to avoid 'contamination' by recording risk factor levels in UC,
34 baseline measurements were only made in a sub-sample of UC patients. Thus, we do not
35 have before and after measurements for 75% of the UC patients.
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47 Our cost-effectiveness analysis did not include partners. If partners were included it might
48 improve the cost-effectiveness, but we have no good measure of the effect on partners to
49 know how substantial the impact on the incremental cost-effectiveness ratio might be.
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6 Our estimates of the risk of future CVD-events are based on published risk equations.[5]
7 These are derived from a large, well characterised cohort (8491 participants) and predict
8 CVD risk as opposed to CHD risk alone. The C statistic for the model ranges from 0.76
9 (men) to 0.79 (women) suggesting that additional risk factors could potentially improve the
10 model's discriminatory power. Other risk models have included risk factors such as family
11 history of CVD, social deprivation and biomarkers e.g. hs-CRP [16-17] although these
12 models also have their own limitations.
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20 However, to date lifestyle factors such as dietary habits and physical inactivity although
21 important in the aetiology of CHD [18] and independent of the other major risk factors, have
22 not been included in such risk scores, because they are difficult to accurately quantify. The
23 omission of these important lifestyle factors in the Framingham risk equations may be
24 particularly relevant in our study as the cornerstone of the EUROACTION programme was
25 lifestyle change which was clearly evident in the study's most striking achievements in this
26 area including significantly higher fruit and vegetable consumption ($p = 0.005$); physical
27 activity levels ($p = 0.01$); and weight loss ($p = 0.005$).
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36 It is thus possible that our estimates of relative differences in absolute risk between the
37 groups may understate the full effects of the intervention on long-term CVD risk. However,
38 we showed that the risk equations are able to predict CHD events in the study population in
39 the one-year follow-up period, but the accuracy of the risk equations over the ten-year period
40 of our study remains untested.
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46 Our modelling also requires an assumption about how long any differential effect of the
47 intervention persists. Nothing is known about the longer-term effects of EUROACTION, and
48 there are few studies that have looked at longer-term changes. The longest follow-up to a
49 relevant life-style change appears to be the OXCHECK study which showed that the benefits
50 of health checks were sustained over three years.[19-20] However, whatever the duration
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6 of effect beyond the trial, and even when a 25-year model was used, the policy conclusions
7 remain the same.
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11 Finally, our model uses a regression analysis approach so that a UK specific estimate can
12 be drawn from the complete multinational EUROACTION dataset on net resource use, costs
13 and net effects of the intervention. The epidemiological, utilities and cost data for the longer-
14 term modelling of risk and events is based on UK data alone. Thus, the results are
15 applicable to the UK and not specifically to the other EUROACTION countries. Whilst formal
16 analysis would be needed to confirm this, the coefficients on the country parameters in the
17 regression analyses of both costs and outcomes suggest that the cost-effectiveness would
18 be broadly similar in the other countries.
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27 **Conclusion**

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29 Although the EUROACTION study demonstrated in high risk patients in primary care
30 significant improvements in lifestyle and CVD risk factors, it is not possible to show, using
31 the best available risk equations, that the intervention was cost-effective. The available risk
32 modelling is based on a limited number of risk factors, which do not include diet or physical
33 activity, and a healthier lifestyle was the most important outcome of this trial. Therefore,
34 whether or not an intervention such as that offered by EUROACTION is cost-effective
35 remains an open question that could be answered by a longer-term trial with major adverse
36 cardiovascular events as the primary endpoint.
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Acknowledgements

EUROACTION Steering Group

A scientific steering group approved the protocol and the design for this matched pair cluster-randomised controlled trial, and is responsible for the scientific integrity of the study.

The steering group has the following membership: D Wood (London, UK, Chairman), G De Backer (Ghent, Belgium), D De Bacquer (Ghent, Belgium), M Buxton (Uxbridge, UK), I Graham (Dublin, Ireland), A Howard (Nice, France), K Kotseva (London, UK), S Logstrup (Brussels, Belgium), H McGee (Dublin, Ireland), M Mioulet (Nice, France), K Smith (Dundee, UK), D Thompson (York, UK), T Thomsen (Glostrup, Denmark), T van der Weijden (Maastricht, the Netherlands).

National co-ordinators

The national co-ordinators for each country are also members of the steering committee.

They are responsible for identifying and recruiting general practices, obtaining ethics committee approval, appointing and supervising staff in the centres and contributing scientifically to the publication of results. The EUROACTION National Co-ordinators and Primary care leaders are as follows:

Denmark: T Thomsen, K Brockelmann; Italy: P Fioretti, A Desideri, S Brusaferrò; Poland: A Pajak, K. Kawecka-Jaszcz, P Jankowski, T Grodzicki; Spain: J De Velasco, A Maiques; Netherlands: T van der Weijden; United Kingdom: D Wood, J Morrell.

Co-ordinating and Data Management Centre

The Co-ordinating and Data Management Centre is the Department of Cardiovascular Medicine, National Heart and Lung Institute at Charing Cross Campus, Imperial College, London, UK (Head Professor David Wood). The following staff have specific responsibilities as described: K Kotseva, Senior Clinical Research Fellow; S Connolly, Research Fellow; C Jennings, Study Nurse Co-ordinator; A Mead, Chief Dietician; J Jones, Superintendent

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6 Physiotherapist; A Holden, Physical activity Co-ordinator; T Collier, Statistician; M Alston, D
7 Charlesworth, P Homewood, K Pandya, M Somaia, IT specialists/Data managers; S Graves,
8 Research Administrator; W Leacock, D Xenikaki, Administrative Assistants. The following
9 experts advised the Co-ordinating Centre on dietary and physical activity assessment:
10
11 Professor Gary Frost, Professor Barry Margetts, Dr Mike Nelson and Dr Charlie Foster.
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13
14

15 16 17 *Central Laboratory*

18 Central Laboratory analysis of total cholesterol, HDL cholesterol, triglycerides, glucose and
19 HbA1c are undertaken by A McLelland, R Birrell and G Beastall in the Department of
20 Pathological Biochemistry, Royal Infirmary, Glasgow (Head of Department J Shepherd).
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24 25 26 *Statistical Centres*

27 The statistical analyses for the primary endpoints were undertaken by D De Bacquer,
28 Statistician, from the Department of Public Health (Head of Department G De Backer),
29 Ghent University, Belgium, and supplementary analyses by T Collier, Statistician,
30 Department of Medical Statistics, London School of Hygiene and Tropical Medicine,
31 University of London, UK.
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38 39 40 *Health Economics Centre*

41 Martin J Buxton, Professor of Health Economics and Director: Health Economics Research
42 Group, Brunel University, UK; Hema Mistry and Matthew Dyer, Research Fellows in Health
43 Economics, Brunel University.
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46 47 48 *Primary Care Centres*

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50 Intervention Centre: Sundhedscenteret Skanderborg. Dr Lisbeth Rosborg, GP/ Practice
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21
22 *Netherlands*

23 Intervention Centre: Gezondheidscentrum Hoensbroek-Noord. Dr Martijn van Nunen and Dr
24 Bem Bruls, GPs; Jasja Janssen, Nurse; Mrs Mathil Sanders, Practice Manager.
25 Usual Care Centre: Dr Mieke Winten-Huisman and Dr Marc Eyck, GPs; Rene van den
26 Heuvel and Claudia Gessing, Nurses.
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31
32 *Poland*

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35 Barbara Waligóra and Irena Smarzyńska, Nurses.
36 Usual Care Centre: Podstawowa Opieka Zdrowotna - Szpital Uniwersytecki w Krakowie. Dr
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38 Helena Kamińska, Nurses.
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46 *Spain*

47 Intervention Centre: Centro de Salud Salvador Pau, Valencia. Dr Jorge Navarro, Principal
48 Investigator; Gemma Méndez Pérez, Nurse; Dr. Maria Jose Donat, Dr. Raquel Prieto, Dr.
49 Rosario Gonzalez, Dr. Teresa Almela, Dr. Amaparo Garcia and Dr. Francisco Cortes, GPs.
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6 Usual Care Centre: Centro de Salud de Manises, Valencia. Dr Lorenzo Pascual, Principal
7 Investigador; Rocio Marco, Nurse; Dr Juan Manuel García, Practice Manager; Dr Antonia
8 Ibañez, Dr. Cecilia Ruiz, Dr. Santos Plaza, Dr. Amparo Moreno and Dr. Carmen Lloret, GPs.
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13 *UK*

14 Intervention Centre: Seaside Medical Centre, Eastbourne. Dr Tim Gietzen, Principal
15 Investigator; Sjouke Ashton, Nurse; George Bordoli, Associate Nurse; Daniel Brookbank and
16 Angela Hughes, Practice Managers.
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19 Usual Care Centre: Green Street Clinic, Eastbourne. Dr Ian McNaughton, Principal
20 Investigator; Shirley Colvin, Nurse; Heather King, Practice Manager.
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25 *Acknowledgement:* EUROACTION is an initiative of the European Society of Cardiology
26 which highlights its commitment to improve the quality of life of the European population by
27 reducing the impact of cardiovascular diseases. The study protocol conforms to the ethical
28 guidelines of the 1995 Declaration of Helsinki with ethics committee approval in all countries
29 and for every centre. Written informed consent was obtained from every subject.
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33 *Competing interest statement:* All authors declare that the answer to the questions on your
34 competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore
35 have nothing to declare.
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39 *Funding:* Sponsored solely by AstraZeneca through the provision of an unconditional
40 educational grant. [AstraZeneca had no involvement in the study design; in the collection,
41 analysis and interpretation of the data; in the writing of the report; and in the decision to
42 submit the paper for publication.](#)
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45 *Author contributions:* DW and MB are part of the steering committee and approved the
46 protocol and the design for this matched paired cluster-randomised trial. DW was
47 responsible for the overall direction of the project. HM and MD conducted the economic
48 analysis under the supervision of SM and MB and with guidance from DW. KK was
49 responsible for local data collection. HM drafted the manuscript with input from all authors;
50 all authors have approved the final manuscript and were involved in the interpretation of the
51 results.
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Table 1: Observed 1-year costs for EUROACTION study (in £ GBP)

2006/2007 prices	Denmark	Italy	Netherlands	Poland	Spain	UK	Total
Intervention							
N	104	165	191	234	199	126	1,019
Mean (SD)	£589 (£379)	£595 (£366)	£756 (£466)	£515 (£179)	£588 (£269)	£625 (£181)	£608 (£329)
Median	£541	£562	£704	£463	£550	£594	£560
IQR	£473 to £614	£451 to £680	£546 to £862	£374 to £616	£420 to £714	£530 to £729	£449 to £714
Range	£268 to £4,054	£179 to £3,733	£166 to £5,064	£282 to £1,578	£139 to £1,669	£163 to £1,206	£139 to £5,064
Usual Care							
N	154	194	123	160	193	181	1,005
Mean (SD)	£295 (£490)	£201 (£365)	£246 (£307)	£159 (£167)	£138 (£207)	£307 (£563)	£221 (£384)
Median	£193	£146	£125	£105	£68	£196	£142
IQR	£152 to £275	£104 to £198	£84 to £250	£84 to £159	£56 to £122	£140 to £303	£90 to £225
Range	£98 to £3,364	£70 to £4,455	£65 to £2,806	£60 to £1,255	£40 to £2,173	£73 to £6,500	£40 to £6,500

Table 2: Baseline characteristics

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	<u>Intervention</u> (n= 1,019)	<u>Usual care</u> subsample (n = 252)	<u>Statistical test</u> [#]
<u>Country</u>			
<u>Denmark</u>	<u>104 (10.2%)</u>	<u>40 (15.9%)</u>	<u>p = 0.012</u>
<u>Italy</u>	<u>165 (16.2%)</u>	<u>47 (18.7%)</u>	
<u>Netherlands</u>	<u>191 (18.7%)</u>	<u>37 (14.7%)</u>	
<u>Poland</u>	<u>234 (23.0%)</u>	<u>45 (17.9%)</u>	
<u>Spain</u>	<u>199 (19.5%)</u>	<u>41 (16.3%)</u>	
<u>UK</u>	<u>126 (12.4%)</u>	<u>42 (16.7%)</u>	
<u>Gender</u>			
<u>Male</u>	<u>507 (49.8%)</u>	<u>133 (52.8%)</u>	<u>p = 0.390</u>
<u>Female</u>	<u>512 (50.3%)</u>	<u>119 (47.2%)</u>	
<u>Risk factors required for the</u> <u>D'Agostino Equation [5]</u> <u>n (%)</u>			
<u>Non-smoker</u>	<u>695 (68.2%)</u>	<u>155 (61.5%)</u>	<u>p = 0.646</u>
<u>Has diabetes</u>	<u>313 (30.7%)</u>	<u>68 (27.0%)</u>	<u>p = 0.247</u>
<u>On anti-hypertensive drugs</u>	<u>432 (42.4%)</u>	<u>97 (38.5%)</u>	<u>p = 0.260</u>
<u>Mean (SD)</u>			
<u>Age</u>	<u>60.5 (7.6)</u>	<u>60.4 (7.3)</u>	<u>p = 0.915</u>
<u>Systolic blood pressure (mm HG)</u>	<u>141.1 (18.6)</u>	<u>141.6 (18.9)</u>	<u>p = 0.693</u>
<u>Total cholesterol (mmol/L)</u>	<u>5.70 (1.02)</u>	<u>5.45 (0.99)</u>	<u>p = 0.001</u>
<u>HDL cholesterol (mmol/L)</u>	<u>1.40 (0.39)</u>	<u>1.35 (0.36)</u>	<u>p = 0.047</u>
<u>10-year CVD risk at baseline</u>	<u>0.115 (0.087)</u>	<u>0.120 (0.093)</u>	<u>p = 0.426</u>

[#] Chi-squared tests conducted for categorical variables and t tests conducted for continuous variables

Table 32: Results from cost-effectiveness model

	Duration of effect of intervention beyond the end of the trial (model time horizon = 11 th years in all cases)			
	0 years	2 years	5 years	10 years
Unadjusted costs and QALYs				
Usual care mean cost (SD)	£2,727 (£29)	£2,727 (£29)	£2,727 (£29)	£2,727 (£29)
Intervention mean cost (SD)	£3,146 (£33)	£3,126 (£31)	£3,105 (£31)	£3,089 (£31)
Usual care mean QALYs (SD)	6.755 (0.021)	6.755 (0.021)	6.755 (0.021)	6.755 (0.021)
Intervention mean QALYs (SD)	6.831 (0.021)	6.835 (0.021)	6.838 (0.021)	6.840 (0.021)
Incremental costs (95% CI)	£419 (£332 to £505)	£399 (£315 to £483)	£378 (£294 to £462)	£362 (£278 to £447)
Incremental QALYs (95% CI)	0.076 (0.017 to 0.135)	0.079 (0.020 to 0.138)	0.083 (0.024 to 0.142)	0.085 (0.026 to 0.144)
ICER	£5,539	£5,031	£4,561	£4,266
95% CI	£2,625 to £29,627	£2,412 to £22,520	£2,202 to £18,155	£2,059 to £15,945
% of bootstrapped ICERs < £20k	95.7%	97.0%	97.9%	98.4%
% of bootstrapped ICERs < £30k	97.6%	98.4%	99.0%	99.2%
Adjusted costs and QALYs†				
Incremental costs (95% CI)	£474 (£368 to £580)	£463 (£358 to £568)	£450 (£343 to £557)	£441 (£331 to £550)
Incremental QALYs (95% CI)	-0.009 (-0.041 to 0.023)	-0.007 (-0.038 to 0.025)	-0.005 (-0.036 to 0.027)	-0.003 (-0.035 to 0.029)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£21,695 to dominated†	£18,495 to dominated†	£15,908 to dominated†	£14,485 to dominated†

% of bootstrapped ICERs <£20k	1.97%	3.16%	4.57%	5.76%
% of bootstrapped ICERs <£30k	5.05%	6.98%	9.42%	11.54%

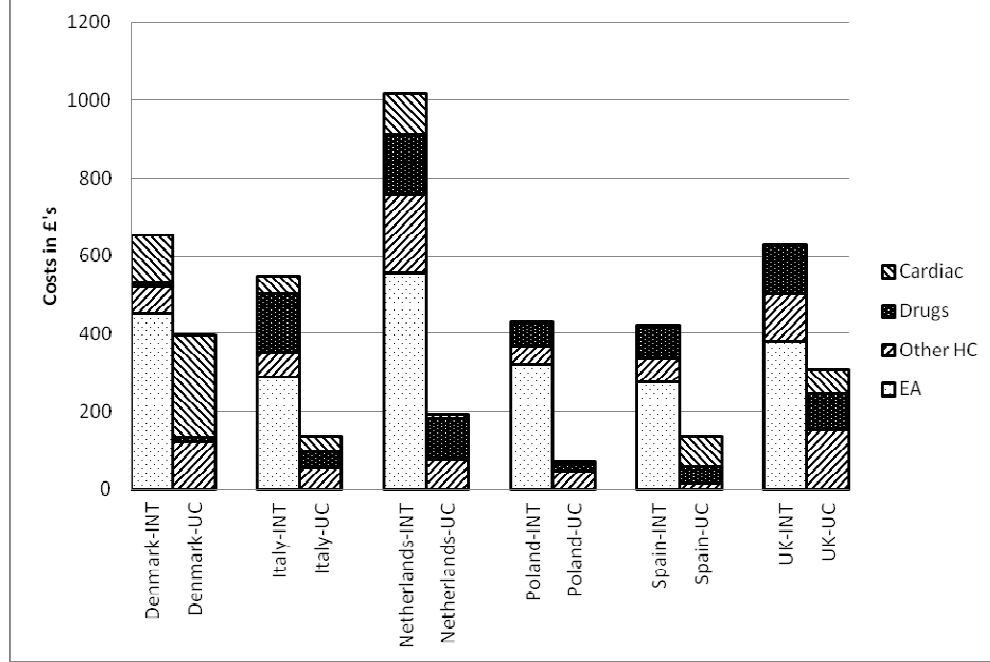
SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

[#] 1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

‡ Adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.

Figure 1a: One-year observed costs for the Intervention and Usual Care groups split by type



Key: EA = EuroAction costs; Other HC = other health care costs; Drugs = cardiac related medication costs; Cardiac = cardiac procedure costs

Figure 1b: Mean costs for the Intervention and Usual Care groups for the main health states in the Markov model

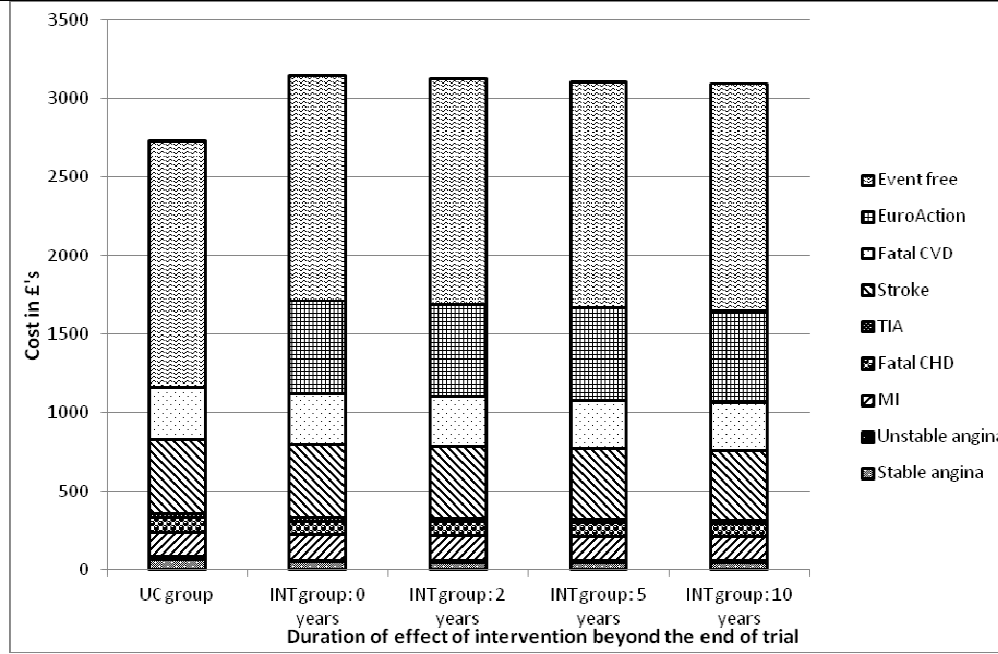
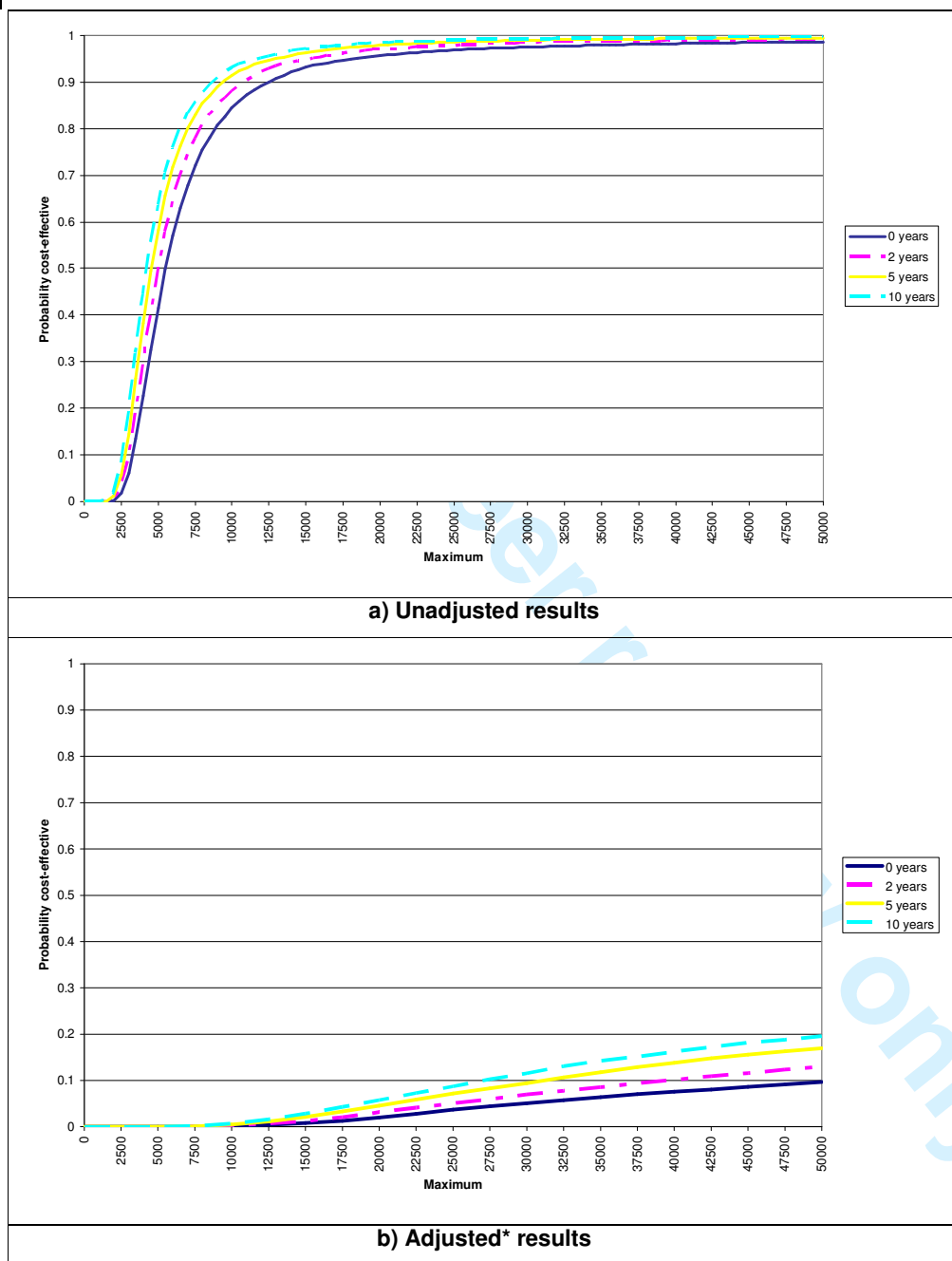


Figure 21: Cost-effectiveness acceptability curves



* Adjusted for differences between groups by age, gender, country and baseline risk factors

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Appendix

Table A1: Costs of health states in cost-effectiveness model

Health State	Cost (2006 prices)	Assumption/Source	Source
Event-Free	£197	Based on a mean cost of cardiac-related medication and health care contacts (outside of EUROACTION programme) incurred by all patients during one year follow-up	Trial data
Stable Angina	£383	Based on 3 times 15 minutes' GP contact plus medication (plus cost of event-free)	Ward et al, 2007 [10]
Post-stable angina	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
Unstable angina	£674	Based on 3 times 15 minutes' GP contact plus medication plus 60% of patients are also prescribed clopidogrel (plus cost of event-free)	Ward et al, 2007 [10]
Post-unstable angina	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
MI	£5,020	Based on data from Nottingham Heart Attack Register include revascularisation for a proportion of patients, plus primary care and medication costs as unstable angina (plus cost of event-free)	Palmer et al, 2002 [21]
Post-MI	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
Fatal CHD event	£1,462	Based on costs of a fatal MI (plus cost of event-free)	Clarke et al, 2003 [22]
TIA	£1,351	Based on medication costs plus costs of test and surgery for appropriate patients (plus cost of event-free)	Ward et al, 2007 [10]
Post-TIA	£483	Based on medication costs only (plus cost of event-free)	Ward et al, 2007 [10]

Stroke	£8,922	Based on cost of acute events (mild, moderate and severe stroke) and weighted by distribution of severity of strokes (plus cost of event-free)	Youman et al, 2003 [23]
Post-Stroke	£2,543	Based on cost of acute events (mild, moderate and severe stroke) and weighted by distribution of severity of strokes (plus cost of event-free)	Youman et al, 2003 [23]
Fatal CVD event	£7,832	Based on cost of fatal stroke (plus cost of event-free)	Youman et al, 2003 [23]

Table A2: Utility values for health states used in the model

Utility value	Event free	Stable angina	Unstable angina	MI	TIA	Stroke
45 - 49	0.869	0.702	0.669	0.660	0.869	0.547
50 - 54	0.848	0.685	0.653	0.644	0.848	0.533
55 - 59	0.826	0.667	0.636	0.628	0.826	0.520
60 - 64	0.805	0.650	0.620	0.612	0.805	0.506
65 - 69	0.784	0.633	0.604	0.596	0.784	0.493
70 - 74	0.763	0.617	0.588	0.580	0.763	0.480
75 - 79	0.741	0.599	0.571	0.563	0.741	0.466
80 - 84	0.720	0.582	0.544	0.547	0.720	0.453
85 - 89	0.699	0.565	0.538	0.531	0.699	0.440
90 - 94	0.678	0.548	0.522	0.515	0.678	0.426
95 - 99	0.656	0.530	0.505	0.499	0.656	0.413
100 +	0.635	0.513	0.489	0.483	0.635	0.399

Sources: Event free (Kind et al, 1998) [13]; Stable angina (Meslop et al, 2003) [24]; Unstable angina and MI (Goodacre et al, 2004) [25]; TIA (Kind et al, 1998) [13]; Stroke (Tengs et al, 2003) [26]

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Table A3: Regression results from adjusted[#] cost-effectiveness analysis (Duration of effect of intervention beyond the end of the trial = 0 years)

	Costs				QALYs			
	<u>Coefficient</u>	<u>Standard error</u>	<u>t</u>	<u>p value</u>	<u>Coefficient</u>	<u>Standard error</u>	<u>t</u>	<u>p value</u>
<u>Group</u> (1 = intervention; 0 = UC)	<u>474.40</u>	<u>54.04</u>	<u>8.78</u>	<u>< 0.001</u>	<u>-0.009</u>	<u>0.016</u>	<u>-0.56</u>	<u>0.575</u>
<u>Gender</u>	<u>1544.10</u>	<u>273.27</u>	<u>5.65</u>	<u>< 0.001</u>	<u>-0.826</u>	<u>0.082</u>	<u>-10.09</u>	<u>< 0.001</u>
<u>Age</u>	<u>57.68</u>	<u>3.24</u>	<u>17.80</u>	<u>< 0.001</u>	<u>-0.090</u>	<u>0.001</u>	<u>-92.79</u>	<u>< 0.001</u>
<u>Gender*Age</u>	<u>-33.11</u>	<u>4.45</u>	<u>-7.44</u>	<u>< 0.001</u>	<u>0.017</u>	<u>0.001</u>	<u>13.12</u>	<u>< 0.001</u>
<u>Italy</u>	<u>106.34</u>	<u>58.58</u>	<u>1.82</u>	<u>0.070</u>	<u>-0.022</u>	<u>0.018</u>	<u>-1.26</u>	<u>0.206</u>
<u>Spain</u>	<u>89.71</u>	<u>60.31</u>	<u>1.49</u>	<u>0.137</u>	<u>-0.041</u>	<u>0.018</u>	<u>-2.26</u>	<u>0.024</u>
<u>Poland</u>	<u>32.58</u>	<u>58.81</u>	<u>0.55</u>	<u>0.580</u>	<u>-0.045</u>	<u>0.018</u>	<u>-2.56</u>	<u>0.010</u>
<u>Denmark</u>	<u>188.87</u>	<u>62.34</u>	<u>3.03</u>	<u>0.002</u>	<u>-0.063</u>	<u>0.019</u>	<u>-3.38</u>	<u>0.001</u>
<u>Netherlands</u>	<u>162.83</u>	<u>61.34</u>	<u>2.65</u>	<u>0.008</u>	<u>-0.058</u>	<u>0.018</u>	<u>-3.17</u>	<u>0.002</u>
<u>Total cholesterol</u>	<u>3.64</u>	<u>0.58</u>	<u>6.24</u>	<u>< 0.001</u>	<u>-0.001</u>	<u>0.000</u>	<u>-4.32</u>	<u>< 0.001</u>
<u>HDL cholesterol</u>	<u>-13.76</u>	<u>1.57</u>	<u>-8.77</u>	<u>< 0.001</u>	<u>0.002</u>	<u>0.000</u>	<u>4.29</u>	<u>< 0.001</u>
<u>Systolic blood pressure</u>	<u>13.38</u>	<u>1.20</u>	<u>11.19</u>	<u>< 0.001</u>	<u>-0.002</u>	<u>0.000</u>	<u>-4.70</u>	<u>< 0.001</u>
<u>Anti-hypertensive drugs</u>	<u>346.22</u>	<u>41.47</u>	<u>8.35</u>	<u>< 0.001</u>	<u>-0.051</u>	<u>0.012</u>	<u>-4.12</u>	<u>< 0.001</u>
<u>Diabetes</u>	<u>588.88</u>	<u>46.62</u>	<u>12.63</u>	<u>< 0.001</u>	<u>-0.116</u>	<u>0.014</u>	<u>-8.35</u>	<u>< 0.001</u>
<u>Smoking</u>	<u>392.41</u>	<u>43.48</u>	<u>9.02</u>	<u>< 0.001</u>	<u>-0.055</u>	<u>0.013</u>	<u>-4.20</u>	<u>< 0.001</u>

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<u>Total cholesterol*</u>	<u>-362.52</u>	<u>544.24</u>	<u>-0.67</u>	<u>0.505</u>	<u>0.037</u>	<u>0.163</u>	<u>0.22</u>	<u>0.823</u>
<u>HDL cholesterol*</u>	<u>238.80</u>	<u>536.53</u>	<u>0.45</u>	<u>0.656</u>	<u>0.023</u>	<u>0.161</u>	<u>0.15</u>	<u>0.884</u>
<u>Systolic blood pressure*</u>	<u>157.56</u>	<u>232.32</u>	<u>0.68</u>	<u>0.498</u>	<u>-0.066</u>	<u>0.070</u>	<u>-0.94</u>	<u>0.346</u>
<u>Anti-hypertensive drugs*</u>	<u>230.88</u>	<u>143.30</u>	<u>1.61</u>	<u>0.107</u>	<u>-0.046</u>	<u>0.043</u>	<u>-1.07</u>	<u>0.284</u>
<u>Smoking*</u>	<u>-302.10</u>	<u>226.48</u>	<u>-1.33</u>	<u>0.182</u>	<u>0.044</u>	<u>0.068</u>	<u>0.65</u>	<u>0.513</u>
<u>Constant</u>	<u>-3068.89</u>	<u>280.08</u>	<u>-10.96</u>	<u>< 0.001</u>	<u>12.572</u>	<u>0.084</u>	<u>149.96</u>	<u>< 0.001</u>
Number of observations	<u>2,024</u>				<u>2,024</u>			
R ²	<u>0.472</u>				<u>0.896</u>			

* Regression model adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.

* Dummy variables created to indicate missing values for each of the risk characteristics

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Table A43: Additional results from the cost-effectiveness model

	Duration of effect of intervention beyond the end of the trial (model time horizon = 11 [#] years in all cases)			
	0 years	2 years	5 years	10 years
Adjusted costs and QALYs				
<i>Controlling for age and gender only</i>				
Incremental costs (95% CI)	£512 (£438 to £589)	£491 (£418 to £563)	£468 (£396 to £541)	£452 (£378 to £525)
Incremental QALYs (95% CI)	-0.016 (-0.036 to 0.004)	-0.012 (-0.032 to 0.008)	-0.008 (-0.028 to 0.012)	-0.006 (-0.026 to 0.014)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£105,653 to dominated†	£54,307 to dominated†	£34,845 to dominated†	£27,907 to dominated†
% of bootstrapped ICERs <£20k	0.01%	0.10%	0.34%	0.71%
% of bootstrapped ICERs <£30k	0.19%	0.52%	1.69%	3.11%
<i>Controlling for age, gender and country</i>				
Incremental costs (95% CI)	£497 (£424 to £571)	£476 (£404 to £548)	£453 (£381 to £526)	£436 (£364 to £509)
Incremental QALYs (95% CI)	-0.011 (-0.031 to 0.009)	-0.007 (-0.027 to 0.013)	-0.003 (-0.023 to 0.017)	-0.001 (-0.021 to 0.019)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£49,903 to dominated†	£33,290 to dominated†	£24,001 to dominated†	£20,342 to dominated†
% of bootstrapped ICERs <£20k	0.07%	0.34%	1.11%	2.32%
% of bootstrapped ICERs <£30k	0.61%	1.81%	4.78%	7.76%

SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

[#] 1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

Table A5: Results from matched age-sex analysis

	Duration of effect of intervention beyond the end of the trial = 10 years (model time horizon = 11[#] years in all cases)			
	Men < 65 years	Men >= 65 years	Women < 65 years	Women > = 65 years
Unadjusted costs and QALYs				
Incremental costs (95% CI)	£413 (£290 to £536)	£527 (£237 to £817)	£387 (£304 to £471)	£546 (£376 to £717)
Incremental QALYs (95% CI)	0.040 (-0.016 to 0.096)	-0.057 (-0.181 to 0.068)	0.026 (-0.017 to 0.069)	-0.043 (-0.139 to 0.052)
ICER	£10,298	Dominated†	£15,006	Dominated†
Adjusted costs and QALYs‡				
Incremental costs (95% CI)	£457 (£282 to £631)	£360 (£83 to £803)	£430 (£313 to £548)	£466 (£222 to £710)
Incremental QALYs (95% CI)	-0.008 (-0.063 to 0.048)	-0.014 (-0.212 to 0.183)	-0.011 (-0.041 to 0.020)	-0.000 (-0.052 to 0.051)
ICER	Dominated†	Dominated†	Dominated†	Dominated†

SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

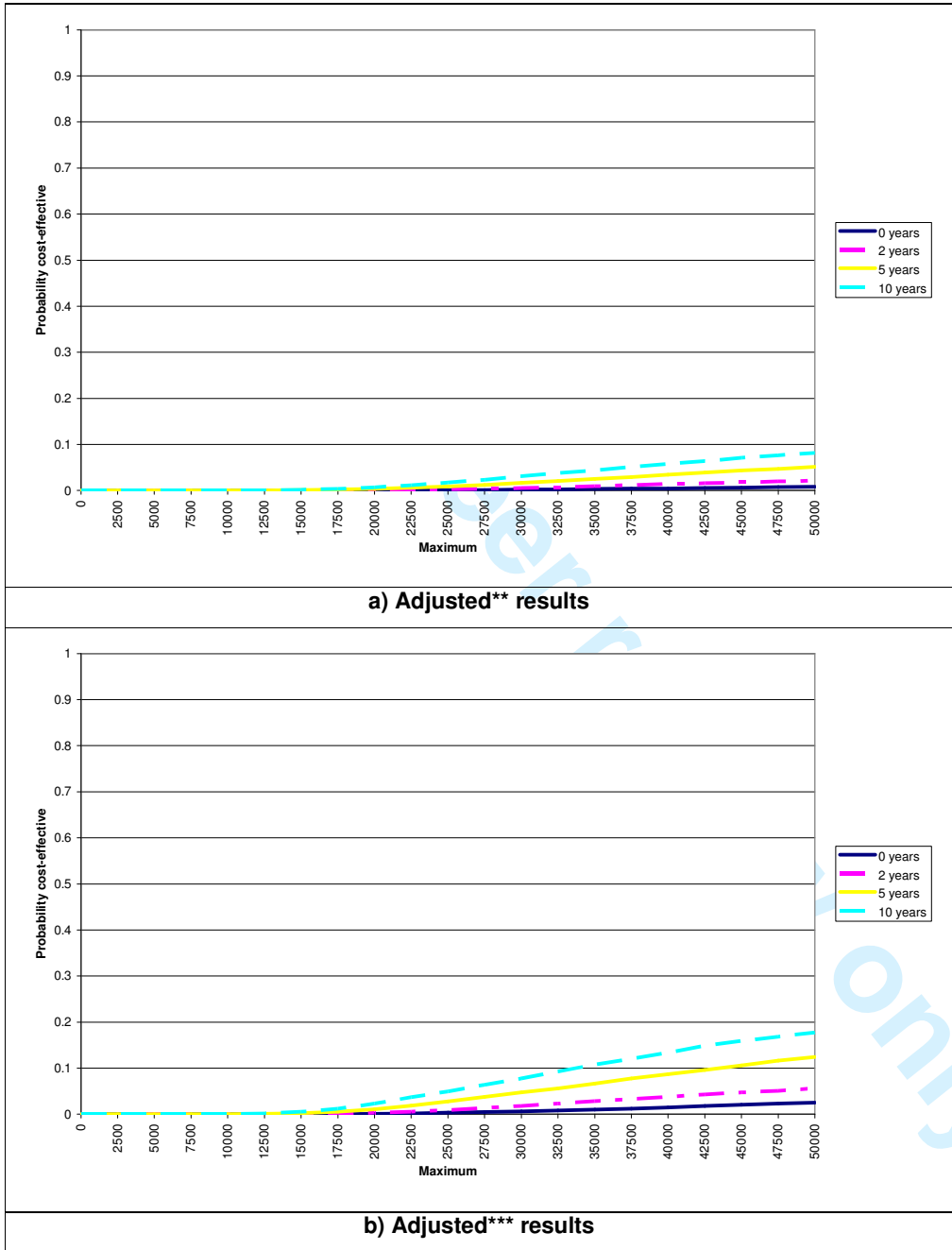
[#] 1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

‡ Adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.

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Figure A1: Adjusted cost-effectiveness results



** Adjusted for differences between groups by age and gender

*** Adjusted for differences between groups by age, gender and country

Additional References for Appendix

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Cost-effectiveness of a European preventive cardiology programme in primary care: A Markov Modelling Approach

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-001029.R2
Article Type:	Research
Date Submitted by the Author:	15-Aug-2012
Complete List of Authors:	Mistry, Hema; University of Birmingham, Health Economics Unit Morris, Stephen; University College London, Department of Applied Health Research Dyer, Matthew; National Institute for Health and Clinical Excellence, Kotseva, Kornelia; Imperial College London, Department of Cardiovascular Medicine Wood, David; Imperial College London, Department of Cardiovascular Medicine Buxton, Martin; Brunel University, Health Economics Research Group
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	HEALTH ECONOMICS, CARDIOLOGY, PRIMARY CARE

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Cost-effectiveness of a European preventive cardiology programme in primary care: a Markov modelling approach

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For peer review only

Abstract (word count 306)

Objective: To investigate the longer-term cost-effectiveness of a nurse-coordinated preventive cardiology programme for primary prevention of cardiovascular disease compared to routine practice from a health service perspective.

Design: A matched, paired cluster-randomised controlled trial.

Setting: Six pairs of general practices in six countries.

Participants: 1,019 patients were randomised to the EUROACTION intervention programme and 1,005 patients to usual care and who completed the one-year follow-up

Outcome measures: Evidence on health outcomes and costs were based on patient level data from the study, which had a one-year follow-up period. Future risk of cardiovascular (CVD) events was modelled, using published risk models based on patient characteristics. An individual level Markov model for each patient was used to extrapolate beyond the end of the trial, which was populated with data from published sources. We used an 11-year time horizon and investigated the impact on cost-effectiveness of varying the duration of the effect of the intervention beyond the end of the trial. Results are expressed as incremental cost per quality-adjusted life year gained.

Results: Unadjusted results found the intervention to be more costly and also more effective than usual care. However, after adjusting for differences in age, gender, country and baseline risk factors, the intervention was dominated by usual care, but this analysis was not able to take into account of lifestyle changes in terms of diet and physical activity.

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3 **Conclusions:** Although the EUROACTION study achieved healthier lifestyle changes and
4 improvements in management of blood pressure and lipids for patients at high risk of CVD,
5 compared to usual care, it was not possible to show, using available risk equations which do
6 not incorporate diet and physical activity, that the intervention reduced longer-term
7 cardiovascular risk cost-effectively. Whether or not an intervention such as that offered by
8 EUROACTION is cost-effective requires a longer term trial with major cardiovascular events
9 as the outcome.
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Article summary

Article focus

- To investigate the longer-term cost-effectiveness of a nurse-coordinated preventive cardiology programme for primary prevention of cardiovascular disease compared to routine practice.

Key messages

- The EUROACTION study achieved healthier lifestyle changes and improvements in management of blood pressure and lipids for patients at high risk of CVD, compared to usual care.
- The unadjusted results of the cost-effectiveness analysis found the intervention to be more effective than usual care but also more costly. However, the adjusted results showed that the intervention was dominated by usual care.
- The published cardiovascular risk equations do not take account of lifestyle changes in terms of diet and physical activity and therefore may be inadequate for the evaluation of whether or not a lifestyle intervention to prevent cardiovascular disease is cost-effective.

Strengths and limitations of the study

- This is the first study assessing the cost-effectiveness of the EUROACTION programme.
- The available cardiovascular risk modelling is based on a limited number of risk factors, which do not include measures of diet or physical activity, and a healthier lifestyle was the most important outcome of the EUROACTION trial.

Trial Registration number: ISRCTN 71715857

Keywords: Multi-centre studies; cardiovascular prevention programme; cost-effectiveness; Markov model; QALYs.

Text word Count: 3,415

Introduction

Evidence has shown that individuals with increased risk of cardiovascular disease (CVD) can reduce their risk of cardiovascular morbidity and mortality by stopping smoking, changing their diet, engaging in physical activity, achieving a healthy body weight, and controlling their blood pressure, cholesterol and diabetes.[1] However, not all patients at high risk of developing CVD manage to achieve these recommended lifestyle and risk factor goals and there remains considerable potential to reduce CVD risk in these patients.[2] The EUROACTION study was designed to address the need for preventive cardiology care in everyday clinical practice.[3]

The EUROACTION study was a matched, paired cluster-randomised controlled trial, across eight countries and 24 hospitals and general practices. The project evaluated the impact of a nurse-coordinated, multidisciplinary preventive cardiology programme for coronary patients in hospital and high risk individuals in general practice. It aimed to help all these high risk patients and their families to achieve recommended lifestyle and risk factor targets for CVD prevention in everyday clinical practice over one year. The principal results concluded that the EUROACTION programme achieved healthier lifestyle changes and improvements in risk factor management for patients with coronary heart disease (CHD) and those at high risk of CVD, together with their partners, compared to usual care.[4]

While there is evidence that the EUROACTION programme is effective in terms of modifying lifestyle and some CVD risk factors, there is no evidence as to its cost-effectiveness.

Therefore, this paper aims to model the long-term cost-effectiveness of the EUROACTION programme in comparison with usual care within the primary care setting.

Methods

Patients

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2 The EUROACTION primary care study took place in Denmark, Italy, Netherlands, Poland,
3 Spain and UK, where a matched pair of general practices was identified, and then
4 randomised to either the EUROACTION programme or to usual care (UC). GPs
5 prospectively identified the study population. The comparison was restricted to patients and
6 did not include partners. Eligibility criteria for patients has previously been published.[4]
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12 All intervention patients were assessed at baseline and one-year. These assessments
13 focussed on smoking habits, diet and physical activity, measurement of body mass index,
14 blood pressure, cholesterol and glucose levels, and cardiac medications were also recorded.
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16 The programme was delivered by specialist nurses, working with GPs, and supported by
17 software programmes , educational materials and group workshops to achieve individual
18 goals. Each person was given a personal record card to record lifestyle and risk factor
19 goals, medications and appointments. To avoid the possibility that undergoing baseline
20 assessments might affect outcomes, only a random sub-sample (~25%) of UC patients were
21 seen at baseline and then all UC patients were invited for assessment at one-year. In the
22 UC arm, patients did not receive any form of special care.
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37 ***Model structure***

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39 We adopted a health service perspective to measure costs and outcomes. Each cycle in the
40 model is of one year's duration. All patients were CVD-free on entering the model. In each
41 subsequent cycle patients may remain CVD-event free, they may have a fatal or non-fatal
42 CVD event, or they may die from non-CVD causes. Once the patient has had an initial CVD
43 event, then in subsequent cycles they move to the post CVD-event states and they may
44 move between different CVD states and/or die from CVD or non-CVD causes.
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53 The CVD event states are: non-fatal myocardial infarction (MI), stable angina, unstable
54 angina, CHD death, transient ischaemic attack (TIA), stroke, CVD death and non-CVD
55 death.
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Measuring initial CVD risk

To estimate the risk of an initial CVD event in a subsequent year we used the D'Agostino et al [5] CVD risk function, derived from the Framingham Heart Study. This calculates individual sex-specific risks for future cardiovascular events (in patients initially free of CVD). These CVD risk equations incorporate as risk factors the natural logarithms of age, total and HDL cholesterol, systolic blood pressure (SBP) if treated with or without anti-hypertensive medications, smoking and diabetes. We used the published calibration factors to focus on the CHD and stroke event states.

Ten-year risks were estimated from the equations and adjusted to one-year values.[6] One-year CVD risk beyond the end of the trial was calculated based on both a) baseline patient characteristics (adjusted for age) for intervention patients only; and b) one-year follow-up characteristics for both groups, in order to evaluate any changes to CVD risk factors as a result of the EUROACTION programme.

Validating the appropriateness of the risk functions of the model

We tested the validity of applying the D'Agostino et al [5] risk equations to the study population, by comparing the observed number of CHD cases with the number predicted at one-year. Because stroke and TIA incidence data was not collected in the study we converted the CVD risk equations to CHD risks using the recommended calibration factors.[5] We present the results of the comparison for both groups.

Transition probabilities

We disaggregated the overall risk of a CVD event into rates for specific events by age and gender, using UK relative incidence rates based on published literature [7-9] and expert opinion, as previously used in Ward et al [10]. These event rates were applied to individual annual CVD risks to calculate individual transition probabilities for moving from the CVD-free

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2 state to the initial CVD-event states. Also, individual patients could die from non-vascular
3 causes, depending on their age and gender. The non-CVD death transition probabilities
4 were taken from Briggs et al.[11] Transition probabilities for moving from primary event
5 health states to subsequent non-fatal health states are taken from Ward et al.[10]
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10 11 12 **Measuring cost**

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14 Data on resources used during the trial and staff contacts were recorded in case record
15 forms and then converted into electronic format. To determine the total one-year costs for
16 each group, we obtained unit costs for all relevant items of resources used in the trial:
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22 *1. Costs relating to EUROACTION programme and other contacts in primary care* were
23 obtained from the programme facilitators and included the EUROACTION nurses costs,
24 training costs, production of patient educational materials and any other costs
25 associated with implementing the programme. The average time spent by staff for all
26 patient contacts at baseline and one-year was provided by each centre. Hourly wage
27 rates of the staff salaries and training were calculated and then applied to these various
28 patient contacts. We costed the EUROACTION family information packs, a pocket-
29 sized personal record card, questionnaires and group sessions that each patient in the
30 intervention group received as part of their prevention programme.
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43 Costs were applied to other contacts with health care professionals, such as GPs,
44 outside of the intervention programme for both arms and these costs were based on
45 national estimates of the staff salaries involved and estimates of the average time spent
46 with the patient provided by the trial co-ordinators.
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53 *2. Cardiac-related drug costs.* Data was collected on patient-specific cardiac-related
54 medications including the drug name and dose at baseline and one-year. This gave
55 point of time information, but no start or end dates. So for each patient it was assumed
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2 that they would remain on the same medication at a constant dose for the entire
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4 duration e.g. from baseline to one-year. National cost estimates for the drugs were
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6 provided by trial co-ordinators from each country and were applied accordingly to the
7
8 relevant dose and length of time on a patient-specific basis.
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12 *3. Cardiac-related procedures and tests.* During the trial, patients within both groups
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14 may have required inpatient or outpatient admissions for cardiac-related procedures, or
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16 undertaken any cardiac-related tests. The procedures were costed according to HRG
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18 episodes for each country and the other tests or bed days as simple unit costs.
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20 National unit cost estimates for cardiac-related procedures and tests for each country
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22 were obtained from a database held by United BioSource Corporation (Erwin De Cock,
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24 personal communication, May 2007) for all countries, except Denmark and Poland. For
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26 these two countries, national unit cost estimates were provided from contacts within the
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28 Centre for Applied Health Services Research and Technology in Denmark (Jan
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30 Sørensen, personal communication, January 2007) and from the Ministry of Health in
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32 Poland (Andrzej Pająk, personal communication, June 2007).
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37 As the study was based in six countries, a costing algorithm was developed to calculate a
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39 total cost per patient for each country. The costs of the programme were valued in local
40
41 currencies and then converted to 2006/2007 £ (GBP) using purchasing power parities.[12]
42
43 Table 1 presents the total one-year costs by group and country. Figure 1a shows that the 1-
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45 year observed costs (split by type of cost) for the intervention group was significantly more
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47 than the usual care group for all countries. This higher cost was explained by the
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49 EUROACTION intervention programme costs and contacts with EUROACTION staff, whilst
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51 neither arms experienced significantly high cost cardiac interventions or cardiac medications.
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55 Subsequent costs relating to health states occupied within the model were based on UK
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57 estimates (see Appendix). It was assumed that patients in a CVD-free state would continue
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2 to receive the cardiac-related medications and primary care contacts (outside of the
3 intervention programme) that they received during the trial. The mean cost of these
4 medications and contacts for all patients across both arms was applied to each individual
5 patient within the model who remained in the event-free health state for subsequent years.
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10 11 12 ***Health state utilities***

13 To estimate quality-adjusted life years (QALYs) the model requires utility values for each
14 state adjusted by age. For patients who were event-free, the utility values were based on
15 UK general population norms [13]; utilities for events/states were taken from Ward et al [10]
16 which were all were based on UK studies and were obtained using the EQ-5D (see
17 Appendix).
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27 ***Measuring the impact of the intervention***

28 The study provided results only for a one-year follow-up. We estimated results for a range of
29 possible durations of effect, assuming that the CVD risk reduction experienced by the
30 intervention patients persisted for 0 through to 10 additional years (11-year time horizon),
31 after which they reverted to their individual CVD risk factor levels at the start of the study
32 (adjusted for age). For UC patients, it was assumed that patients would remain at their one-
33 year CVD risk (adjusted annually by age) throughout the model.
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44 ***Measuring cost-effectiveness***

45 Using the Markov model we calculated for each patient their expected quality-adjusted
46 survival (based on their likelihood of surviving each cycle and their expected health state
47 utility value) and their expected costs. Cost-effectiveness was measured in terms of the
48 incremental cost per QALY gained (ICER). Future costs and benefits were discounted at
49 3.5%. [14]
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58 ***Statistical analyses***

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2 All statistical analyses were performed in Stata version 10 [15] or Microsoft Excel and a p-
3 value ≤ 0.05 was considered to be statistically significant. We present unadjusted and
4 adjusted cost-effectiveness results. The adjusted results controlled for group allocation, age,
5 gender, age*gender interactions, country, and baseline risk factors using OLS regressions.
6 As only a random sub-sample of UC patients were seen at baseline, regression analyses
7 were used to predict baseline values for those patients who had missing values. For total
8 and HDL cholesterol and SBP, OLS regression was used to predict values in those patients
9 with missing values, as a function of age, gender and country. For the three binary variables
10 (medications, smoking and diabetes), logistic regression models were used to predict the
11 probability of each binary outcome. Predicted values ≥ 0.5 were categorised to a value of 1
12 and values < 0.5 were categorised as 0. In the adjusted models we also included an
13 indicator for whether or not each control variable was missing.
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29 We represented uncertainty due to sampling variation in both the unadjusted and adjusted
30 cost-effectiveness ratios using non-parametric bootstrapping. In the unadjusted analyses we
31 sampled individuals in our model with replacement and used their costs and outcomes over
32 the 11-year period to compute replications of the incremental cost per QALY gained. We
33 repeated this approach in the adjusted analyses, also adding the regressions to control for
34 confounding factors. In each case, we generated 10,000 bootstrap replications of the cost-
35 effectiveness ratios and used these to construct 95% confidence intervals around the point
36 estimate of cost-effectiveness.
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47 ***Sensitivity analysis***

48 The main analysis modelling was limited to ten years, in the absence of robust longer-term
49 risk models. As a sensitivity analysis, we used a simplified longer-term model to check
50 whether the conclusions of the main analysis would have been likely to be different if a
51 longer-term perspective had been adopted e.g. 25 years. This model essentially assumed
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2 no further effect of the intervention but modelled out fully the possible QALY gains from the
3 medium-term (11 year) differences in mortality and event rates.
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8 **Results**

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10 The baseline characteristics for the intervention group as a whole and the usual care
11 subsample who were seen at baseline are shown in Table 2. There were significant
12 differences in the distribution between countries. Mean total and HDL cholesterol levels
13 were significantly higher for the intervention compared with the UC group. Whilst no
14 statistically significant differences were observed for other baseline characteristics, but the
15 10-year CVD risk at baseline [5] was numerically higher for the UC group than the
16 intervention arm.
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26 We modelled 1,019 patients in the intervention arm and 1,005 patients in the UC arm who
27 were assessed at one-year.[4] The intervention group had fewer males than the UC group:
28 49.8% vs. 57.4% male ($p=0.001$), and was significantly younger (mean age at one-year:
29 intervention: 61.5 years vs. usual care: 62.3 years, $p=0.011$).
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37 When testing the validity of the Framingham risk equations to the study population we found
38 that 8 intervention patients and 1 UC sub-sample patient experienced a CHD-event. The
39 risk equations produced a close match, predicting 8.5 patients with a first CHD-event in the
40 intervention group and 2.0 in the UC sub-sample.
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47 Figure 1b further emphasises that the observed additional costs of the EUROACTION
48 intervention programme and staff costs were not offset by the estimated reduced costs of
49 cardiac interventions in the subsequent years. In terms of the unadjusted results, the
50 incremental costs of the intervention are £362-£419 depending on the duration of the effect
51 of the intervention and the incremental QALYs are 0.076-0.085 (see Table 3). As expected,
52 the incremental costs fall and the incremental QALYs rise as the duration of the effect of the
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2 intervention beyond the end of the trial increases. The incremental cost per QALY gained
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4 range from £5,539 (95% CI £2,625-£29,627) to £4,266 (95% CI £2,059-£15,945). The
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6 unadjusted CEACs under each scenario are in Figure 2a and highlights the results in Table
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8 3 that in all scenarios over 95% of the bootstrapped replications are less than £20,000.
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12 After controlling for differences in age, gender, country and baseline risk factors, the
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14 intervention is associated with higher costs and lower QALYs than the UC arm in
15
16 every scenario (an example of the various regression models is shown in the
17
18 Appendix). As a result, the intervention is dominated by UC. Although there is
19
20 considerable uncertainty around those point estimates with the 95% confidence
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22 intervals ranging from acceptably cost-effective to highly dominated, but the
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24 probability of being cost-effective are very low, as shown in the adjusted CEACs in
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26 Figure 2b (additional adjusted CEACs, controlling for age, gender and country only
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28 are in the Appendix). At a cost-effectiveness threshold of £20,000 the
29
30 EUROACTION intervention will be cost-effective in under 6% of cases.
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34 Due to baseline differences, we conducted age-sex matched subgroup analyses and the
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36 adjusted results confirmed that the intervention remained dominated, even when an
37
38 optimistic timeframe was considered (an example of age-sex matched subgroup analysis is
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40 shown in the Appendix).
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45 The sensitivity analysis produced predictable results that in no way changed the conclusions
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47 of the analysis. Using the unadjusted data, the cost-effectiveness of the intervention was
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49 further enhanced, and using the adjusted data the domination of UC over the intervention
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51 remained.
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53 54 55 **Discussion** 56 57 58 59 60

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2 Although this large European trial demonstrated that a nurse-coordinated preventive
3 cardiology programme in primary care helped more high risk patients to achieve the lifestyle
4 and risk factor targets in comparison with UC this does not appear to be cost-effective.
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6 However, these cost-effectiveness analyses require careful qualification because they are
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8 subject to a number of uncertainties which are a consequence of the study design and
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10 important limitations in the statistical model used.
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16 The differences in the adjusted and unadjusted results emphasise that the study design,
17 based on matching pairs of general practices in each country, did not eliminate baseline
18 differences between the two groups in cardiovascular risk factors. These differences meant
19 that the two groups had different levels of baseline risk, higher in intervention than usual
20 care, but the economic results have adjusted for these baseline differences. Though these
21 differences were small in absolute terms they have a substantial effect on the estimates of
22 absolute risk of future cardiovascular events, and therefore on the difference in effectiveness
23 between intervention and UC. Additionally, the study recorded its primary endpoints at
24 baseline and one-year, and to avoid 'contamination' by recording risk factor levels in UC,
25 baseline measurements were only made in a sub-sample of UC patients. Thus, we do not
26 have before and after measurements for 75% of the UC patients.
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41 Our cost-effectiveness analysis did not include partners. If partners were included it might
42 improve the cost-effectiveness, but we have no good measure of the effect on partners to
43 know how substantial the impact on the incremental cost-effectiveness ratio might be.
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49 Our estimates of the risk of future CVD-events are based on published risk equations.[5]
50 These are derived from a large, well characterised cohort (8491 participants) and predict
51 CVD risk as opposed to CHD risk alone. The C statistic for the model ranges from 0.76
52 (men) to 0.79 (women) suggesting that additional risk factors could potentially improve the
53 model's discriminatory power. Other risk models have included risk factors such as family
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2 history of CVD, social deprivation and biomarkers e.g. hs-CRP [16-17] although these
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4 models also have their own limitations.
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9 However, to date lifestyle factors such as dietary habits and physical inactivity although
10 important in the aetiology of CHD [18] and independent of the other major risk factors, have
11 not been included in such risk scores, because they are difficult to accurately quantify. The
12 omission of these important lifestyle factors in the Framingham risk equations may be
13 particularly relevant in our study as the cornerstone of the EUROACTION programme was
14 lifestyle change which was clearly evident in the study's most striking achievements in this
15 area including significantly higher fruit and vegetable consumption ($p = 0.005$); physical
16 activity levels ($p = 0.01$); and weight loss ($p = 0.005$).
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27 It is thus possible that our estimates of relative differences in absolute risk between the
28 groups may understate the full effects of the intervention on long-term CVD risk. However,
29 we showed that the risk equations are able to predict CHD events in the study population in
30 the one-year follow-up period, but the accuracy of the risk equations over the ten-year period
31 of our study remains untested.
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39 Our modelling also requires an assumption about how long any differential effect of the
40 intervention persists. Nothing is known about the longer-term effects of EUROACTION, and
41 there are few studies that have looked at longer-term changes. The longest follow-up to a
42 relevant life-style change appears to be the OXCHECK study which showed that the benefits
43 of health checks were sustained over three years.[19-20] However, whatever the duration
44 of effect beyond the trial, and even when a 25-year model was used, the policy conclusions
45 remain the same.
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56 Finally, our model uses a regression analysis approach so that a UK specific estimate can
57 be drawn from the complete multinational EUROACTION dataset on net resource use, costs
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2 and net effects of the intervention. The epidemiological, utilities and cost data for the longer-
3 term modelling of risk and events is based on UK data alone. Thus, the results are
4 applicable to the UK and not specifically to the other EUROACTION countries. Whilst formal
5 analysis would be needed to confirm this, the coefficients on the country parameters in the
6 regression analyses of both costs and outcomes suggest that the cost-effectiveness would
7 be broadly similar in the other countries.
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14 15 16 17 **Conclusion**

18 Although the EUROACTION study demonstrated in high risk patients in primary care
19 significant improvements in lifestyle and CVD risk factors, it is not possible to show, using
20 the best available risk equations, that the intervention was cost-effective. The available risk
21 modelling is based on a limited number of risk factors, which do not include diet or physical
22 activity, and a healthier lifestyle was the most important outcome of this trial. Therefore,
23 whether or not an intervention such as that offered by EUROACTION is cost-effective
24 remains an open question that could be answered by a longer-term trial with major adverse
25 cardiovascular events as the primary endpoint.
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Acknowledgements

EUROACTION Steering Group

A scientific steering group approved the protocol and the design for this matched pair cluster-randomised controlled trial, and is responsible for the scientific integrity of the study.

The steering group has the following membership: D Wood (London, UK, Chairman), G De Backer (Ghent, Belgium), D De Bacquer (Ghent, Belgium), M Buxton (Uxbridge, UK), I Graham (Dublin, Ireland), A Howard (Nice, France), K Kotseva (London, UK), S Logstrup (Brussels, Belgium), H McGee (Dublin, Ireland), M Mioulet (Nice, France), K Smith (Dundee, UK), D Thompson (York, UK), T Thomsen (Glostrup, Denmark), T van der Weijden (Maastricht, the Netherlands).

National co-ordinators

The national co-ordinators for each country are also members of the steering committee.

They are responsible for identifying and recruiting general practices, obtaining ethics committee approval, appointing and supervising staff in the centres and contributing scientifically to the publication of results. The EUROACTION National Co-ordinators and Primary care leaders are as follows:

Denmark: T Thomsen, K Brockelmann; Italy: P Fioretti, A Desideri, S Brusaferrò; Poland: A Pajak, K. Kawecka-Jaszcz, P Jankowski, T Grodzicki; Spain: J De Velasco, A Maiques; Netherlands: T van der Weijden; United Kingdom: D Wood, J Morrell.

Co-ordinating and Data Management Centre

The Co-ordinating and Data Management Centre is the Department of Cardiovascular Medicine, National Heart and Lung Institute at Charing Cross Campus, Imperial College, London, UK (Head Professor David Wood). The following staff have specific responsibilities as described: K Kotseva, Senior Clinical Research Fellow; S Connolly, Research Fellow; C Jennings, Study Nurse Co-ordinator; A Mead, Chief Dietician; J Jones, Superintendent

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Physiotherapist; A Holden, Physical activity Co-ordinator; T Collier, Statistician; M Alston, D Charlesworth, P Homewood, K Pandya, M Somaia, IT specialists/Data managers; S Graves, Research Administrator; W Leacock, D Xenikaki, Administrative Assistants. The following experts advised the Co-ordinating Centre on dietary and physical activity assessment: Professor Gary Frost, Professor Barry Margetts, Dr Mike Nelson and Dr Charlie Foster.

Central Laboratory

Central Laboratory analysis of total cholesterol, HDL cholesterol, triglycerides, glucose and HbA1c are undertaken by A McLelland, R Birrell and G Beastall in the Department of Pathological Biochemistry, Royal Infirmary, Glasgow (Head of Department J Shepherd).

Statistical Centres

The statistical analyses for the primary endpoints were undertaken by D De Bacquer, Statistician, from the Department of Public Health (Head of Department G De Backer), Ghent University, Belgium, and supplementary analyses by T Collier, Statistician, Department of Medical Statistics, London School of Hygiene and Tropical Medicine, University of London, UK.

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Martin J Buxton, Professor of Health Economics and Director: Health Economics Research Group, Brunel University, UK; Hema Mistry and Matthew Dyer, Research Fellows in Health Economics, Brunel University.

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Usual Care Centre: Dr Mieke Winten-Huisman and Dr Marc Eyck, GPs; Rene van den Heuvel and Claudia Gessing, Nurses.

Poland

Intervention Centre: Centrum Medycyny Profilaktycznej w Krakowie. Dr Krystyna Pająk, Principal Investigator; Lidia Dwojak, Practice Manager; Joanna Śladek-Ratajewicz, GP; Barbara Waligóra and Irena Smarzyńska, Nurses.

Usual Care Centre: Podstawowa Opieka Zdrowotna - Szpital Uniwersytecki w Krakowie. Dr Maria Fornal, Principal Investigator; Dr Jolanta Walczewska, GP; Barbara Wojtanis and Helena Kamińska, Nurses.

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Intervention Centre: Centro de Salud Salvador Pau, Valencia. Dr Jorge Navarro, Principal Investigator; Gemma Méndez Pérez, Nurse; Dr. Maria Jose Donat, Dr. Raquel Prieto, Dr. Rosario Gonzalez, Dr. Teresa Almela, Dr. Amaparo Garcia and Dr. Francisco Cortes, GPs.

1
2 Usual Care Centre: Centro de Salud de Manises, Valencia. Dr Lorenzo Pascual, Principal
3 Investigador; Rocio Marco, Nurse; Dr Juan Manuel García, Practice Manager; Dr Antonia
4 Ibañez, Dr. Cecilia Ruiz, Dr. Santos Plaza, Dr. Amparo Moreno and Dr. Carmen Lloret, GPs.
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10 *UK*

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12 Intervention Centre: Seaside Medical Centre, Eastbourne. Dr Tim Gietzen, Principal
13 Investigator; Sjouke Ashton, Nurse; George Bordoli, Associate Nurse; Daniel Brookbank and
14 Angela Hughes, Practice Managers.
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18 Usual Care Centre: Green Street Clinic, Eastbourne. Dr Ian McNaughton, Principal
19 Investigator; Shirley Colvin, Nurse; Heather King, Practice Manager.
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25 *Acknowledgement:* EUROACTION is an initiative of the European Society of Cardiology
26 which highlights its commitment to improve the quality of life of the European population by
27 reducing the impact of cardiovascular diseases. The study protocol conforms to the ethical
28 guidelines of the 1995 Declaration of Helsinki with ethics committee approval in all countries
29 and for every centre. Written informed consent was obtained from every subject.
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34 *Competing interest statement:* All authors declare that the answer to the questions on your
35 competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore
36 have nothing to declare.
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40 *Funding:* Sponsored solely by AstraZeneca through the provision of an unconditional
41 educational grant. AstraZeneca had no involvement in the study design; in the collection,
42 analysis and interpretation of the data; in the writing of the report; and in the decision to
43 submit the paper for publication.
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47 *Author contributions:* DW and MB are part of the steering committee and approved the
48 protocol and the design for this matched paired cluster-randomised trial. DW was
49 responsible for the overall direction of the project. HM and MD conducted the economic
50 analysis under the supervision of SM and MB and with guidance from DW. KK was
51 responsible for local data collection. HM drafted the manuscript with input from all authors;
52 all authors have approved the final manuscript and were involved in the interpretation of the
53 results.
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Table 1: Observed 1-year costs for EUROACTION study (in £ GBP)

2006/2007 prices	Denmark	Italy	Netherlands	Poland	Spain	UK	Total
Intervention							
N	104	165	191	234	199	126	1,019
Mean (SD)	£589 (£379)	£595 (£366)	£756 (£466)	£515 (£179)	£588 (£269)	£625 (£181)	£608 (£329)
Median	£541	£562	£704	£463	£550	£594	£560
IQR	£473 to £614	£451 to £680	£546 to £862	£374 to £616	£420 to £714	£530 to £729	£449 to £714
Range	£268 to £4,054	£179 to £3,733	£166 to £5,064	£282 to £1,578	£139 to £1,669	£163 to £1,206	£139 to £5,064
Usual Care							
N	154	194	123	160	193	181	1,005
Mean (SD)	£295 (£490)	£201 (£365)	£246 (£307)	£159 (£167)	£138 (£207)	£307 (£563)	£221 (£384)
Median	£193	£146	£125	£105	£68	£196	£142
IQR	£152 to £275	£104 to £198	£84 to £250	£84 to £159	£56 to £122	£140 to £303	£90 to £225
Range	£98 to £3,364	£70 to £4,455	£65 to £2,806	£60 to £1,255	£40 to £2,173	£73 to £6,500	£40 to £6,500

Table 2: Baseline characteristics

	Intervention (n= 1,019)	Usual care subsample (n = 252)	Usual care all (n = 1,005)	Statistical test [#] (Int. vs. UC subsample)	Statistical test [#] (Int. vs. UC all)
<i>Country</i>					
Denmark	104 (10.2%)	40 (15.9%)	154 (15.3%)	p = 0.012	p < 0.001
Italy	165 (16.2%)	47 (18.7%)	194 (19.3%)		
Netherlands	191 (18.7%)	37 (14.7%)	123 (12.2%)		
Poland	234 (23.0%)	45 (17.9%)	160 (15.9%)		
Spain	199 (19.5%)	41 (16.3%)	193 (19.2%)		
UK	126 (12.4%)	42 (16.7%)	181 (18.0%)		
<i>Gender</i>					
Male	507 (49.8%)	133 (52.8%)	577 (57.4%)	p = 0.390	p = 0.001
Female	512 (50.3%)	119 (47.2%)	428 (42.6%)		
<i>Risk factors required for the D'Agostino Equation [5]</i>					
<i>n (%)</i>					
Non-smoker				p = 0.646	-
Has diabetes	695 (68.2%)	155 (61.5%)	-		
On anti-hypertensive drugs	313 (30.7%)	68 (27.0%)	-		

Mean (SD)	432 (42.4%)	97 (38.5%)	-	p = 0.260	-
Age					
Systolic blood pressure (mm HG)	60.5 (7.6)	60.4 (7.3)	61.3 (7.3)	p = 0.915	p = 0.011
Total cholesterol (mmol/L)	141.1 (18.6)	141.6 (18.9)	-	p = 0.693	-
HDL cholesterol (mmol/L)	5.70 (1.02)	5.45 (0.99)	-	p = 0.001	-
	1.40 (0.39)	1.35 (0.36)	-	p = 0.047	-
10-year CVD risk at baseline	0.115 (0.087)	0.120 (0.093)	-	p = 0.426	-

Chi-squared tests conducted for categorical variables and t tests conducted for continuous variables

Table 3: Results from cost-effectiveness model

	Duration of effect of intervention beyond the end of the trial (model time horizon = 11* years in all cases)			
	0 years	2 years	5 years	10 years
Unadjusted costs and QALYs				
Usual care mean cost (SD)	£2,727 (£29)	£2,727 (£29)	£2,727 (£29)	£2,727 (£29)
Intervention mean cost (SD)	£3,146 (£33)	£3,126 (£31)	£3,105 (£31)	£3,089 (£31)
Usual care mean QALYs (SD)	6.755 (0.021)	6.755 (0.021)	6.755 (0.021)	6.755 (0.021)
Intervention mean QALYs (SD)	6.831 (0.021)	6.835 (0.021)	6.838 (0.021)	6.840 (0.021)
Incremental costs (95% CI)	£419 (£332 to £505)	£399 (£315 to £483)	£378 (£294 to £462)	£362 (£278 to £447)
Incremental QALYs (95% CI)	0.076 (0.017 to 0.135)	0.079 (0.020 to 0.138)	0.083 (0.024 to 0.142)	0.085 (0.026 to 0.144)

ICER	£5,539	£5,031	£4,561	£4,266
95% CI	£2,625 to £29,627	£2,412 to £22,520	£2,202 to £18,155	£2,059 to £15,945
% of bootstrapped ICERs < £20k	95.7%	97.0%	97.9%	98.4%
% of bootstrapped ICERs < £30k	97.6%	98.4%	99.0%	99.2%
Adjusted costs and QALYs‡				
Incremental costs (95% CI)	£474 (£368 to £580)	£463 (£358 to £568)	£450 (£343 to £557)	£441 (£331 to £550)
Incremental QALYs (95% CI)	-0.009 (-0.041 to 0.023)	-0.007 (-0.038 to 0.025)	-0.005 (-0.036 to 0.027)	-0.003 (-0.035 to 0.029)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£21,695 to dominated†	£18,495 to dominated†	£15,908 to dominated†	£14,485 to dominated†
% of bootstrapped ICERs <£20k	1.97%	3.16%	4.57%	5.76%
% of bootstrapped ICERs <£30k	5.05%	6.98%	9.42%	11.54%

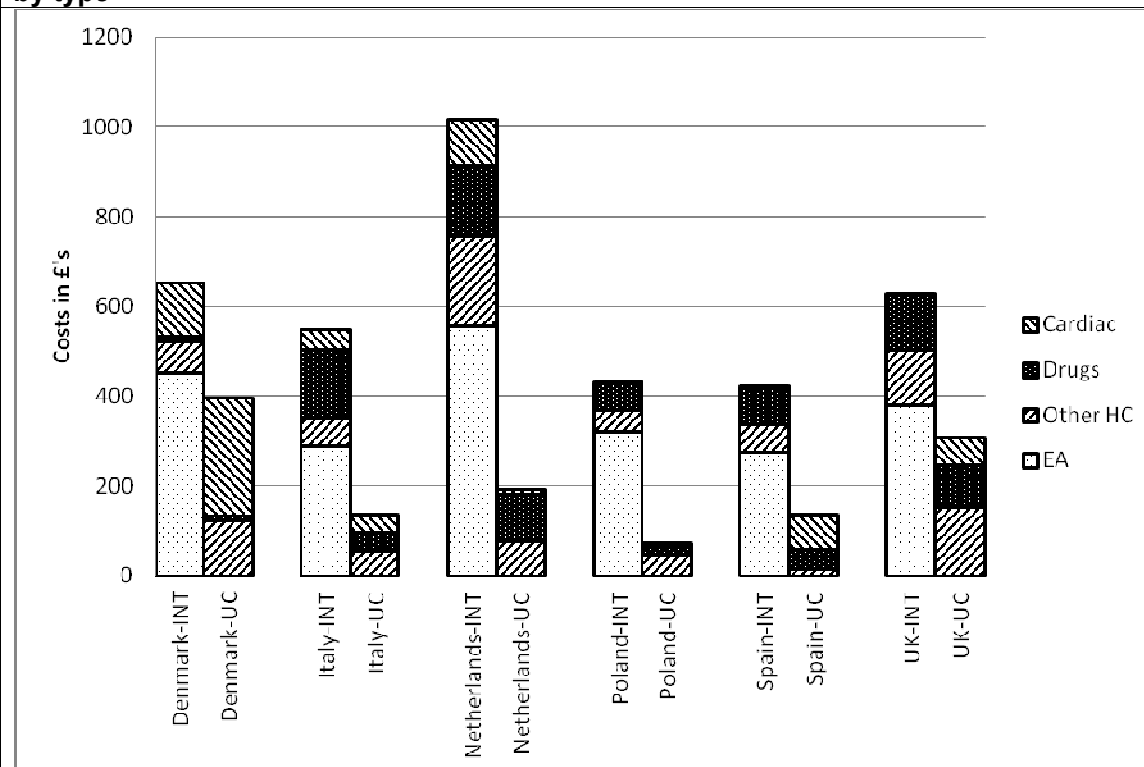
SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

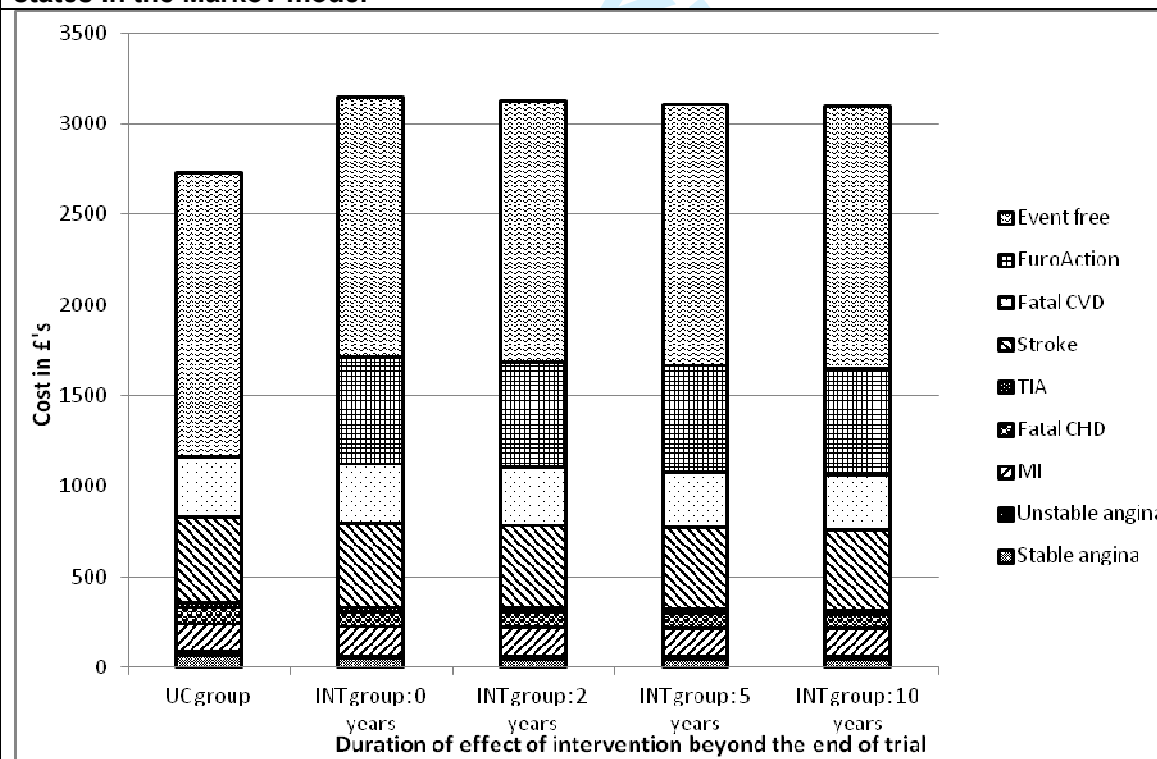
‡ Adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.

Figure 1a: One-year observed costs for the Intervention and Usual Care groups split by type



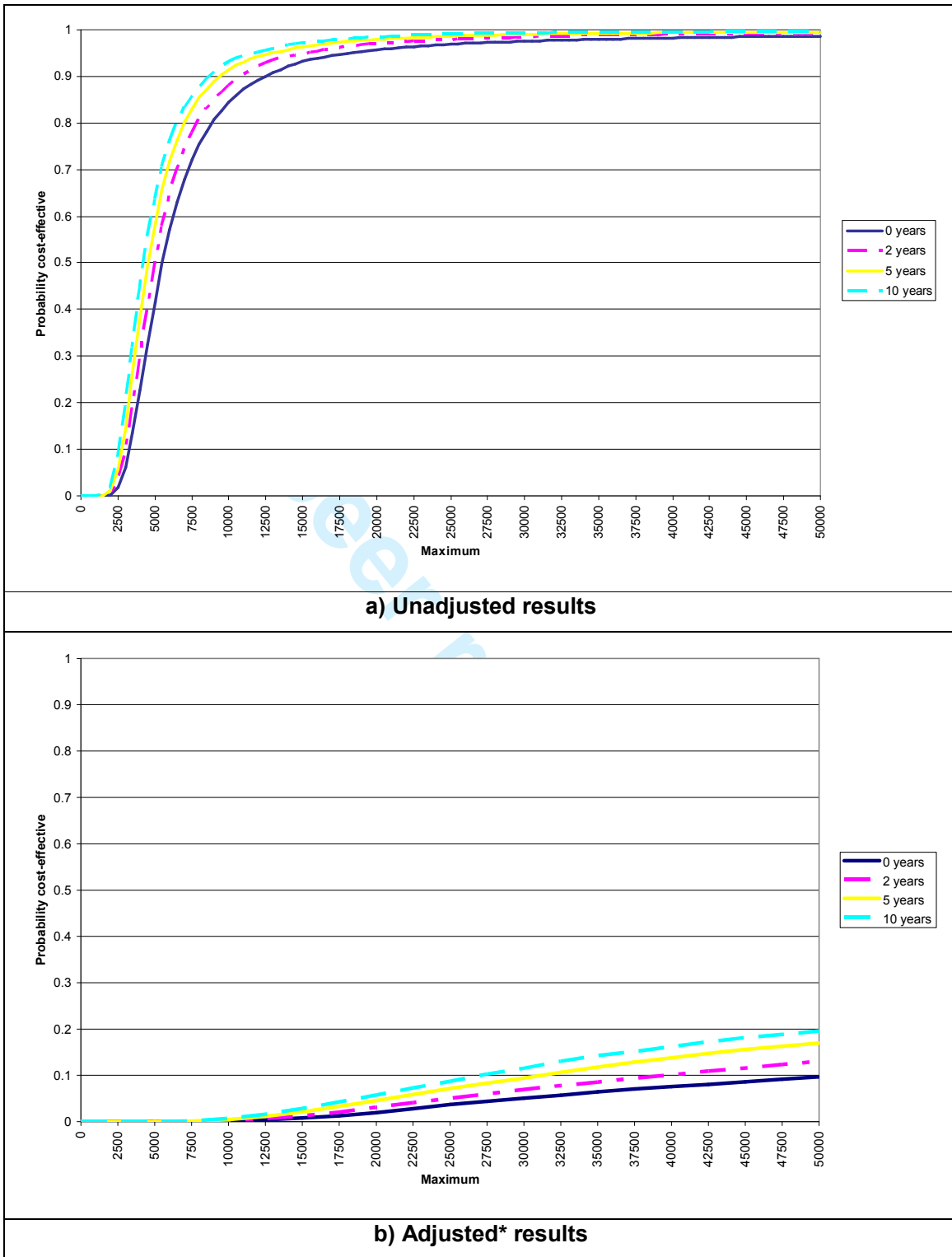
Key: EA = EuroAction costs; Other HC = other health care costs; Drugs = cardiac related medication costs; Cardiac = cardiac procedure costs

Figure 1b: Mean costs for the Intervention and Usual Care groups for the main health states in the Markov model



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Figure 2: Cost-effectiveness acceptability curves



* Adjusted for differences between groups by age, gender, country and baseline risk factors

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Appendix
Table A1: Costs of health states in cost-effectiveness model

Health State	Cost (2006 prices)	Assumption/Source	Source
Event-Free	£197	Based on a mean cost of cardiac-related medication and health care contacts (outside of EUROACTION programme) incurred by all patients during one year follow-up	Trial data
Stable Angina	£383	Based on 3 times 15 minutes' GP contact plus medication (plus cost of event-free)	Ward et al, 2007 [10]
Post-stable angina	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
Unstable angina	£674	Based on 3 times 15 minutes' GP contact plus medication plus 60% of patients are also prescribed clopidogrel (plus cost of event-free)	Ward et al, 2007 [10]
Post-unstable angina	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
MI	£5,020	Based on data from Nottingham Heart Attack Register include revascularisation for a proportion of patients, plus primary care and medication costs as unstable angina (plus cost of event-free)	Palmer et al, 2002 [21]
Post-MI	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
Fatal CHD event	£1,462	Based on costs of a fatal MI (plus cost of event-free)	Clarke et al, 2003 [22]
TIA	£1,351	Based on medication costs plus costs of test and surgery for appropriate patients (plus cost of event-free)	Ward et al, 2007 [10]
Post-TIA	£483	Based on medication costs only (plus cost of event-free)	Ward et al, 2007 [10]

Stroke	£8,922	Based on cost of acute events (mild, moderate and severe stroke) and weighted by distribution of severity of strokes (plus cost of event-free)	Youman et al, 2003 [23]
Post-Stroke	£2,543	Based on cost of acute events (mild, moderate and severe stroke) and weighted by distribution of severity of strokes (plus cost of event-free)	Youman et al, 2003 [23]
Fatal CVD event	£7,832	Based on cost of fatal stroke (plus cost of event-free)	Youman et al, 2003 [23]

Table A2: Utility values for health states used in the model

Utility value	Event free	Stable angina	Unstable angina	MI	TIA	Stroke
45 - 49	0.869	0.702	0.669	0.660	0.869	0.547
50 - 54	0.848	0.685	0.653	0.644	0.848	0.533
55 - 59	0.826	0.667	0.636	0.628	0.826	0.520
60 - 64	0.805	0.650	0.620	0.612	0.805	0.506
65 - 69	0.784	0.633	0.604	0.596	0.784	0.493
70 - 74	0.763	0.617	0.588	0.580	0.763	0.480
75 - 79	0.741	0.599	0.571	0.563	0.741	0.466
80 - 84	0.720	0.582	0.544	0.547	0.720	0.453
85 - 89	0.699	0.565	0.538	0.531	0.699	0.440
90 - 94	0.678	0.548	0.522	0.515	0.678	0.426
95 - 99	0.656	0.530	0.505	0.499	0.656	0.413
100 +	0.635	0.513	0.489	0.483	0.635	0.399

Sources: Event free (Kind et al, 1998) [13]; Stable angina (Meslop et al, 2003) [24]; Unstable angina and MI (Goodacre et al, 2004) [25]; TIA (Kind et al, 1998) [13]; Stroke (Tengs et al, 2003) [26]

Table A3: Regression results from adjusted[#] cost-effectiveness analysis (Duration of effect of intervention beyond the end of the trial = 0 years)

	Costs				QALYs			
	Coefficient	Standard error	t	p value	Coefficient	Standard error	t	p value
Group (1 = intervention; 0 = UC)	474.40	54.04	8.78	< 0.001	-0.009	0.016	-0.56	0.575
Gender	1544.10	273.27	5.65	< 0.001	-0.826	0.082	-10.09	< 0.001
Age	57.68	3.24	17.80	< 0.001	-0.090	0.001	-92.79	< 0.001
Gender*Age	-33.11	4.45	-7.44	< 0.001	0.017	0.001	13.12	< 0.001
Italy	106.34	58.58	1.82	0.070	-0.022	0.018	-1.26	0.206
Spain	89.71	60.31	1.49	0.137	-0.041	0.018	-2.26	0.024
Poland	32.58	58.81	0.55	0.580	-0.045	0.018	-2.56	0.010
Denmark	188.87	62.34	3.03	0.002	-0.063	0.019	-3.38	0.001
Netherlands	162.83	61.34	2.65	0.008	-0.058	0.018	-3.17	0.002
Total cholesterol	3.64	0.58	6.24	< 0.001	-0.001	0.000	-4.32	< 0.001
HDL cholesterol	-13.76	1.57	-8.77	< 0.001	0.002	0.000	4.29	< 0.001
Systolic blood pressure	13.38	1.20	11.19	< 0.001	-0.002	0.000	-4.70	< 0.001
Anti-hypertensive drugs	346.22	41.47	8.35	< 0.001	-0.051	0.012	-4.12	< 0.001
Diabetes	588.88	46.62	12.63	< 0.001	-0.116	0.014	-8.35	< 0.001
Smoking	392.41	43.48	9.02	< 0.001	-0.055	0.013	-4.20	< 0.001

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Total cholesterol*	-362.52	544.24	-0.67	0.505	0.037	0.163	0.22	0.823
HDL cholesterol*	238.80	536.53	0.45	0.656	0.023	0.161	0.15	0.884
Systolic blood pressure*	157.56	232.32	0.68	0.498	-0.066	0.070	-0.94	0.346
Anti-hypertensive drugs*	230.88	143.30	1.61	0.107	-0.046	0.043	-1.07	0.284
Smoking*	-302.10	226.48	-1.33	0.182	0.044	0.068	0.65	0.513
Constant	-3068.89	280.08	-10.96	< 0.001	12.572	0.084	149.96	< 0.001
Number of observations	2,024				2,024			
R ²	0.472				0.896			

* Regression model adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.

* Dummy variables created to indicate missing values for each of the risk characteristics

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Table A4: Additional results from the cost-effectiveness model

	Duration of effect of intervention beyond the end of the trial (model time horizon = 11 [#] years in all cases)			
	0 years	2 years	5 years	10 years
Adjusted costs and QALYs				
Controlling for age and gender only				
Incremental costs (95% CI)	£512 (£438 to £589)	£491 (£418 to £563)	£468 (£396 to £541)	£452 (£378 to £525)
Incremental QALYs (95% CI)	-0.016 (-0.036 to 0.004)	-0.012 (-0.032 to 0.008)	-0.008 (-0.028 to 0.012)	-0.006 (-0.026 to 0.014)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£105,653 to dominated†	£54,307 to dominated†	£34,845 to dominated†	£27,907 to dominated†
% of bootstrapped ICERs <£20k	0.01%	0.10%	0.34%	0.71%
% of bootstrapped ICERs <£30k	0.19%	0.52%	1.69%	3.11%
Controlling for age, gender and country				
Incremental costs (95% CI)	£497 (£424 to £571)	£476 (£404 to £548)	£453 (£381 to £526)	£436 (£364 to £509)
Incremental QALYs (95% CI)	-0.011 (-0.031 to 0.009)	-0.007 (-0.027 to 0.013)	-0.003 (-0.023 to 0.017)	-0.001 (-0.021 to 0.019)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£49,903 to dominated†	£33,290 to dominated†	£24,001 to dominated†	£20,342 to dominated†
% of bootstrapped ICERs <£20k	0.07%	0.34%	1.11%	2.32%
% of bootstrapped ICERs <£30k	0.61%	1.81%	4.78%	7.76%

SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

[#] 1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

Table A5: Results from matched age-sex analysis

	Duration of effect of intervention beyond the end of the trial = 10 years (model time horizon = 11* years in all cases)			
	Men < 65 years	Men >= 65 years	Women < 65 years	Women > = 65 years
Unadjusted costs and QALYs				
Incremental costs (95% CI)	£413 (£290 to £536)	£527 (£237 to £817)	£387 (£304 to £471)	£546 (£376 to £717)
Incremental QALYs (95% CI)	0.040 (-0.016 to 0.096)	-0.057 (-0.181 to 0.068)	0.026 (-0.017 to 0.069)	-0.043 (-0.139 to 0.052)
ICER	£10,298	Dominated†	£15,006	Dominated†
Adjusted costs and QALYs‡				
Incremental costs (95% CI)	£457 (£282 to £631)	£360 (£83 to £803)	£430 (£313 to £548)	£466 (£222 to £710)
Incremental QALYs (95% CI)	-0.008 (-0.063 to 0.048)	-0.014 (-0.212 to 0.183)	-0.011 (-0.041 to 0.020)	-0.000 (-0.052 to 0.051)
ICER	Dominated†	Dominated†	Dominated†	Dominated†

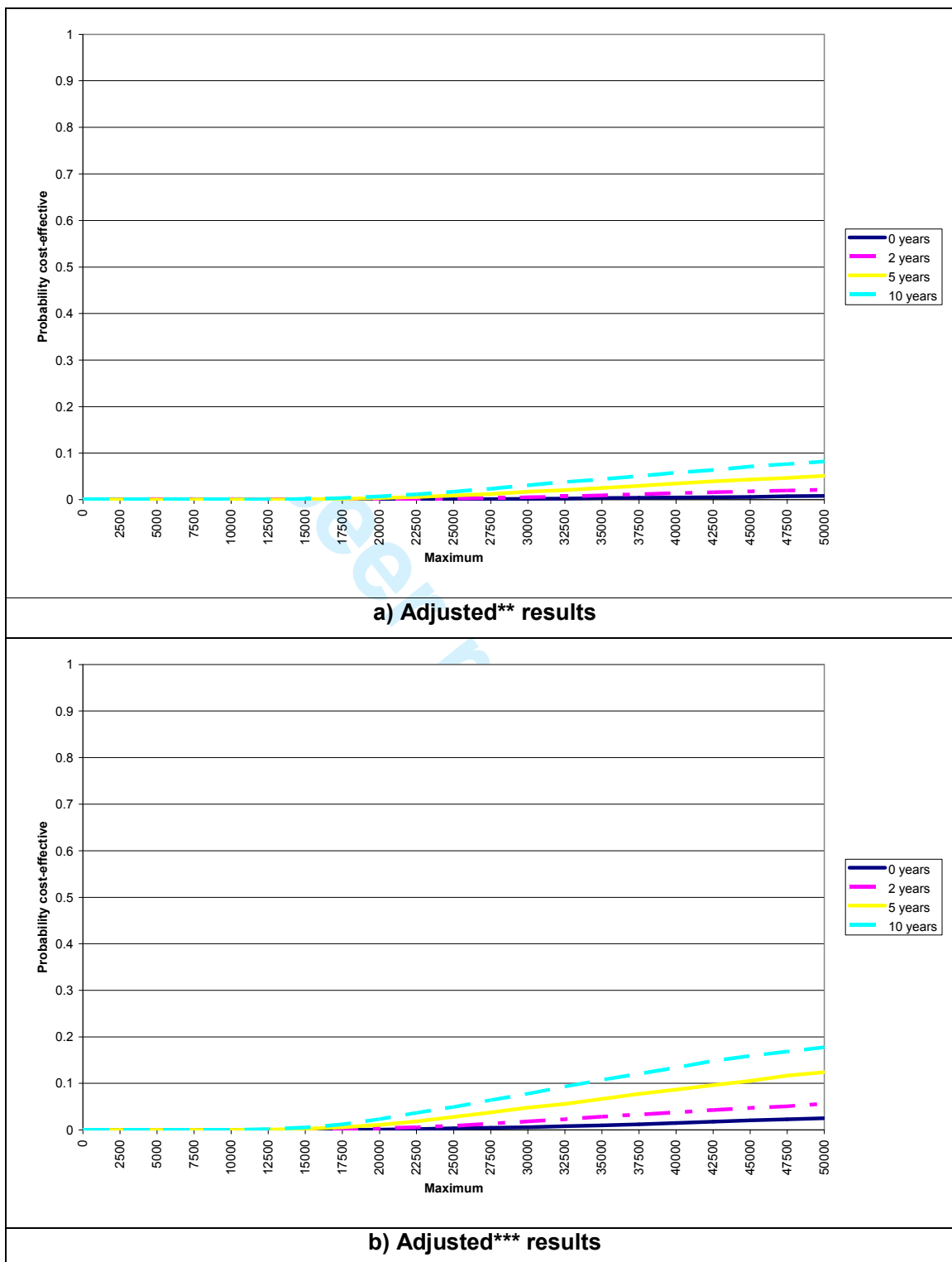
SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

* 1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

‡ Adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.

Figure A1: Adjusted cost-effectiveness results



** Adjusted for differences between groups by age and gender

*** Adjusted for differences between groups by age, gender and country

Additional References for Appendix

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Cost-effectiveness of a European preventive cardiology programme in primary care: a Markov modelling approach

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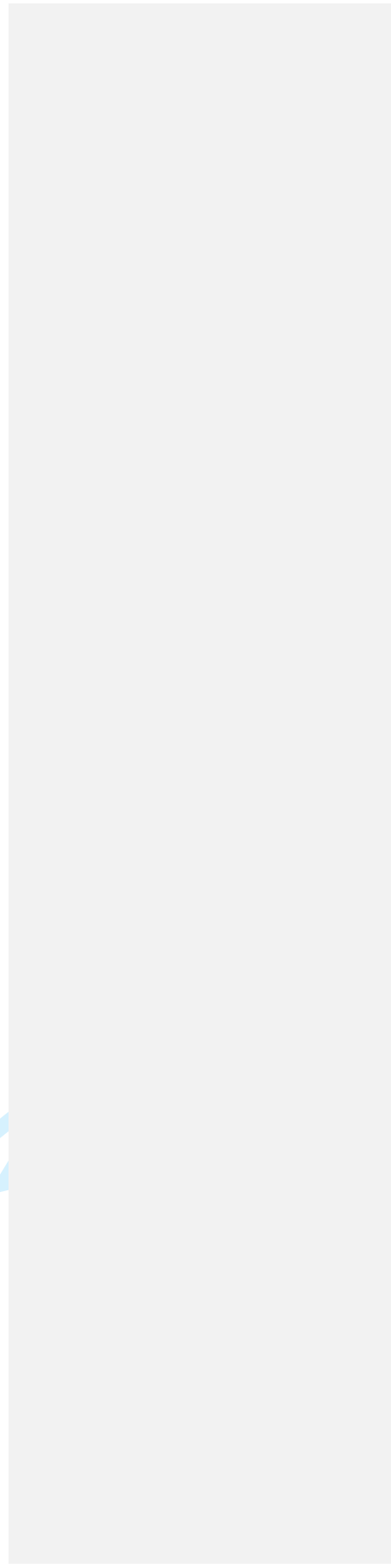
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6 **Abstract (word count 3096)**
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10 **Objective:** To investigate the longer-term cost-effectiveness of a nurse-coordinated
11 preventive cardiology programme for primary prevention of cardiovascular disease
12 compared to routine practice from a health service perspective.
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17 **Design:** A matched, paired cluster-randomised controlled trial.
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20 **Setting:** Six pairs of general practices in six countries.
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24 **Participants:** 1,019 patients were randomised to the EUROACTION intervention
25 programme and 1,005 patients to usual care and who completed the one-year follow-up-
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29 **Outcome measures:** Evidence on health outcomes and costs were based on patient level
30 data from the study, which had a one-year follow-up period. Future risk of cardiovascular
31 (CVD) events was modelled, using published risk models based on patient characteristics.
32 An individual level Markov model for each patient was used to extrapolate beyond the end of
33 the trial, which was populated with data from published sources. We used an 11-year time
34 horizon and investigated the impact on cost-effectiveness of varying the duration of the
35 effect of the intervention beyond the end of the trial. Results are expressed as incremental
36 cost per quality-adjusted life year gained.
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45 **Results:** Unadjusted results found the intervention to be more costly and also more effective
46 than usual care. However, after adjusting for differences in age, gender, country and
47 baseline risk factors, the intervention was dominated by usual care, but this analysis was not
48 able to take into account of lifestyle changes in terms of diet and physical activity.
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6 **Conclusions:** Although the EUROACTION study achieved healthier lifestyle changes and
7 improvements in management of blood pressure and lipids for patients at high risk of CVD,
8 compared to usual care, it was not possible to show, using available risk equations which do
9 not incorporate diet and physical activity, that the intervention reduced longer-term
10 cardiovascular risk cost-effectively. Whether or not an intervention such as that offered by
11 EUROACTION is cost-effective requires a longer term trial with major cardiovascular events
12 as the outcome.
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Article summary

Article focus

- To investigate the longer-term cost-effectiveness of a nurse-coordinated preventive cardiology programme for primary prevention of cardiovascular disease compared to routine practice.

Key messages

- The EUROACTION study achieved healthier lifestyle changes and improvements in management of blood pressure and lipids for patients at high risk of CVD, compared to usual care.
- The unadjusted results of the cost-effectiveness analysis found the intervention to be more effective than usual care but also more costly. However, the adjusted results showed that the intervention was dominated by usual care.
- The published cardiovascular risk equations do not take account of lifestyle changes in terms of diet and physical activity and therefore may be inadequate for the evaluation of whether or not a lifestyle intervention to prevent cardiovascular disease is cost-effective.

Strengths and limitations of the study

- This is the first study assessing the cost-effectiveness of the EUROACTION programme.
- The available cardiovascular risk modelling is based on a limited number of risk factors, which do not include measures of diet or physical activity, and a healthier lifestyle was the most important outcome of the EUROACTION trial.

Trial Registration number: ISRCTN 71715857

Keywords: Multi-centre studies; cardiovascular prevention programme; cost-effectiveness; Markov model; QALYs.

Text word Count: 3,415064

Introduction

Evidence has shown that individuals with increased risk of cardiovascular disease (CVD) can reduce their risk of cardiovascular morbidity and mortality by stopping smoking, changing their diet, engaging in physical activity, achieving a healthy body weight, and controlling their blood pressure, cholesterol and diabetes.[1] However, not all patients at high risk of developing CVD manage to achieve these recommended lifestyle and risk factor goals and there remains considerable potential to reduce CVD risk in these patients.[2] The EUROACTION study was designed to address the need for preventive cardiology care in everyday clinical practice.[3]

The EUROACTION study was a matched, paired cluster-randomised controlled trial, across eight countries and 24 hospitals and general practices. The project evaluated the impact of a nurse-coordinated, multidisciplinary preventive cardiology programme for coronary patients in hospital and high risk individuals in general practice. It aimed to help all these high risk patients and their families to achieve recommended lifestyle and risk factor targets for CVD prevention in everyday clinical practice over one year. The principal results concluded that the EUROACTION programme achieved healthier lifestyle changes and improvements in risk factor management for patients with coronary heart disease (CHD) and those at high risk of CVD, together with their partners, compared to usual care.[4]

While there is evidence that the EUROACTION programme is effective in terms of modifying lifestyle and some CVD risk factors, there is no evidence as to its cost-effectiveness.

Therefore, this paper aims to model the long-term cost-effectiveness of the EUROACTION programme in comparison with usual care within the primary care setting.

Methods

Patients

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6 The EUROACTION primary care study took place in Denmark, Italy, Netherlands, Poland,
7 Spain and UK, where a matched pair of general practices was identified, and then
8 randomised to either the EUROACTION programme or to usual care (UC). GPs
9 prospectively identified the study population. The comparison was restricted to patients and
10 did not include partners. Eligibility criteria for patients has previously been published.[4]
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16 All intervention patients were assessed at baseline and one-year. These assessments
17 focussed on smoking habits, diet and physical activity, measurement of body mass index,
18 blood pressure, cholesterol and glucose levels, and cardiac medications were also recorded.
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20 The programme was delivered by specialist nurses, working with GPs, and supported by
21 software programmes (HEARTSCORE), educational materials and group workshops to
22 achieve individual goals. Each person was given a personal record card to record lifestyle
23 and risk factor goals, medications and appointments. To avoid the possibility that
24 undergoing baseline assessments might affect outcomes, only a random sub-sample
25 (~25%) of UC patients were seen at baseline and then all UC patients were invited for
26 assessment at one-year. In the UC arm, patients did not receive any form of special care.
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36 **Model structure**

37 We adopted a health service perspective to measure costs and outcomes. Each cycle in the
38 model is of one year's duration. All patients were CVD-free on entering the model. In each
39 subsequent cycle patients may remain CVD-event free, they may have a fatal or non-fatal
40 CVD event, or they may die from non-CVD causes. Once the patient has had an initial CVD
41 event, then in subsequent cycles they move to the post CVD-event states and they may
42 move between different CVD states and/or die from CVD or non-CVD causes.
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50 The CVD event states are: non-fatal myocardial infarction (MI), stable angina, unstable
51 angina, CHD death, transient ischaemic attack (TIA), stroke, CVD death and non-CVD
52 death.
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Measuring initial CVD risk

To estimate the risk of an initial CVD event in a subsequent year we used the D'Agostino et al [5] CVD risk function, derived from the Framingham Heart Study. This calculates individual sex-specific risks for future cardiovascular events (in patients initially free of CVD). These CVD risk equations incorporate as risk factors the natural logarithms of age, total and HDL cholesterol, systolic blood pressure (SBP) if treated with or without anti-hypertensive medications, smoking and diabetes. We used the published calibration factors to focus on the CHD and stroke event states.

Ten-year risks were estimated from the equations and adjusted to one-year values.[6] One-year CVD risk beyond the end of the trial was calculated based on both a) baseline patient characteristics (adjusted for age) for intervention patients only; and b) one-year follow-up characteristics for both groups, in order to evaluate any changes to CVD risk factors as a result of the EUROACTION programme.

Validating the appropriateness of the risk functions of the model

We tested the validity of applying the D'Agostino et al [5] risk equations to the study population, by comparing the observed number of CHD cases with the number predicted at one-year. Because stroke and TIA incidence data was not collected in the study we converted the CVD risk equations to CHD risks using the recommended calibration factors.[5] We present the results of the comparison for both groups.

Transition probabilities

We disaggregated the overall risk of a CVD event into rates for specific events by age and gender, using UK relative incidence rates based on published literature [7-9] and expert opinion, as previously used in Ward et al [10]. These event rates were applied to individual annual CVD risks to calculate individual transition probabilities for moving from the CVD-free

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6 state to the initial CVD-event states. Also, individual patients could die from non-vascular
7 causes, depending on their age and gender. The non-CVD death transition probabilities
8 were taken from Briggs et al.[11] Transition probabilities for moving from primary event
9 health states to subsequent non-fatal health states are taken from Ward et al.[10]
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13 14 15 **Measuring cost**

16 Data on resources used during the trial and staff contacts were recorded in case record
17 forms and then converted into electronic format. To determine the total one-year costs for
18 each group, we obtained unit costs for all relevant items of resources used in the trial:
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24 *1. Costs relating to EUROACTION programme and other contacts in primary care* were
25 obtained from the programme facilitators and included the EUROACTION nurses costs,
26 training costs, production of patient educational materials and any other costs
27 associated with implementing the programme. The average time spent by staff for all
28 patient contacts at baseline and one-year was provided by each centre. Hourly wage
29 rates of the staff salaries and training were calculated and then applied to these various
30 patient contacts. We costed the EUROACTION family information packs, a pocket-
31 sized personal record card, questionnaires and group sessions that each patient in the
32 intervention group received as part of their prevention programme.
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41 Costs were applied to other contacts with health care professionals, such as GPs,
42 outside of the intervention programme for both arms and these costs were based on
43 national estimates of the staff salaries involved and estimates of the average time spent
44 with the patient provided by the trial co-ordinators.
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50 *2. Cardiac-related drug costs.* Data was collected on patient-specific cardiac-related
51 medications including the drug name and dose at baseline and one-year. This gave
52 point of time information, but no start or end dates. So for each patient it was assumed
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6 that they would remain on the same medication at a constant dose for the entire
7 duration e.g. from baseline to one-year. National cost estimates for the drugs were
8 provided by trial co-ordinators from each country and were applied accordingly to the
9 relevant dose and length of time on a patient-specific basis.
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15 *3. Cardiac-related procedures and tests.* During the trial, patients within both groups
16 may have required inpatient or outpatient admissions for cardiac-related procedures, or
17 undertaken any cardiac-related tests. The procedures were costed according to HRG
18 episodes for each country and the other tests or bed days as simple unit costs.
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20 National unit cost estimates for cardiac-related procedures and tests for each country
21 were obtained from a database held by United BioSource Corporation (Erwin De Cock,
22 personal communication, May 2007) for all countries, except Denmark and Poland. For
23 these two countries, national unit cost estimates were provided from contacts within the
24 Centre for Applied Health Services Research and Technology in Denmark (Jan
25 Sørensen, personal communication, January 2007) and from the Ministry of Health in
26 Poland (Andrzej Pająk, personal communication, June 2007).
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36 As the study was based in six countries, a costing algorithm was developed to calculate a
37 total cost per patient for each country. The costs of the programme were valued in local
38 currencies and then converted to 2006/2007 £ (GBP) using purchasing power parities.[12]
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41 Table 1 presents the total one-year costs by group and country. Figure 1a shows that the 1-
42 year observed costs (split by type of cost) for the intervention group was significantly more
43 than the usual care group for all countries. This higher cost was explained by the
44 EUROACTION intervention programme costs and contacts with EUROACTION staff, whilst
45 neither arms experienced significantly high cost cardiac interventions or cardiac medications.
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52 Subsequent costs relating to health states occupied within the model were based on UK
53 estimates (see Appendix). It was assumed that patients in a CVD-free state would continue
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6 to receive the cardiac-related medications and primary care contacts (outside of the
7 intervention programme) that they received during the trial. The mean cost of these
8 medications and contacts for all patients across both arms was applied to each individual
9 patient within the model who remained in the event-free health state for subsequent years.
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13 14 15 **Health state utilities**

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17 To estimate quality-adjusted life years (QALYs) the model requires utility values for each
18 state adjusted by age. For patients who were event-free, the utility values were based on
19 UK general population norms [13]; utilities for events/states were taken from Ward et al [10]
20 which were all were based on UK studies and were obtained using the EQ-5D (see
21 Appendix).
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25 26 27 **Measuring the impact of the intervention**

28
29 The study provided results only for a one-year follow-up. We estimated results for a range of
30 possible durations of effect, assuming that the CVD risk reduction experienced by the
31 intervention patients persisted for 0 through to 10 additional years (11-year time horizon),
32 after which they reverted to their individual CVD risk factor levels at the start of the study
33 (adjusted for age). For UC patients, it was assumed that patients would remain at their one-
34 year CVD risk (adjusted annually by age) throughout the model.
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41 42 **Measuring cost-effectiveness**

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44 Using the Markov model we calculated for each patient their expected quality-adjusted
45 survival (based on their likelihood of surviving each cycle and their expected health state
46 utility value) and their expected costs. Cost-effectiveness was measured in terms of the
47 incremental cost per QALY gained (ICER). Future costs and benefits were discounted at
48 3.5%. [14]
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53 54 **Statistical analyses**

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6 All statistical analyses were performed in Stata version 10 [15] or Microsoft Excel and a p-
7 value ≤ 0.05 was considered to be statistically significant. We present unadjusted and
8 adjusted cost-effectiveness results. The adjusted results controlled for group allocation, age,
9 gender, age*gender interactions, country, and baseline risk factors using OLS regressions.
10 As only a random sub-sample of UC patients were seen at baseline, regression analyses
11 were used to predict baseline values for those patients who had missing values. For total
12 and HDL cholesterol and SBP, OLS regression was used to predict values in those patients
13 with missing values, as a function of age, gender and country. For the three binary variables
14 (medications, smoking and diabetes), logistic regression models were used to predict the
15 probability of each binary outcome. Predicted values ≥ 0.5 were categorised to a value of 1
16 and values < 0.5 were categorised as 0. In the adjusted models we also included an
17 indicator for whether or not each control variable was missing.
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29 ~~Bootstrapping was undertaken on both unadjusted and adjusted costs and effects using~~
30 ~~10,000 replications to provide 95% confidence intervals around the mean. Probabilistic~~
31 ~~sensitivity analyses were conducted to obtain cost-effectiveness acceptability curves~~
32 ~~(CEACs).~~
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34 We represented uncertainty due to sampling variation in both the unadjusted and adjusted
35 cost-effectiveness ratios using non-parametric bootstrapping. In the unadjusted analyses we
36 sampled individuals in our model with replacement and used their costs and outcomes over
37 the 11-year period to compute replications of the incremental cost per QALY gained. We
38 repeated this approach in the adjusted analyses, also adding the regressions to control for
39 confounding factors. In each case, we generated 10,000 bootstrap replications of the cost-
40 effectiveness ratios and used these to construct 95% confidence intervals around the point
41 estimate of cost-effectiveness.
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51 **Sensitivity analysis**

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6 The main analysis modelling was limited to ten years, in the absence of robust longer-term
7 risk models. As a sensitivity analysis, we used a simplified longer-term model to check
8 whether the conclusions of the main analysis would have been likely to be different if a
9 longer-term perspective had been adopted e.g. 25 years. This model essentially assumed
10 no further effect of the intervention but modelled out fully the possible QALY gains from the
11 medium-term (11 year) differences in mortality and event rates.
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18 Results

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20 The baseline characteristics for the intervention group as a whole and the usual care
21 subsample who were seen at baseline are shown in Table 2. There were significant
22 differences in the distribution between countries. Mean total and HDL cholesterol levels
23 were significantly higher for the intervention compared with the UC group. Whilst no
24 statistically significant differences were observed for other baseline characteristics, but the
25 10-year CVD risk at baseline [5] was numerically higher for the UC group than the
26 intervention arm.
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34 We modelled 1,019 patients in the intervention arm and 1,005 patients in the UC arm who
35 were assessed at one-year.[4] The intervention group had fewer males than the UC group:
36 49.8% vs. 57.4% male ($p=0.001$), and was significantly younger (mean age at one-year:
37 intervention: 61.5 years vs. usual care: 62.3 years, $p=0.011$).
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43 When testing the validity of the Framingham risk equations to the study population we found
44 that 8 intervention patients and 1 UC sub-sample patient experienced a CHD-event. The
45 risk equations produced a close match, predicting 8.5 patients with a first CHD-event in the
46 intervention group and 2.0 in the UC sub-sample.
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52 Figure 1b further emphasises that the observed additional costs of the EUROACTION
53 intervention programme and staff costs were not offset by the estimated reduced costs of
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6 cardiac interventions in the subsequent years. In terms of the unadjusted results, the
7 incremental costs of the intervention are £362-£419 depending on the duration of the effect
8 of the intervention and the incremental QALYs are 0.076-0.085 (see Table 32). As
9 expected, the incremental costs fall and the incremental QALYs rise as the duration of the
10 effect of the intervention beyond the end of the trial increases. The incremental cost per
11 QALY gained range from £5,539 (95% CI £2,625-£29,627) to £4,266 (95% CI £2,059-
12 £15,945). The unadjusted CEACs under each scenario are in Figure 24a and highlights the
13 results in Table 32 that in all scenarios over 95% of the bootstrapped replications are less
14 than £20,000.

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24 After controlling for differences in age, gender, country and baseline risk factors, the
25 intervention is associated with higher costs and lower QALYs than the UC arm in every
26 scenario (an example of the various regression models is shown in the Appendix). As a
27 result, the intervention is dominated by UC. Although there is considerable uncertainty
28 around those point estimates with the 95% confidence intervals ranging from acceptably
29 cost-effective to highly dominated, but the probability of being cost-effective are very low, as
30 shown in ~~T~~the adjusted CEACs are in Figure 4b-2b (additional adjusted CEACs, controlling
31 for age, gender and country only are in the Appendix). At a cost-effectiveness threshold of
32 £20,000 the EUROACTION intervention will be cost-effective in under 6% of cases.

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41 Due to baseline differences, we conducted age-sex matched subgroup analyses and the
42 adjusted results confirmed that the intervention remained dominated, even when an
43 optimistic timeframe was considered (an example of age-sex matched subgroup analysis is
44 shown in the Appendix).

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50 The sensitivity analysis produced predictable results that in no way changed the conclusions
51 of the analysis. Using the unadjusted data, the cost-effectiveness of the intervention was

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6 further enhanced, and using the adjusted data the domination of UC over the intervention
7
8 remained.

11 Discussion

13 Although this large European trial demonstrated that a nurse-coordinated preventive
14 cardiology programme in primary care helped more high risk patients to achieve the lifestyle
15 and risk factor targets in comparison with UC this does not appear to be cost-effective.
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18 However, these cost-effectiveness analyses require careful qualification because they are
19 subject to a number of uncertainties which are a consequence of the study design and
20 important limitations in the statistical model used.
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25 The differences in the adjusted and unadjusted results emphasise that the study design,
26 based on matching pairs of general practices in each country, did not eliminate baseline
27 differences between the two groups in cardiovascular risk factors. These differences meant
28 that the two groups had different levels of baseline risk, higher in intervention than usual
29 care, but the economic results have adjusted for these baseline differences. Though these
30 differences were small in absolute terms they have a substantial effect on the estimates of
31 absolute risk of future cardiovascular events, and therefore on the difference in effectiveness
32 between intervention and UC. Additionally, the study recorded its primary endpoints at
33 baseline and one-year, and to avoid 'contamination' by recording risk factor levels in UC,
34 baseline measurements were only made in a sub-sample of UC patients. Thus, we do not
35 have before and after measurements for 75% of the UC patients.
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47 Our cost-effectiveness analysis did not include partners. If partners were included it might
48 improve the cost-effectiveness, but we have no good measure of the effect on partners to
49 know how substantial the impact on the incremental cost-effectiveness ratio might be.
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6 Our estimates of the risk of future CVD-events are based on published risk equations.[5]
7 These are derived from a large, well characterised cohort (8491 participants) and predict
8 CVD risk as opposed to CHD risk alone. The C statistic for the model ranges from 0.76
9 (men) to 0.79 (women) suggesting that additional risk factors could potentially improve the
10 model's discriminatory power. Other risk models have included risk factors such as family
11 history of CVD, social deprivation and biomarkers e.g. hs-CRP [16-17] although these
12 models also have their own limitations.
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20 However, to date lifestyle factors such as dietary habits and physical inactivity although
21 important in the aetiology of CHD [18] and independent of the other major risk factors, have
22 not been included in such risk scores, because they are difficult to accurately quantify. The
23 omission of these important lifestyle factors in the Framingham risk equations may be
24 particularly relevant in our study as the cornerstone of the EUROACTION programme was
25 lifestyle change which was clearly evident in the study's most striking achievements in this
26 area including significantly higher fruit and vegetable consumption ($p = 0.005$); physical
27 activity levels ($p = 0.01$); and weight loss ($p = 0.005$).
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36 It is thus possible that our estimates of relative differences in absolute risk between the
37 groups may understate the full effects of the intervention on long-term CVD risk. However,
38 we showed that the risk equations are able to predict CHD events in the study population in
39 the one-year follow-up period, but the accuracy of the risk equations over the ten-year period
40 of our study remains untested.
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46 Our modelling also requires an assumption about how long any differential effect of the
47 intervention persists. Nothing is known about the longer-term effects of EUROACTION, and
48 there are few studies that have looked at longer-term changes. The longest follow-up to a
49 relevant life-style change appears to be the OXCHECK study which showed that the benefits
50 of health checks were sustained over three years.[19-20] However, whatever the duration
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6 of effect beyond the trial, and even when a 25-year model was used, the policy conclusions
7 remain the same.
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11 Finally, our model uses a regression analysis approach so that a UK specific estimate can
12 be drawn from the complete multinational EUROACTION dataset on net resource use, costs
13 and net effects of the intervention. The epidemiological, utilities and cost data for the longer-
14 term modelling of risk and events is based on UK data alone. Thus, the results are
15 applicable to the UK and not specifically to the other EUROACTION countries. Whilst formal
16 analysis would be needed to confirm this, the coefficients on the country parameters in the
17 regression analyses of both costs and outcomes suggest that the cost-effectiveness would
18 be broadly similar in the other countries.
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27 **Conclusion**

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29 Although the EUROACTION study demonstrated in high risk patients in primary care
30 significant improvements in lifestyle and CVD risk factors, it is not possible to show, using
31 the best available risk equations, that the intervention was cost-effective. The available risk
32 modelling is based on a limited number of risk factors, which do not include diet or physical
33 activity, and a healthier lifestyle was the most important outcome of this trial. Therefore,
34 whether or not an intervention such as that offered by EUROACTION is cost-effective
35 remains an open question that could be answered by a longer-term trial with major adverse
36 cardiovascular events as the primary endpoint.
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Acknowledgements

EUROACTION Steering Group

A scientific steering group approved the protocol and the design for this matched pair cluster-randomised controlled trial, and is responsible for the scientific integrity of the study.

The steering group has the following membership: D Wood (London, UK, Chairman), G De Backer (Ghent, Belgium), D De Bacquer (Ghent, Belgium), M Buxton (Uxbridge, UK), I Graham (Dublin, Ireland), A Howard (Nice, France), K Kotseva (London, UK), S Logstrup (Brussels, Belgium), H McGee (Dublin, Ireland), M Mioulet (Nice, France), K Smith (Dundee, UK), D Thompson (York, UK), T Thomsen (Glostrup, Denmark), T van der Weijden (Maastricht, the Netherlands).

National co-ordinators

The national co-ordinators for each country are also members of the steering committee.

They are responsible for identifying and recruiting general practices, obtaining ethics committee approval, appointing and supervising staff in the centres and contributing scientifically to the publication of results. The EUROACTION National Co-ordinators and Primary care leaders are as follows:

Denmark: T Thomsen, K Brockelmann; Italy: P Fioretti, A Desideri, S Brusaferrò; Poland: A Pajak, K. Kawecka-Jaszcz, P Jankowski, T Grodzicki; Spain: J De Velasco, A Maiques; Netherlands: T van der Weijden; United Kingdom: D Wood, J Morrell.

Co-ordinating and Data Management Centre

The Co-ordinating and Data Management Centre is the Department of Cardiovascular Medicine, National Heart and Lung Institute at Charing Cross Campus, Imperial College, London, UK (Head Professor David Wood). The following staff have specific responsibilities as described: K Kotseva, Senior Clinical Research Fellow; S Connolly, Research Fellow; C Jennings, Study Nurse Co-ordinator; A Mead, Chief Dietician; J Jones, Superintendent

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6 Physiotherapist; A Holden, Physical activity Co-ordinator; T Collier, Statistician; M Alston, D
7 Charlesworth, P Homewood, K Pandya, M Somaia, IT specialists/Data managers; S Graves,
8 Research Administrator; W Leacock, D Xenikaki, Administrative Assistants. The following
9 experts advised the Co-ordinating Centre on dietary and physical activity assessment:
10
11 Professor Gary Frost, Professor Barry Margetts, Dr Mike Nelson and Dr Charlie Foster.
12
13
14

15 16 17 *Central Laboratory*

18 Central Laboratory analysis of total cholesterol, HDL cholesterol, triglycerides, glucose and
19 HbA1c are undertaken by A McLelland, R Birrell and G Beastall in the Department of
20 Pathological Biochemistry, Royal Infirmary, Glasgow (Head of Department J Shepherd).
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23

24 25 26 *Statistical Centres*

27 The statistical analyses for the primary endpoints were undertaken by D De Bacquer,
28 Statistician, from the Department of Public Health (Head of Department G De Backer),
29 Ghent University, Belgium, and supplementary analyses by T Collier, Statistician,
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31 University of London, UK.
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43 Economics, Brunel University.
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25 Usual Care Centre: Dr Mieke Winten-Huisman and Dr Marc Eyck, GPs; Rene van den
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38 Helena Kamińska, Nurses.
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48 Investigator; Gemma Méndez Pérez, Nurse; Dr. Maria Jose Donat, Dr. Raquel Prieto, Dr.
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6 Usual Care Centre: Centro de Salud de Manises, Valencia. Dr Lorenzo Pascual, Principal
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15 Investigator; Sjouke Ashton, Nurse; George Bordoli, Associate Nurse; Daniel Brookbank and
16 Angela Hughes, Practice Managers.
17
18

19 Usual Care Centre: Green Street Clinic, Eastbourne. Dr Ian McNaughton, Principal
20 Investigator; Shirley Colvin, Nurse; Heather King, Practice Manager.
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24
25 *Acknowledgement:* EUROACTION is an initiative of the European Society of Cardiology
26 which highlights its commitment to improve the quality of life of the European population by
27 reducing the impact of cardiovascular diseases. The study protocol conforms to the ethical
28 guidelines of the 1995 Declaration of Helsinki with ethics committee approval in all countries
29 and for every centre. Written informed consent was obtained from every subject.
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33 *Competing interest statement:* All authors declare that the answer to the questions on your
34 competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore
35 have nothing to declare.
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38
39 *Funding:* Sponsored solely by AstraZeneca through the provision of an unconditional
40 educational grant. [AstraZeneca had no involvement in the study design; in the collection,](#)
41 [analysis and interpretation of the data; in the writing of the report; and in the decision to](#)
42 [submit the paper for publication.](#)
43
44

45 *Author contributions:* DW and MB are part of the steering committee and approved the
46 protocol and the design for this matched paired cluster-randomised trial. DW was
47 responsible for the overall direction of the project. HM and MD conducted the economic
48 analysis under the supervision of SM and MB and with guidance from DW. KK was
49 responsible for local data collection. HM drafted the manuscript with input from all authors;
50 all authors have approved the final manuscript and were involved in the interpretation of the
51 results.
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Table 1: Observed 1-year costs for EUROACTION study (in £ GBP)

2006/2007 prices	Denmark	Italy	Netherlands	Poland	Spain	UK	Total
Intervention							
N	104	165	191	234	199	126	1,019
Mean (SD)	£589 (£379)	£595 (£366)	£756 (£466)	£515 (£179)	£588 (£269)	£625 (£181)	£608 (£329)
Median	£541	£562	£704	£463	£550	£594	£560
IQR	£473 to £614	£451 to £680	£546 to £862	£374 to £616	£420 to £714	£530 to £729	£449 to £714
Range	£268 to £4,054	£179 to £3,733	£166 to £5,064	£282 to £1,578	£139 to £1,669	£163 to £1,206	£139 to £5,064
Usual Care							
N	154	194	123	160	193	181	1,005
Mean (SD)	£295 (£490)	£201 (£365)	£246 (£307)	£159 (£167)	£138 (£207)	£307 (£563)	£221 (£384)
Median	£193	£146	£125	£105	£68	£196	£142
IQR	£152 to £275	£104 to £198	£84 to £250	£84 to £159	£56 to £122	£140 to £303	£90 to £225
Range	£98 to £3,364	£70 to £4,455	£65 to £2,806	£60 to £1,255	£40 to £2,173	£73 to £6,500	£40 to £6,500

Table 2: Baseline characteristics

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	<u>Intervention</u> (n = 1,019)	<u>Usual care</u> subsample (n = 252)	<u>Usual care</u> all (n = 1,005)	<u>Statistical test[#]</u> (Int. vs. UC subsample)	<u>Statistical test[#]</u> (Int. vs. UC all)
<u>Country</u>					
<u>Denmark</u>	<u>104 (10.2%)</u>	<u>40 (15.9%)</u>	<u>154 (15.3%)</u>		
<u>Italy</u>	<u>165 (16.2%)</u>	<u>47 (18.7%)</u>	<u>194 (19.3%)</u>	<u>p = 0.012</u>	<u>p < 0.001</u>
<u>Netherlands</u>	<u>191 (18.7%)</u>	<u>37 (14.7%)</u>	<u>123 (12.2%)</u>		
<u>Poland</u>	<u>234 (23.0%)</u>	<u>45 (17.9%)</u>	<u>160 (15.9%)</u>		
<u>Spain</u>	<u>199 (19.5%)</u>	<u>41 (16.3%)</u>	<u>193 (19.2%)</u>		
<u>UK</u>	<u>126 (12.4%)</u>	<u>42 (16.7%)</u>	<u>181 (18.0%)</u>		
<u>Gender</u>					
<u>Male</u>	<u>507 (49.8%)</u>	<u>133 (52.8%)</u>	<u>577 (57.4%)</u>	<u>p = 0.390</u>	<u>p = 0.001</u>
<u>Female</u>	<u>512 (50.3%)</u>	<u>119 (47.2%)</u>	<u>428 (42.6%)</u>		
<u>Risk factors required for the</u> <u>D'Agostino Equation [5]</u> <u>n (%)</u>					
<u>Non-smoker</u>	<u>695 (68.2%)</u>	<u>155 (61.5%)</u>	<u>-</u>	<u>p = 0.646</u>	<u>-</u>
<u>Has diabetes</u>	<u>313 (30.7%)</u>	<u>68 (27.0%)</u>	<u>-</u>	<u>p = 0.247</u>	<u>-</u>
<u>On anti-hypertensive drugs</u>	<u>432 (42.4%)</u>	<u>97 (38.5%)</u>	<u>-</u>	<u>p = 0.260</u>	<u>-</u>
<u>Mean (SD)</u>					
<u>Age</u>	<u>60.5 (7.6)</u>	<u>60.4 (7.3)</u>	<u>61.3 (7.3)</u>	<u>p = 0.915</u>	<u>p = 0.011</u>
<u>Systolic blood pressure (mm HG)</u>	<u>141.1 (18.6)</u>	<u>141.6 (18.9)</u>	<u>-</u>	<u>p = 0.693</u>	<u>-</u>
<u>Total cholesterol (mmol/L)</u>	<u>5.70 (1.02)</u>	<u>5.45 (0.99)</u>	<u>-</u>	<u>p = 0.001</u>	<u>-</u>
<u>HDL cholesterol (mmol/L)</u>	<u>1.40 (0.39)</u>	<u>1.35 (0.36)</u>	<u>-</u>	<u>p = 0.047</u>	<u>-</u>
<u>10-year CVD risk at baseline</u>	<u>0.115</u> <u>(0.087)</u>	<u>0.120</u> <u>(0.093)</u>	<u>-</u>	<u>p = 0.426</u>	<u>-</u>

[#] Chi-squared tests conducted for categorical variables and t tests conducted for continuous variables

Table 32: Results from cost-effectiveness model

	Duration of effect of intervention beyond the end of the trial (model time horizon = 11 th years in all cases)			
	0 years	2 years	5 years	10 years
Unadjusted costs and QALYs				
Usual care mean cost (SD)	£2,727 (£29)	£2,727 (£29)	£2,727 (£29)	£2,727 (£29)
Intervention mean cost (SD)	£3,146 (£33)	£3,126 (£31)	£3,105 (£31)	£3,089 (£31)
Usual care mean QALYs (SD)	6.755 (0.021)	6.755 (0.021)	6.755 (0.021)	6.755 (0.021)
Intervention mean QALYs (SD)	6.831 (0.021)	6.835 (0.021)	6.838 (0.021)	6.840 (0.021)
Incremental costs (95% CI)	£419 (£332 to £505)	£399 (£315 to £483)	£378 (£294 to £462)	£362 (£278 to £447)
Incremental QALYs (95% CI)	0.076 (0.017 to 0.135)	0.079 (0.020 to 0.138)	0.083 (0.024 to 0.142)	0.085 (0.026 to 0.144)
ICER	£5,539	£5,031	£4,561	£4,266
95% CI	£2,625 to £29,627	£2,412 to £22,520	£2,202 to £18,155	£2,059 to £15,945
% of bootstrapped ICERs < £20k	95.7%	97.0%	97.9%	98.4%
% of bootstrapped ICERs < £30k	97.6%	98.4%	99.0%	99.2%
Adjusted costs and QALYs†				
Incremental costs (95% CI)	£474 (£368 to £580)	£463 (£358 to £568)	£450 (£343 to £557)	£441 (£331 to £550)
Incremental QALYs (95% CI)	-0.009 (-0.041 to 0.023)	-0.007 (-0.038 to 0.025)	-0.005 (-0.036 to 0.027)	-0.003 (-0.035 to 0.029)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£21,695 to dominated†	£18,495 to dominated†	£15,908 to dominated†	£14,485 to dominated†

% of bootstrapped ICERs <£20k	1.97%	3.16%	4.57%	5.76%
% of bootstrapped ICERs <£30k	5.05%	6.98%	9.42%	11.54%

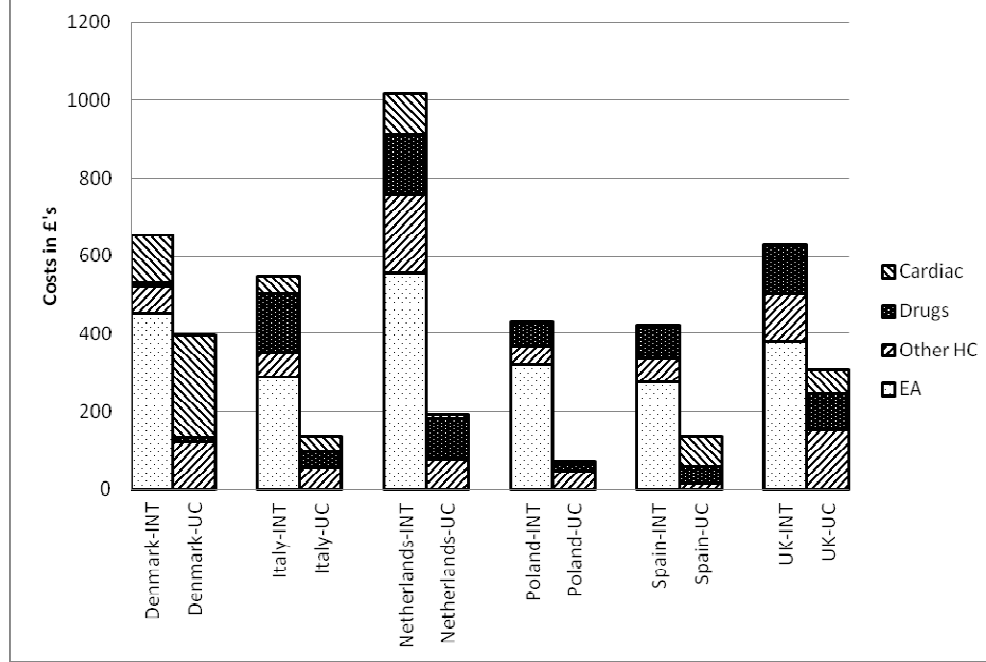
SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

[#] 1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

‡ Adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.

Figure 1a: One-year observed costs for the Intervention and Usual Care groups split by type



Key: EA = EuroAction costs; Other HC = other health care costs; Drugs = cardiac related medication costs; Cardiac = cardiac procedure costs

Figure 1b: Mean costs for the Intervention and Usual Care groups for the main health states in the Markov model

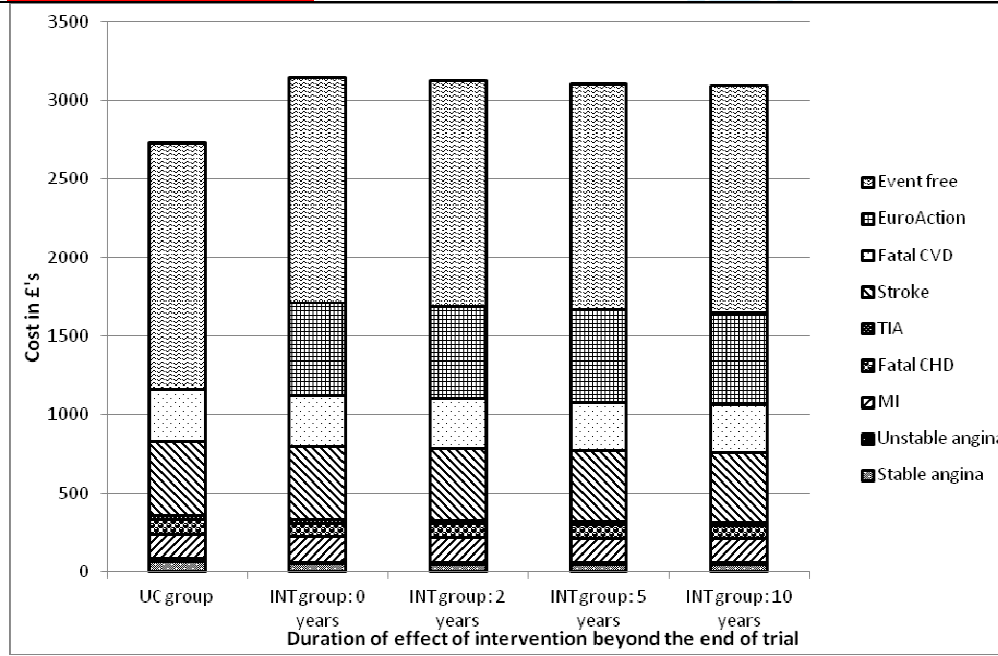
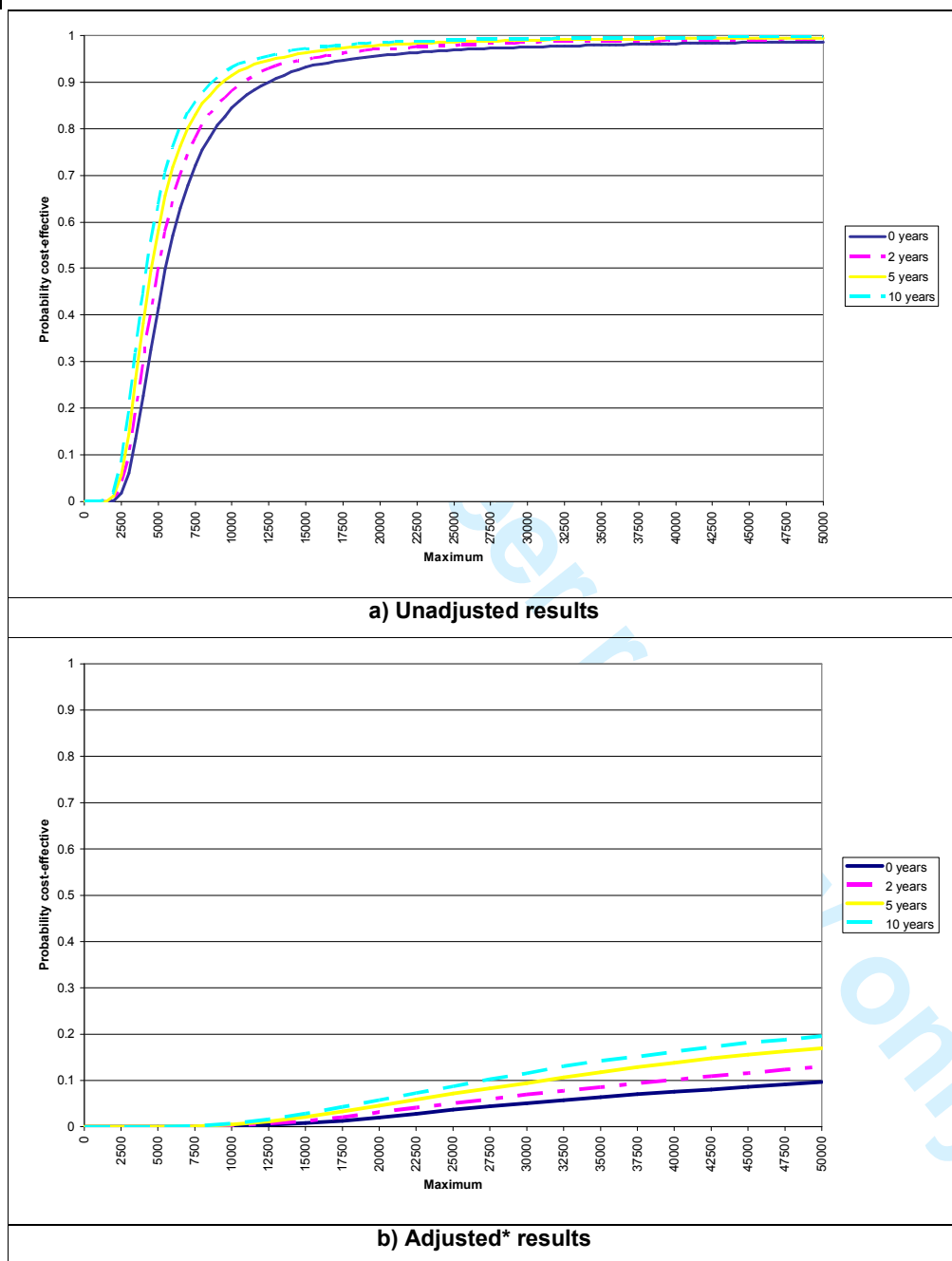


Figure 24: Cost-effectiveness acceptability curves



* Adjusted for differences between groups by age, gender, country and baseline risk factors

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Appendix

Table A1: Costs of health states in cost-effectiveness model

Health State	Cost (2006 prices)	Assumption/Source	Source
Event-Free	£197	Based on a mean cost of cardiac-related medication and health care contacts (outside of EUROACTION programme) incurred by all patients during one year follow-up	Trial data
Stable Angina	£383	Based on 3 times 15 minutes' GP contact plus medication (plus cost of event-free)	Ward et al, 2007 [10]
Post-stable angina	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
Unstable angina	£674	Based on 3 times 15 minutes' GP contact plus medication plus 60% of patients are also prescribed clopidogrel (plus cost of event-free)	Ward et al, 2007 [10]
Post-unstable angina	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
MI	£5,020	Based on data from Nottingham Heart Attack Register include revascularisation for a proportion of patients, plus primary care and medication costs as unstable angina (plus cost of event-free)	Palmer et al, 2002 [21]
Post-MI	£383	Based on 3 times 15 minutes' GP contact plus medication costs (plus cost of event-free)	Ward et al, 2007 [10]
Fatal CHD event	£1,462	Based on costs of a fatal MI (plus cost of event-free)	Clarke et al, 2003 [22]
TIA	£1,351	Based on medication costs plus costs of test and surgery for appropriate patients (plus cost of event-free)	Ward et al, 2007 [10]
Post-TIA	£483	Based on medication costs only (plus cost of event-free)	Ward et al, 2007 [10]

Stroke	£8,922	Based on cost of acute events (mild, moderate and severe stroke) and weighted by distribution of severity of strokes (plus cost of event-free)	Youman et al, 2003 [23]
Post-Stroke	£2,543	Based on cost of acute events (mild, moderate and severe stroke) and weighted by distribution of severity of strokes (plus cost of event-free)	Youman et al, 2003 [23]
Fatal CVD event	£7,832	Based on cost of fatal stroke (plus cost of event-free)	Youman et al, 2003 [23]

Table A2: Utility values for health states used in the model

Utility value	Event free	Stable angina	Unstable angina	MI	TIA	Stroke
45 - 49	0.869	0.702	0.669	0.660	0.869	0.547
50 - 54	0.848	0.685	0.653	0.644	0.848	0.533
55 - 59	0.826	0.667	0.636	0.628	0.826	0.520
60 - 64	0.805	0.650	0.620	0.612	0.805	0.506
65 - 69	0.784	0.633	0.604	0.596	0.784	0.493
70 - 74	0.763	0.617	0.588	0.580	0.763	0.480
75 - 79	0.741	0.599	0.571	0.563	0.741	0.466
80 - 84	0.720	0.582	0.544	0.547	0.720	0.453
85 - 89	0.699	0.565	0.538	0.531	0.699	0.440
90 - 94	0.678	0.548	0.522	0.515	0.678	0.426
95 - 99	0.656	0.530	0.505	0.499	0.656	0.413
100 +	0.635	0.513	0.489	0.483	0.635	0.399

Sources: Event free (Kind et al, 1998) [13]; Stable angina (Meslop et al, 2003) [24]; Unstable angina and MI (Goodacre et al, 2004) [25]; TIA (Kind et al, 1998) [13]; Stroke (Tengs et al, 2003) [26]

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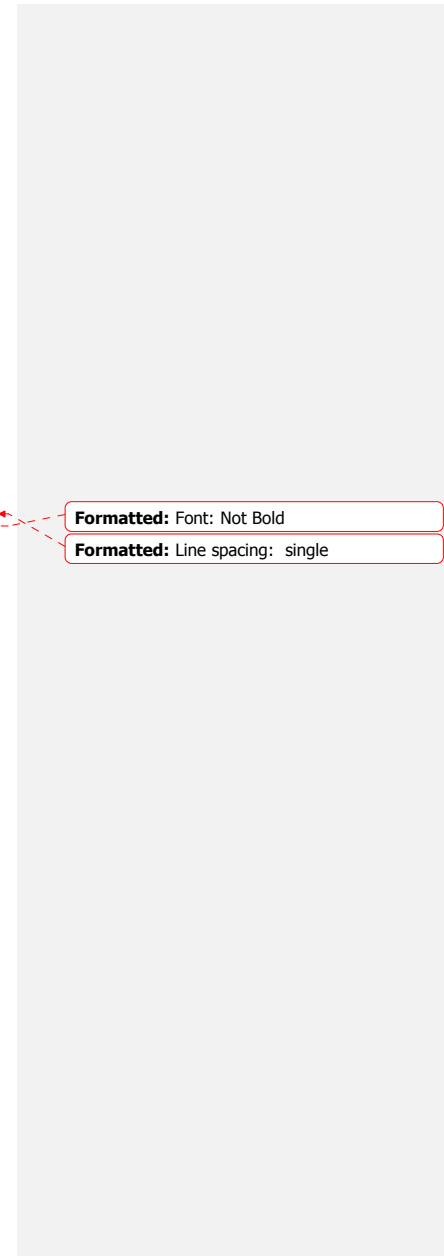
Table A3: Regression results from adjusted[#] cost-effectiveness analysis (Duration of effect of intervention beyond the end of the trial = 0 years)

	Costs				QALYs			
	<u>Coefficient</u>	<u>Standard error</u>	<u>t</u>	<u>p value</u>	<u>Coefficient</u>	<u>Standard error</u>	<u>t</u>	<u>p value</u>
<u>Group</u> (1 = intervention; 0 = UC)	<u>474.40</u>	<u>54.04</u>	<u>8.78</u>	<u>< 0.001</u>	<u>-0.009</u>	<u>0.016</u>	<u>-0.56</u>	<u>0.575</u>
<u>Gender</u>	<u>1544.10</u>	<u>273.27</u>	<u>5.65</u>	<u>< 0.001</u>	<u>-0.826</u>	<u>0.082</u>	<u>-10.09</u>	<u>< 0.001</u>
<u>Age</u>	<u>57.68</u>	<u>3.24</u>	<u>17.80</u>	<u>< 0.001</u>	<u>-0.090</u>	<u>0.001</u>	<u>-92.79</u>	<u>< 0.001</u>
<u>Gender*Age</u>	<u>-33.11</u>	<u>4.45</u>	<u>-7.44</u>	<u>< 0.001</u>	<u>0.017</u>	<u>0.001</u>	<u>13.12</u>	<u>< 0.001</u>
<u>Italy</u>	<u>106.34</u>	<u>58.58</u>	<u>1.82</u>	<u>0.070</u>	<u>-0.022</u>	<u>0.018</u>	<u>-1.26</u>	<u>0.206</u>
<u>Spain</u>	<u>89.71</u>	<u>60.31</u>	<u>1.49</u>	<u>0.137</u>	<u>-0.041</u>	<u>0.018</u>	<u>-2.26</u>	<u>0.024</u>
<u>Poland</u>	<u>32.58</u>	<u>58.81</u>	<u>0.55</u>	<u>0.580</u>	<u>-0.045</u>	<u>0.018</u>	<u>-2.56</u>	<u>0.010</u>
<u>Denmark</u>	<u>188.87</u>	<u>62.34</u>	<u>3.03</u>	<u>0.002</u>	<u>-0.063</u>	<u>0.019</u>	<u>-3.38</u>	<u>0.001</u>
<u>Netherlands</u>	<u>162.83</u>	<u>61.34</u>	<u>2.65</u>	<u>0.008</u>	<u>-0.058</u>	<u>0.018</u>	<u>-3.17</u>	<u>0.002</u>
<u>Total cholesterol</u>	<u>3.64</u>	<u>0.58</u>	<u>6.24</u>	<u>< 0.001</u>	<u>-0.001</u>	<u>0.000</u>	<u>-4.32</u>	<u>< 0.001</u>
<u>HDL cholesterol</u>	<u>-13.76</u>	<u>1.57</u>	<u>-8.77</u>	<u>< 0.001</u>	<u>0.002</u>	<u>0.000</u>	<u>4.29</u>	<u>< 0.001</u>
<u>Systolic blood pressure</u>	<u>13.38</u>	<u>1.20</u>	<u>11.19</u>	<u>< 0.001</u>	<u>-0.002</u>	<u>0.000</u>	<u>-4.70</u>	<u>< 0.001</u>
<u>Anti-hypertensive drugs</u>	<u>346.22</u>	<u>41.47</u>	<u>8.35</u>	<u>< 0.001</u>	<u>-0.051</u>	<u>0.012</u>	<u>-4.12</u>	<u>< 0.001</u>
<u>Diabetes</u>	<u>588.88</u>	<u>46.62</u>	<u>12.63</u>	<u>< 0.001</u>	<u>-0.116</u>	<u>0.014</u>	<u>-8.35</u>	<u>< 0.001</u>
<u>Smoking</u>	<u>392.41</u>	<u>43.48</u>	<u>9.02</u>	<u>< 0.001</u>	<u>-0.055</u>	<u>0.013</u>	<u>-4.20</u>	<u>< 0.001</u>

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<u>Total cholesterol*</u>	<u>-362.52</u>	<u>544.24</u>	<u>-0.67</u>	<u>0.505</u>	<u>0.037</u>	<u>0.163</u>	<u>0.22</u>	<u>0.823</u>
<u>HDL cholesterol*</u>	<u>238.80</u>	<u>536.53</u>	<u>0.45</u>	<u>0.656</u>	<u>0.023</u>	<u>0.161</u>	<u>0.15</u>	<u>0.884</u>
<u>Systolic blood pressure*</u>	<u>157.56</u>	<u>232.32</u>	<u>0.68</u>	<u>0.498</u>	<u>-0.066</u>	<u>0.070</u>	<u>-0.94</u>	<u>0.346</u>
<u>Anti-hypertensive drugs*</u>	<u>230.88</u>	<u>143.30</u>	<u>1.61</u>	<u>0.107</u>	<u>-0.046</u>	<u>0.043</u>	<u>-1.07</u>	<u>0.284</u>
<u>Smoking*</u>	<u>-302.10</u>	<u>226.48</u>	<u>-1.33</u>	<u>0.182</u>	<u>0.044</u>	<u>0.068</u>	<u>0.65</u>	<u>0.513</u>
<u>Constant</u>	<u>-3068.89</u>	<u>280.08</u>	<u>-10.96</u>	<u>< 0.001</u>	<u>12.572</u>	<u>0.084</u>	<u>149.96</u>	<u>< 0.001</u>
Number of observations	<u>2,024</u>				<u>2,024</u>			
<u>R²</u>	<u>0.472</u>				<u>0.896</u>			

* Regression model adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.
 * Dummy variables created to indicate missing values for each of the risk characteristics



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Table A43: Additional results from the cost-effectiveness model

	Duration of effect of intervention beyond the end of the trial (model time horizon = 11* years in all cases)			
	0 years	2 years	5 years	10 years
Adjusted costs and QALYs				
<i>Controlling for age and gender only</i>				
Incremental costs (95% CI)	£512 (£438 to £589)	£491 (£418 to £563)	£468 (£396 to £541)	£452 (£378 to £525)
Incremental QALYs (95% CI)	-0.016 (-0.036 to 0.004)	-0.012 (-0.032 to 0.008)	-0.008 (-0.028 to 0.012)	-0.006 (-0.026 to 0.014)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£105,653 to dominated†	£54,307 to dominated†	£34,845 to dominated†	£27,907 to dominated†
% of bootstrapped ICERs <£20k	0.01%	0.10%	0.34%	0.71%
% of bootstrapped ICERs <£30k	0.19%	0.52%	1.69%	3.11%
<i>Controlling for age, gender and country</i>				
Incremental costs (95% CI)	£497 (£424 to £571)	£476 (£404 to £548)	£453 (£381 to £526)	£436 (£364 to £509)
Incremental QALYs (95% CI)	-0.011 (-0.031 to 0.009)	-0.007 (-0.027 to 0.013)	-0.003 (-0.023 to 0.017)	-0.001 (-0.021 to 0.019)
ICER	Dominated†	Dominated†	Dominated†	Dominated†
95% CI	£49,903 to dominated†	£33,290 to dominated†	£24,001 to dominated†	£20,342 to dominated†
% of bootstrapped ICERs <£20k	0.07%	0.34%	1.11%	2.32%
% of bootstrapped ICERs <£30k	0.61%	1.81%	4.78%	7.76%

SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

* 1 year study follow-up period plus a 10 year model

† The intervention is more costly and yield fewer QALYs than usual care

Table A5: Results from matched age-sex analysis

	Duration of effect of intervention beyond the end of the trial = 10 years (model time horizon = 11[#] years in all cases)			
	Men < 65 years	Men >= 65 years	Women < 65 years	Women > = 65 years
Unadjusted costs and QALYs				
Incremental costs (95% CI)	£413 (£290 to £536)	£527 (£237 to £817)	£387 (£304 to £471)	£546 (£376 to £717)
Incremental QALYs (95% CI)	0.040 (-0.016 to 0.096)	-0.057 (-0.181 to 0.068)	0.026 (-0.017 to 0.069)	-0.043 (-0.139 to 0.052)
ICER	£10,298	Dominated‡	£15,006	Dominated‡
Adjusted costs and QALYs‡				
Incremental costs (95% CI)	£457 (£282 to £631)	£360 (£83 to £803)	£430 (£313 to £548)	£466 (£222 to £710)
Incremental QALYs (95% CI)	-0.008 (-0.063 to 0.048)	-0.014 (-0.212 to 0.183)	-0.011 (-0.041 to 0.020)	-0.000 (-0.052 to 0.051)
ICER	Dominated‡	Dominated‡	Dominated‡	Dominated‡

SD = standard deviation; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval

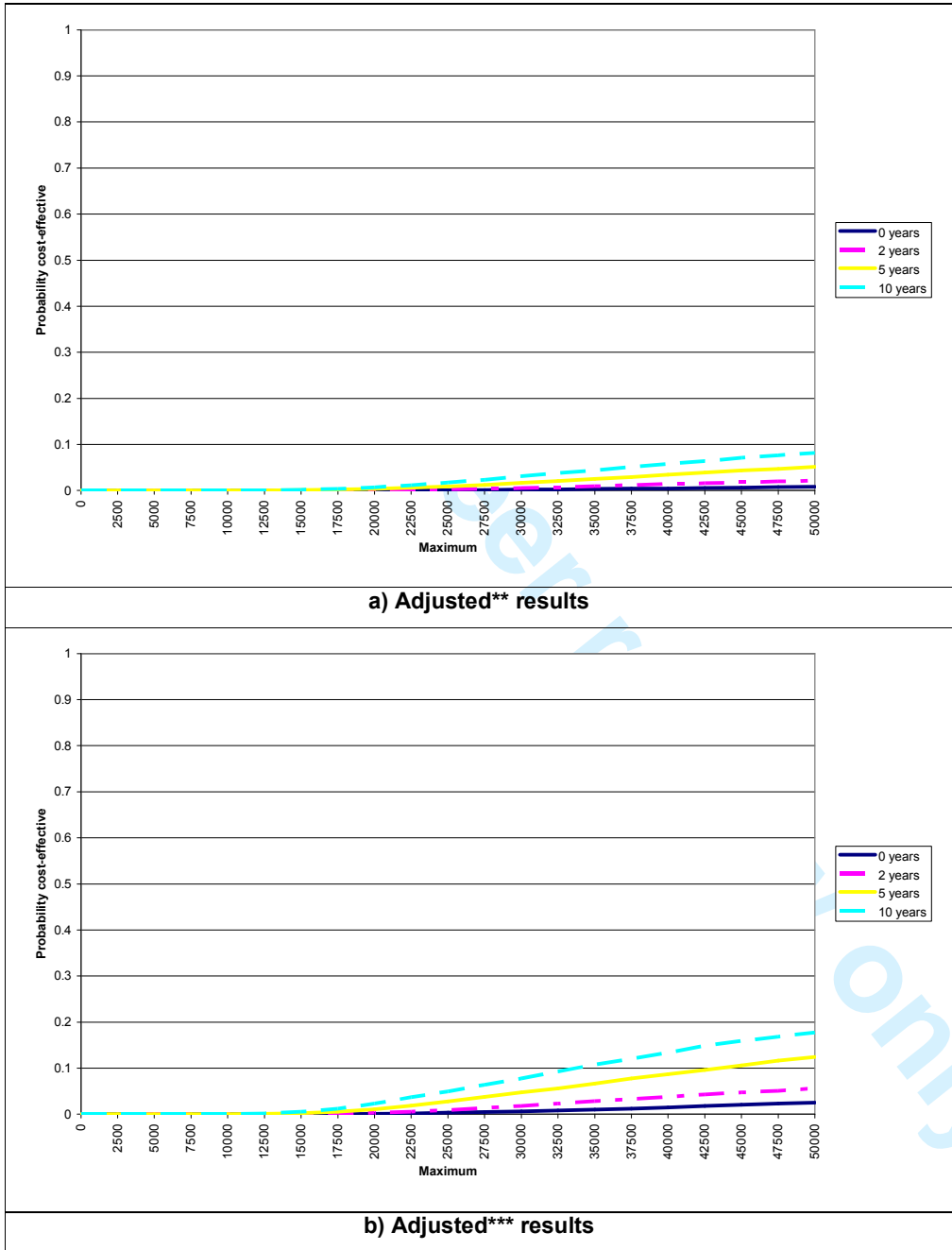
[#] 1 year study follow-up period plus a 10 year model

‡ The intervention is more costly and yield fewer QALYs than usual care

‡ Adjusting for the following baseline characteristics: age, gender, age*gender, country, total and HDL cholesterol, SBP, anti-hypertensive medications, smoking and diabetes.

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Figure A1: Adjusted cost-effectiveness results



** Adjusted for differences between groups by age and gender
 *** Adjusted for differences between groups by age, gender and country

Additional References for Appendix

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Cost-effectiveness of a European preventive cardiology programme in primary care

Hema Mistry, Stephen Morris, Matthew Dyer, Kornelia Kotseva, David Wood, Martin Buxton
and on behalf of the EUROACTION study group

Health economics checklist

Requirement	Manuscript page
Study design	
(1) The research question is stated	2, 4
(2) The economic importance of the research question is stated	2, 4
(3) The viewpoint(s) of the analysis are clearly stated and justified	2,5
(4) The rationale for choosing the alternative programmes or interventions compared is stated	4
(5) The alternatives being compared are clearly described	5
(6) The form of economic evaluation used is stated	4,9
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	9
Data collection	
(8) The source(s) of effectiveness estimates used are stated	9
(9) Details of the design and results of effectiveness study are given	9, 11
(10) Method of synthesis/meta-analysis of estimates are given	NA
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	2, 9
(12) Methods to value health states and other benefits are stated	9
(13) Details of the subjects from whom valuations were obtained are given	9
(14) Productivity changes (if included) are reported separately	NA
(15) The relevance of productivity changes to question is discussed	NA
(16) Quantities of resources are reported separately from their unit costs	7-9, 26-27
(17) Methods for the estimation of quantities and unit costs are described	7-9
(18) Currency and price data are recorded	8
(19) Details of currency of price adjustments for inflation or currency conversion are given	8
(20) Details of any model used are given	5-10
(21) The choice of model used and the key parameters are justified	5-10
Analysis and interpretation of results	
(22) Time horizon of costs and benefits is stated	9
(23) The discount rate(s) is stated	9
(24) The choice of rate(s) is justified	9
(25) An explanation is given if costs or benefits are not discounted	NA
(26) Details of statistical tests and confidence intervals are given for stochastic data	9-10
(27) The approach to sensitivity analysis is given	10
(28) The choice of variables for sensitivity analysis is justified	10
(29) The ranges over which the variables are varied are stated	10
(30) Relevant alternatives are compared	11-12
(31) Incremental analysis is reported	11-12
(32) Major outcomes are presented in a disaggregated as well as aggregated form	11-12, 20-21
(33) The answer to the study question is given	12, 14
(34) Conclusions follow from the data reported	12-14
(35) Conclusions are accompanied by the appropriate caveats	12-14