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Cost-effectiveness modelling of telehealth for patients with raised cardiovascular disease risk: Evidence from a cohort simulation conducted alongside the Healthlines randomised controlled trial

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Short title: Lifetime cost-effectiveness modelling of telehealth in CVD

Abstract

Objectives: To investigate the long-term cost-effectiveness (measured as the ratio of incremental NHS cost to incremental quality-adjusted life years) of a telehealth intervention for patients with raised cardiovascular disease (CVD) risk.

Design: A cohort simulation model developed as part of the economic evaluation conducted alongside the Healthlines randomised controlled trial.

Setting: Patients recruited through primary care, and intervention delivered via telehealth service.

Participants: Participants with a 10 year CVD risk ≥20%, as measured by the QRISK2 algorithm, and with at least one modifiable risk factor, individually randomised from 42 general practices in England.

Intervention: A telehealth service delivered over a 12 month period. The intervention involved a series of responsive, theory-led encounters between patients and trained health information advisors who provided access to information resources and supported medication adherence and coordination of care.

Primary and secondary outcome measures: Cost-effectiveness measured by net monetary benefit over the simulated lifetime of trial participants from a UK National Health Service perspective.

Results: The probability that the intervention was cost-effective depended on the duration of the effect of the intervention. The intervention was cost-effective with high probability if effects persisted over the lifetime of intervention recipients. The probability of cost-effectiveness was lower for shorter durations of effect.

Conclusions: The intervention was likely to be cost-effective under a lifetime perspective.

Trial registration: ISRCTN27508731, prospectively registered 05/07/2012

Strengths and limitations

- The Healthlines trial was one of the largest RCTs designed to evaluate a telehealth-based complex intervention for the management of cardiovascular disease risk.
- This study complements and extends the findings of a within-trial evaluation carried out on outcomes at 12 months from randomisation by evaluating the cost-effectiveness of the telehealth intervention over the lifetime of trial participants using a cohort simulation model
- The intervention is likely to be cost-effective from a health system perspective, but we cannot identify the most plausible duration of intervention effect

Introduction

Cardiovascular disease (CVD) is a prevalent long-term condition associated with substantial morbidity and mortality.[1] Effective care for patients with raised CVD risk requires attention to, and management of, underlying risk factors such as high blood pressure and obesity.[2] A challenge in estimating the cost-effectiveness of interventions intended to reduce CVD risk is that randomised controlled trials (RCTs) may have follow-up periods that are shorter than the period over which an intervention may affect CVD risk. This is in spite of the impact that interventions to reduce CVD risk – such as blood pressure management and weight management programmes – might have in reducing the future occurrence of debilitating events such as acute myocardial infarction and stroke.

Telehealth is one form of condition management that may be relevant to long-term conditions in general and to CVD in particular.[3] However, there is a lack of high-

quality evidence regarding the cost-effectiveness of telehealth. [4 5 6 7] To estimate the clinical and cost-effectiveness of a de novo telehealth intervention, the Healthlines CVD risk RCT individually randomised 641 participants to receive either usual care or a theory-based telehealth intervention that encouraged participants to engage in beneficial behaviour change. The primary clinical outcome of the trial was 10-year CVD risk, measured using the QRISK2 risk prediction algorithm[8], at the end of 12-months of follow-up.

In the absence of data from long-term follow-up, there is no means of assessing the enduring impact on cost-effectiveness of the changes in modifiable risk factors that the intervention may have wrought. For example, it is plausible that some patients who managed to reduce their blood pressure (BP), body mass index (BMI) or whose medication adherence was improved as a result of the intervention may continue with newly acquired beneficial behaviours after the end of the 12 months of trial follow-up. Indeed, it is implausible that all trial participants would immediately revert to their pre-intervention BP or BMI immediately on trial completion.

This paper describes the development and analysis of a state transition cohort simulation cost-effectiveness model intended to estimate the expected net benefits of the Healthlines telehealth intervention over the lifetime of trial participants. This approach is consistent with the principles of economic evaluation,[9] guidance from the National Institute for Health and Care Excellence (NICE)[10], and ISPOR guidelines [11] which recommend that cost-effectiveness analyses be undertaken over a time period that reflects differences in cost and effect attributable to an intervention or treatment. The long-term cost-effectiveness analysis complements the analysis of cost-effectiveness of the intervention at 12 months post-randomisation published in a companion paper.[12]

The Healthlines RCT

The trial protocol, methods, results and cost-effectiveness analyses have been reported elsewhere.[3] Briefly, patients aged between 40 and 74 with ten-year CVD risk ≥20% (measured by the QRISK2 algorithm) and at least one modifiable risk factor (for example, weight management or smoking) were recruited from 42 GP practices in England. Individuals were not considered if they had a confirmed diagnosis of CVD, were pregnant, did not have access to the internet and telephones or were unable to communicate verbally. More detail on these and other exclusion criteria is available in Salisbury et al.[3] In total, 641 patients were randomised, and received either unmodified usual care (n=316), or a telehealth intervention in addition to usual care (n=325), for a follow-up period of 12 months.

Participants in the intervention arm could receive up to 13 responsive, tailored telehealth encounters with trained Health Information Advisors (HIAs). Participants were encouraged to access and use online material and apps related to CVD risk. Participants with systolic blood pressure ≥140 mmHg and without atrial fibrillation were offered a blood pressure monitor to use at home, and could upload readings to a portal to monitor progress. Telephone calls focused on goal setting, stimulus control and the management of CVD risk in a way that was relevant to the circumstances of each individual participant and which was in line with NICE guidelines. This included ensuring that patients were taking appropriate drug treatment, and addressing problems with medication adherence.

The within-trial economic evaluation at the end of 12 months of follow-up adopted an NHS perspective. The cost-effectiveness of the intervention was estimated against NICE thresholds using NHS cost data collected from medical records and questionnaires during the trial, and using data on quality-adjusted life years (QALYs) estimated from responses to the EQ-5D-5L[13] generic quality-of-life measure at

baseline, and six and 12 months from randomisation. Mean incremental NHS costs in 2012/13 prices were estimated to be £138 per patient (i.e. the intervention was more expensive), and mean incremental QALY gains were estimated to be 0.012. The estimated ICER was £10,859, and the estimated net benefit at a threshold of £20,000 was estimated to be £116 (95% confidence interval: -£58 to £291). The probability that the intervention was cost-effective at this threshold value was 0.77.

Methods

Model structure

Cohorts of 1,000 patients were simulated. These cohorts were based on the characteristics of the 641 trial participants. Cohorts differed according to age at randomisation, sex and trial allocation of the patient groups modelled. A set of discrete, mutually exclusive states were created and defined by the presence (or absence) of a CVD-related condition, or with death (Figure 1). Sequences of states experienced by the simulated cohort members defined clinical pathways in which QALYs (associated with utilities and mortality) and costs were accumulated. Cost-effectiveness, as measured by the averages of costs and QALYs in each arm, was the primary outcome. These averages were calculated and allowed for the construction of net benefit statistics. Costs were expressed in 2012/13 sterling prices.

The model is based on adapted updated versions of models used in previous health technology assessments in the area of CVD risk.[14 15] A National Health System perspective was adopted. The model cycled annually. Both costs and outcomes were subject to a half-cycle correction.[16] Consistent with the inclusion criteria of the trial, and the construction of the QRISK2 algorithm,[8] patients were assumed to be free of CVD when they entered the model – this corresponds to the 'event free' state. Subsequent states correspond to the occurrence of the events used in the QRISK2

algorithm – acute myocardial infarction (AMI), angina, transient ischaemic attack (TIA) and stroke – and to post-event states, e.g. a 'post-stroke' state (Figure 1).

Patients cycled the model until death, or age 100, at which point they were assumed to die. A total of 1,000 iterations of the model were simulated, in which values of input parameters were varied simultaneously. Each iteration used a value drawn from probability distributions assigned to particular input parameters of the model as described below, in the supplementary material and in Salisbury et al.[3] Probabilistic sensitivity analysis was used to quantify uncertainty around point estimates of net benefit. The model was implemented in Excel 2013 (Microsoft: Redmond, Washington).

Probability of transitioning to primary and secondary states

The probability of entering a particular state is determined by CVD risk. Initial risk scores of patients at the beginning of the model, corresponding to the event-free state, were based on information collected in the RCT (Table 1). CVD risk in the initial year (year 0) is thus average participant baseline QRISK2 score. Change in CVD risk at the end of this year/start of the next year (year 1) is measured by QRISK2 score calculated at 12-month follow-up and adjusted for baseline risk, details of which are provided in Salisbury et al.[3] CVD risk in subsequent years was obtained by adding percentage increases obtained from growth rates in annual risk in males when all input values to the QRISK2 algorithm other than age were held constant.

Growth rates from males were used because the level of CVD risk is higher for males than for females at all ages, other variables being constant. Using the relatively more rapid growth rates observed in female risk levels as a basis for extrapolation would

have meant that at some ages female risk was much higher than male risk. The use of male risk growth rates constrains female risk levels to be below male levels at all ages, ensures that risk does not rise above 100%, better reflects estimated prevalence of risk in males and females, and more generally ensures that the cost-effectiveness results are based on plausible risk profiles.[3]

The QRISK2 algorithm is not validated for ages beyond 84. Risk for patients surviving to 85 and above was obtained by extrapolating 10-year risk by 1% per annum, which corresponds to the coefficient obtained from an ordinary least squares regression of QRISK2 scores on age.

Ten-year risk scores were converted into an annual risk of any event to reflect the annual cycles of the model. Annual risk scores of *any* defined CVD event were then disaggregated into the risk of a *specific* event – AMI, angina, TIA and stroke – using data on the incidence of these conditions by age and sex. The sources for these data and the input values used are described in the online supplementary material. Further detail on their calculation is available in Salisbury et al.[3]

These incidence rates establish the probability of moving from the event-free state to a specific CVD-related event state; that is, they establish the risk of a primary event. Transitions to secondary events (any event after the primary event) are determined by the age and sex-specific transition probabilities given in Ara et al,[14] who describe in detail the data sources and methods used in their construction. Permitted transitions between states are listed in the online supplementary material (Table A1).

The probability of death due to causes not related to CVD risk was based on standardised mortality ratios calculated from the most recently available (2012) Office of National Statistics Interim Life Tables.[17] This mortality ratio excluded CVD-related

ICD-10 codes (I20-I25 and I60-I69). The risks of mortality used in each iteration of the model were based on draws from a univariate normal distribution.

Simulated participants were constrained to experience no more than three CVD events, an assumption that reflected data availability and model tractability. The same assumption was used in Ara et al.[14] However, few of the 1,000 simulated participants approached experiencing three events, and therefore the assumption is unlikely to have influenced cost-effectiveness conclusions.

Duration of effect of intervention

The duration of the effect of the Healthlines intervention on CVD risk beyond the end of trial follow-up is unknown, but the modelling thereof is the principal motivation for undertaking the simulation modelling described here. Four different scenarios based on different durations of effect were modelled, and their implications for cost-effectiveness compared. This is similar to the approach of Mistry et al.[18]

The scenarios modelled are of durations of intervention effect of one, two, and five years from baseline, and for remaining lifetime. If, for example, the duration effect is two years, then participants in the intervention arm receive the benefit of lower risk for two years, after which they are modelled as having the same sex- and age-adjusted risk as participants in the control arm. Similar logic applies to the other scenarios. In the case of a lifetime duration of effect, risk is permanently lower in the intervention arm. To avoid sudden 'jumps' in risk at the point at which the intervention ends, the model uses a smoothing adjustment which calculates the average score of intervention arm risk and usual care risk for the year after which the modelled duration of effect expires.

Data on utility

QALYs in year zero of the model were obtained from participant responses to the EQ-5D-5L measure at baseline, six and 12 months of RCT follow-up, and were 'cross-walked' to UK EQ-5D-3L instrument and valued using the Euroqol UK value set.[19] QALYs were adjusted to account for between-arm differences observed at the end of trial follow-up. For other years of the model, age- and sex-adjusted population EQ-5D norms were estimated from Ara and Brazier[20] to provide baseline utility scores that applied to the event-free state. These EQ-5D data were used to calculate QALYs.

Multiplicative adjustments, which assume a constant proportional effect on baseline utility,[20] were made to reflect the decremental impact of experiencing CVD-related health states. Ara and Brazier[20] was used as the source of state-specific utilities other than TIA, which were drawn from Luengo-Fernandez et al,[21] and for unstable angina. It was assumed that the utility estimates for angina in Ara and Brazier related to stable angina; it was further assumed that utility associated with the unstable angina health state would be 90% of the stable angina values, as in Ara et al.[14]

Condition-specific utility values were drawn from univariate normal distributions, as recommended by Ara and Wailoo,[22] to reflect uncertainty in mean values. Utilities corresponding to post-event states were never lower than for the event state itself. This means, for example, that utilities of the "post-stroke" event state were higher than or equal to the "stroke" state, implying that experiencing a stroke had a greater negative impact on average on patient utility than did experiencing the "post-stroke" state.

It was assumed that the second and third events (such as second and third non-fatal strokes) had the same impact on utility as the first event. This rules out multiplicative

impacts of events on quality of life. The utility values associated with different states are presented in the online supplementary material (Table A2).

Data on cost

A health-system perspective was adopted for the analysis, and hence only NHS costs were considered. This excluded consideration of any personal or societal costs associated with, for example, incapacity and exit from the labour force connected with a debilitating but non-fatal stroke

The costs of health states were based, in most cases, on Ward et al[23] and Ara et al.[14] The first year of the model also included costs of the intervention, and NHS costs incurred in each arm. The costs of each health state is described in the online supplementary material.

The cost estimates in Ward et al[23] and Ara et al[14], derived from systematic reviews, were updated where appropriate and possible with new data, as described in more detail in Salisbury et al.[3] Mean costs enter the simulation model at each iteration as draws from a gamma distribution.

Cost effectiveness analysis

The simulation model uses information on the NHS costs and QALYs observed during the 12-months of trial follow-up in the initial year (year 0). All subsequent costs and QALYs are simulated by the model as a function of QRISK2 scores using the methods described above. Costs and outcomes were both discounted at 3.5% per year, in line with NICE recommendations.[10] Cumulative costs and QALYs were obtained for the lifetime of cohort members by calculating probability-weighted averages of the number of patients in each state, the length of time patients have

been in particular states, and the costs, mortality and quality of life associated with each state.

Results

The mean age of males (females) in the trial was 67 (69), and males comprised 80% of trial participants. Table 1 contains baseline and adjusted 12 month QRISK2 scores – higher scores indicate higher CVD risk.

Table 2 provides the results of the cost-effectiveness analysis for different durations of intervention effect. The longer the assumed duration of effect, the more likely it is that the intervention is cost-effective at cost effectiveness thresholds conventionally employed (i.e. £20,000 per QALY). It is notable that, even if the beneficial effects of the intervention on CVD risk last only one year, the intervention is likely to be cost-effective. This is also apparent in the cost-effectiveness acceptability curves, where a monotonic relationship between duration of the probability of cost-effectiveness is evident (Figure 2).

The small QRISK2 difference between arms means that the control and intervention groups have very similar risk profiles once the assumed duration of effect expires. The lifetime cost-effectiveness results are therefore influenced, especially at short durations of effect, by the inclusion of costs and QALYs observed during the 12-month period of trial follow-up. The between-arm cost and QALY differences in the initial 12 months are propagated forward over the remaining lifetime of trial participants, and are more influential than the subsequent minor differences in costs and QALYs associated with different levels of simulated QRISK2. Nevertheless, the differences in QRISK2 are consequential at longer durations of effect, since they are associated with fewer CVD events in the intervention arm.

Discussion

Cost-effectiveness over the lifetime of participants in the Healthlines telehealth trial was estimated using a cohort simulation model. The probability of cost-effectiveness increased with longer durations of effect, but even with the shortest duration of effect the intervention was estimated to be cost-effective. These results reflect the cost-effectiveness analysis at 12 months: because of the small difference in QRISK2 between arms, the QALY difference observed at the end of trial follow-up has a major influence on lifetime cost-effectiveness.

The model is subject to a number of limitations. The quality of the output reflects the assumptions and data used to construct and populate the model. The QRISK2 algorithm is not validated for ages beyond 84, and we made an assumption as to growth in risk for the small number of simulated trial participants who lived to 85 and beyond.

As in all modelling exercises of this type, the results may be sensitive to structural assumptions, such as the number of health states modelled.[11] We cannot eliminate the possibility that alternative representations of clinical pathways may produce different conclusions. However, we have relied on a representation of health states that is consistent with the QRISK2 algorithm, the defined events (e.g. stroke) of which are represented as distinct states in the model.

The model understates uncertainty associated with QRISK2 because the variance structures underlying the algorithm are not published or otherwise available, and the consequence of this is to narrow confidence intervals around net monetary benefit statistics. This may have implications, in particular, for the probability of cost-effectiveness.

We have not accounted for non-health service costs, which may have consequences for carers and the wider economy for some of the conditions modelled, such as stroke.[24] However, it is not clear if accounting for these costs would necessarily alter the between-arm comparison of cost-effectiveness, since slightly fewer fatal and non-fatal strokes would be experienced in the intervention arm.

Finally, the analysis does not identify the most plausible duration of effect. Evidence from long-term follow-up is necessary to conclusively answer this question, although synthesis of evidence from similar trials and relevant observational studies may also offer a useful complementary approach to long-term follow-up.

Comparison with other literature

Comparison of the findings of this study with other literature assessing the long-term cost-effectiveness of interventions directed at managing CVD risk is complicated by differences in the study design used to inform the modelling, patient profiles, and the nature of the interventions examined. However, the approach of using different assumed durations of effect, or different effect sizes, is encountered in similar studies.

For example, the evaluations of CVD interventions from a long-term perspective undertaken by Mistry et al[18], Asaria et al[25] and Penaloza-Ramos et al[26] are all sensitive to some degree to assumptions made concerning the duration of intervention effect. This is in spite of differences between these studies in population characteristics, CVD risk equation used and interventions studied, which preclude a comparison of the findings of the present study and these other analyses.

Studies also differ in the study design used to inform long-term cost-effectiveness modelling. The effect estimates used as the basis of modelling in our study are those

of the 'intention to treat' analysis of the Healthlines RCT. This is a source of difference between the present paper and, for example, the economic modelling undertaken in support of the routine use of "health checks" in the NHS in England.[27] The economic model developed to analyse the consequences of these health checks was based on a much more extensive simulation involving synthesis of various model parameters, compliance rates and effect estimates from a variety of sources.

Ultimately, although modelling and evidence synthesis will continue to be important sources of evidence in this area, definitive evidence on the long-term consequences for CVD risk of Healthlines (and similar interventions) will require RCTs with long-term follow-up.

CONCLUSION

The Healthlines telehealth service is likely to be cost-effective for individuals with raised CVD risk when a lifetime perspective is adopted. Results are somewhat sensitive to the assumed duration of intervention effect. When considering the deployment of large scale telehealth programmes in this area, decision makers may need to consider the longevity of the behavioural and other changes rendered by the type of telehealth service studied in the Healthlines RCT, alongside other evidence concerning the long-term cost effectiveness of similar interventions for CVD risk.

Tables and figures

Table 1 QRISK2 scores at baseline and after 12-months of follow-up

	Control arm		Intervention arm	
	Baseline	12 month follow-up, adjusted for baseline	Baseline	12 month follow-up, adjusted for baseline
QRISK2 score for males	31.59	32.00	31.83	31.60
QRISK2 score for females	27.73	28.24	27.86	27.84

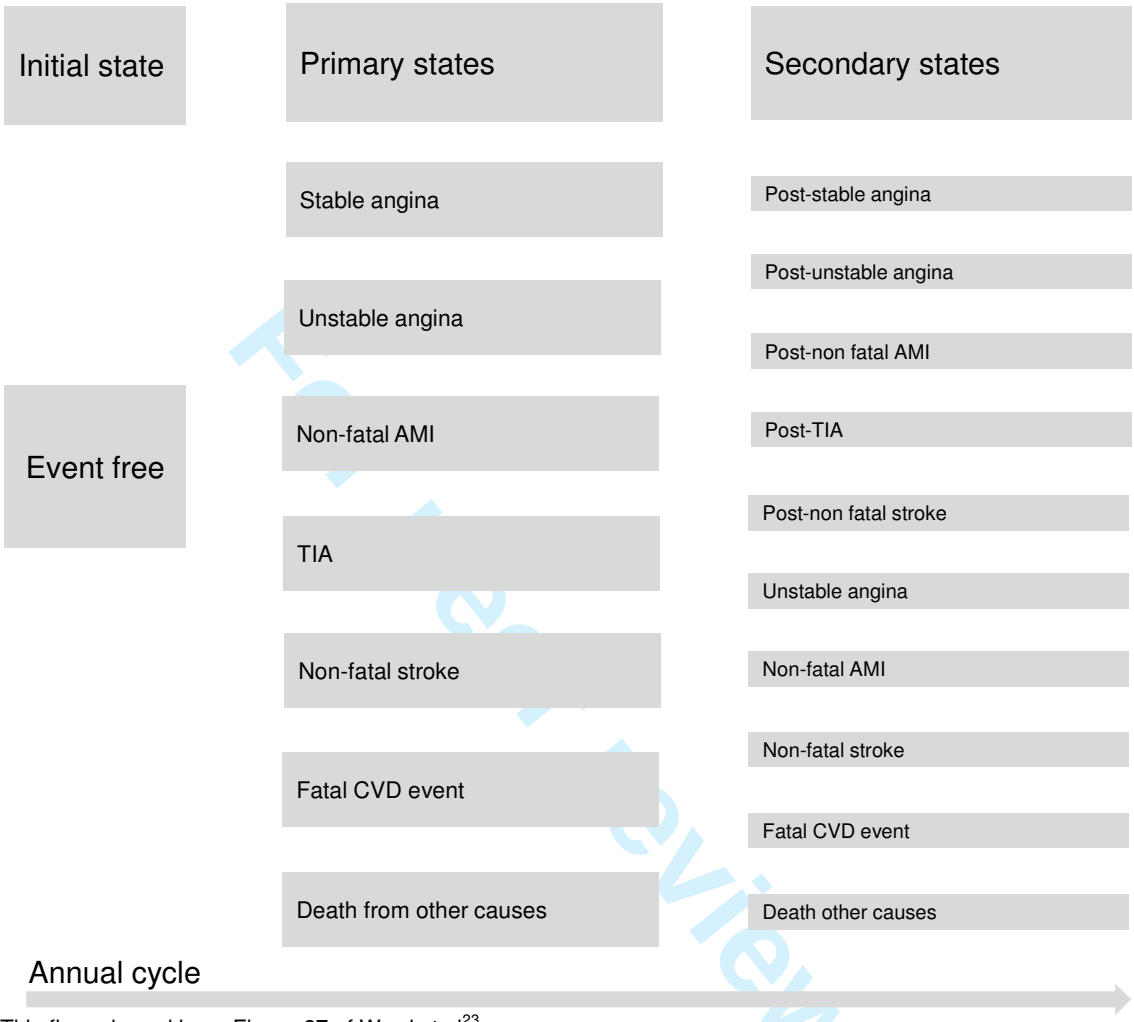
Note: The data are presented as levels of QRISK2 as it is the level of risk that determines the probability of events such as stroke or acute myocardial infarction.
These data are based on imputed QRISK2 scores – multiply imputed data are used in the base case economic evaluation at 12 months from randomisation.[3] These data are based on CVD risk of all of those randomised (n=641) in the RCT. The methods used for multiple imputation are described in further detail in the companion 12 month economic evaluation paper. [12]

Table 2 Base case cost-effectiveness results for different durations of effect: per-patient average costs and effects

	Modelled duration of effect			
	1 year	**2 years**	**5 years**	**Lifetime (permanent) effect**
Control arm NHS costs	£6,595	£6,617	£6,608	£6,602
Intervention arm NHS costs	£6,726	£6,741	£6,714	£6,657
Control arm QALYs	8.573	8.573	8.573	8.572
Intervention arm QALYs	8.584	8.586	8.589	8.598
Incremental costs (95% CI)	£131 (£125 to 138)	£124 (£118 to 130)	£107 (101 to 112)	£55 (49 to 61)
Incremental QALYs (95% CI)	0.011 (0 .011 to 0 .011)	0.013 (0 .012 to 0 .013)	0.016 (0.016 to 0.017)	0.026 (0.026 to 0.027)
ICER	£11,776	£9,886	£6,477	£2,091
Probability cost effective at £20,000 threshold	0.74	0.84	0.95	0.99
Probability cost effective at £30,000 threshold	0.87	0.93	0.99	1.00
NMB at threshold of £20,000 (95% CI)	£92 (-172 to 352)	£127 (-144 to 382)	£223 (-153 to 468)	£472 (197 to 728)

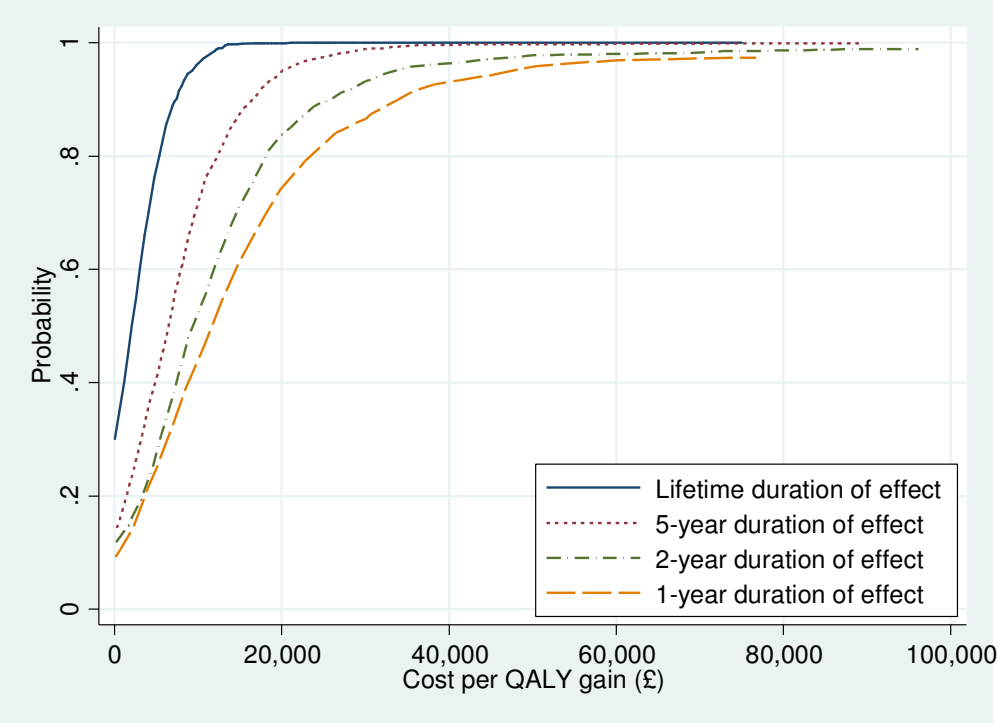
SD: Standard deviation; CI = Confidence interval; QALYs = Quality-adjusted life years; ICER = Incremental cost-effectiveness ratio; CE = Cost-effectiveness; NMB = Net monetary benefit

Figure 1 Simulated model states



This figure based is on Figure 27 of Ward et al[23]

Figure 2 CEACs from lifetime simulation assuming different durations of effect



Contributorship statemement: PD and SH: Conducted economic analysis. RA: Led development of original simulation model, which was updated and modified by PD for the Healthlines study. Provided advice on model development and adaptation. LE: Acted as trial manager. Undertook participant recruitment and follow-up, data collection and data entry. AF: Participant recruitment and follow-up, data collection and data entry for the RCT. CS: Led protocol development and the funding application for the programme grant, acted as chief investigator with overall responsibility for conduct of the RCT. All authors had a role in interpreting the data. PD wrote the first draft of this article, and all authors contributed to subsequent revisions. All authors approved the final version for submission.

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Ethics: The Healthlines trial was approved by the National Research Ethics Service Committee South West – Frenchay (Reference 12/SW/0009). All participants provided informed consent to take part in the trial.

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Appendix – online supplementary information

A1 Permitted transitions in simulation model

Event free state to primary states

Event free to Primary Stable Angina (SA)

Event free to Primary Unstable Angina (USA)

Event free to Primary AMI

Event free to Primary TIA

Event free to Primary Stroke

Event free to Fatal CVD event (FCVD)

Event free to Death other causes (DOC)

Primary states to subsequent states

PRIMARY_SA to SECONDARY_(USA or 1st AMI or 1st Stroke or FCVD or DOC) else post SA

PRIMARY_USA to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post USA

PRIMARY_AMI to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post AMI

PRIMARY_TIA to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post TIA

PRIMARY_Stroke to SECONDARY_(1st Stroke or FCVD or DOC) else post Stroke

Post-primary states to subsequent states

Post PRIMARY_SA to SECONDARY_(USA or 1st AMI or 1st Stroke or FCVD or DOC) else post SA

Post PRIMARY_USA to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post USA

Post PRIMARY_AMI to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post AMI

Post PRIMARY_TIA to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post TIA

Post PRIMARY_Stroke to SECONDARY_(1st Stroke or FCVD or DOC) else post Stroke

Secondary state transitions

SECONDARY_SA to SECONDARY_((USA or 2nd AMI or 2nd Stroke or FCVD or DOC) else post SA

SECONDARY_USA to SECONDARY_((2nd AMI or 2nd Stroke or FCVD or DOC) else post USA

SECONDARY_AMI to SECONDARY_((2nd AMI or 2nd Stroke or FCVD or DOC) else post AMI

SECONDARY_TIA to SECONDARY_((2nd AMI or 2nd Stroke or FCVD or DOC) else post TIA

SECONDARY_Stroke to SECONDARY_((2nd Stroke or FCVD or DOC) else post Stroke

Post SECONDARY_SA to SECONDARY_(USA or 2nd AMI or 2nd Stroke or FCVD or DOC) else post SA

Post SECONDARY_USA to SECONDARY_(2nd AMI or 2nd Stroke or FCVD or DOC) else post USA

Post SECONDARY_AMI to SECONDARY_(2nd AMI or 2nd Stroke or FCVD or DOC) else post AMI

Post SECONDARY_TIA to SECONDARY_(2nd AMI or 2nd Stroke or FCVD or DOC) else post TIA

Post SECONDARY_Stroke to SECONDARY_(2nd Stroke or FCVD or DOC) else post Stroke

Notes to A1: SA = Stable angina; USA = Unstable angina; AMI = Acute myocardial infarction; TIA = Transient ischaemic attack; FCVD = Fatal cardiovascular disease event; DOC = Death other causes
This is the same list of permitted transitions described as in Ara et al [1] and Ara et al [2]. A1 contains the same information as Table 82 in Ara et al [1].

INPUT VALUES, REFERENCES AND PROBABILITY DISTRIBUTIONS FOR MODEL PARAMETERS

Table A2 provides a map to the various model parameters, input values, and associated probability distributions from which input values for specific model runs were drawn, and which are presented in more detail where applicable.

A2 Key input parameters and associated probability distributions

Parameter	Input values	Probability distribution	Comments
Health state utility values	Various; listed in Table A3	Normal	Ara and Wailoo[3] recommend the use of normal distributions to characterise the uncertainty in mean utilities
Health state costs	Various, listed in Table A4	Gamma	A number of sources, eg Gray et al [4], recommend using gamma distributions in characterising uncertainty in cost variables
Incidence rates for primary CVD events	Various, listed in Table A5 and Table A6	N/A	We follow Ward et al[5] and Ara et al[2] in using the mean values of published incidence rates in each model run
CVD Risk	Based on age and sex adjusted QRISK2 scores from baseline and 12m follow-up that are	N/A	The variance structures underlying the QRISK2 algorithm are not published and hence we

	presented in Table 1 in the main text, and then adjusted subsequently using the QRISK2 algorithm		could not characterise uncertainty in this measure. See Discussion in main paper.
Risk of death from non-CVD causes	Based on standardised mortality ratios published by the ONS	Normal distribution	We follow Ara et al[2] in using a normal distribution for model draws

UTILITIES

Ara and Brazier[6] was used as the source of state-specific utilities other than TIA, which are based on Luengo-Fernandez et al[7]. It was assumed that the utility estimates for angina in Ara and Brazier related to stable angina, and that unstable angina health utilities would be 90% of the stable angina values, as in Ara et al.[2]

As further noted in the main text, any 'third' events, i.e. those occurring after a secondary event, have the same utility as the 'second' event.

A3 Health state utility values

Health state	Mean utility value
Primary stable angina	0.615
Primary unstable angina	0.556
Primary AMI	0.721
Primary TIA	0.760
Primary stroke	0.626
Post-primary angina	0.775
Post-primary unstable angina	0.701
Post-primary AMI	0.742
Post-primary TIA	0.78
Post-primary stroke	0.668
Secondary stable angina	0.541
Secondary unstable angina	0.489
Secondary AMI	0.431
Secondary TIA	0.760
Secondary stroke	0.479
Post-secondary stable angina	0.715
Post-secondary unstable angina	0.647
Post-secondary AMI	0.685
Post-secondary TIA	0.78
Post-secondary stroke	0.641

Costs

A detailed discussion of the cost data used to model each state is provided in Salisbury et al.[8] Briefly, the costs of stable and unstable angina, of non-fatal acute myocardial infarction a are based on Ward et al[5] and Ara et al.[2] The cost of fatal

acute myocardial infarction are based on Clarke et al.[9] The costs of non-fatal stroke and of transient ischaemic attack are based on Luengo-Fernadez et al.[7] The cost of fatal stroke is based on Youman et al.[10] In all cases, costs were adjusted to 2012/13 sterling prices as described in Salisbury et al.[8]

A4 Health state costs

Health state	Mean cost in 2012/13 £ prices
Stable angina	606
Stable angina in subsequent years	356
Unstable angina	4,324
Unstable angina in subsequent years	453
Non-fatal acute myocardial infarction	3,362
Post non-fatal acute myocardial infarction	356
Fatal acute myocardial infarction	1,846
Transient ischaemic attack	3,963
Transient ischaemic attack in subsequent years	1,380
Non-fatal stroke	8,989
Non-fatal stroke in subsequent years	1,976
Fatal stroke	9,493

INCIDENCE RATES FOR PRIMARY EVENTS

Incidence rates for primary events are used to calculate the probability of one of stable angina, unstable angina, acute myocardial infarction (AMI), stroke, and transient ischaemic attack (TIA). These incidence rates are then used to disaggregate the risk of any such event, measured by the QRISK2 score, into the risk of a single event.

The data sources and adjustments made to data are described in more detail in Salisbury et al. [8] Here, we briefly describe these sources, and present in A5 and A6 the incidence data used in the simulation model.

The incidence of angina was taken from data for England reported British Heart Foundation Coronary Heart Disease Statistics 2012,[11] using the data reported for England. This was split into incidences of stable and unstable angina using incidences reported in Sutcliffe et al. [12] Incidence of fatal and non-fatal AMI was also taken from British Heart Foundation Coronary Heart Disease Statistics 2012.[11] Incidence of first ever stroke was based on Wang et al, [13] and incidence on mortality from strokes was based on Lee et al. [14]

Incidence of TIA is taken from British Heart Foundation Stroke Statistics 2009. [15]

A5 Incidence rates of CVD events per 1,000 males per year

Age band	Stable angina	Unstable angina	Non-fatal AMI	Fatal AMI	TIA	Non-fatal stroke	Fatal stroke
55-64	0.84	0.25	0.28	0.04	0.74	0.65	0.08
65-74	1.16	0.35	0.42	0.11	1.45	1.27	0.16
75-84	0.75	0.23	0.73	0.29	3.27	2.73	0.35
85+	0.75	0.23	1.23	0.76	7.94	5.12	0.65

A6 Incidence rates of CVD events per 1,000 females per year

Age band	Stable angina	Unstable angina	Non-fatal AMI	Fatal AMI	TIA	Non-fatal stroke	Fatal stroke
55-64	0.35	0.11	0.07	0.02	1.05	0.63	0.14
65-74	0.74	0.22	0.18	0.06	2.18	1.23	0.28
75-84	0.57	0.17	0.38	0.22	5.61	2.64	0.6
85+	0.57	0.17	0.75	0.64	9.14	4.95	1.13

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CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Lines 60-87
		Present the study question and its relevance for health policy or practice decisions.	Lines 88-97
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Lines 99-108
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Lines 99-103
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Lines 119-120
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Lines 109-118
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Lines 88-97
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Lines 262-263
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Line 139-140
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Estimates are based on effectiveness data from the Healthlines RCT (Lines 109-129)
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Not applicable
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Lines 220-226
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate	Lines 246-257 in main text, and page5-6 of

Section/item	Item No	Recommendation	Reported on page No/ line No
		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	supplementary material
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Line 141
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Lines 132-140 and Figure 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Lines 142-202
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Lines 132-218
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 in main text, and Tables A2, A3, A4, A5and A6 in the appendix
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2 in main text
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Not applicable
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Table 2 and Figure 2 in the main text
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Lines 291 to 347
Other			
Source of funding	23	Describe how the study was funded and the role of	Page 1

Section/item	Item No	Recommendation	Reported on page No/ line No
		the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 2

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

BMJ Open

Cost-effectiveness modelling of telehealth for patients with raised cardiovascular disease risk: Evidence from a cohort simulation conducted alongside the Healthlines randomised controlled trial

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Cost-effectiveness modelling of telehealth for patients with raised cardiovascular disease risk: Evidence from a cohort simulation conducted alongside the Healthlines randomised controlled trial

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Short title: Lifetime cost-effectiveness modelling of telehealth in CVD

Abstract

Objectives: To investigate the long-term cost-effectiveness (measured as the ratio of incremental NHS cost to incremental quality-adjusted life years) of a telehealth intervention for patients with raised cardiovascular disease (CVD) risk.

Design: A cohort simulation model developed as part of the economic evaluation conducted alongside the Healthlines randomised controlled trial.

Setting: Patients recruited through primary care, and intervention delivered via telehealth service.

Participants: Participants with a 10 year CVD risk ≥20%, as measured by the QRISK2 algorithm, and with at least one modifiable risk factor, individually randomised from 42 general practices in England.

Intervention: A telehealth service delivered over a 12 month period. The intervention involved a series of responsive, theory-led encounters between patients and trained health information advisors who provided access to information resources and supported medication adherence and coordination of care.

Primary and secondary outcome measures: Cost-effectiveness measured by net monetary benefit over the simulated lifetime of trial participants from a UK National Health Service perspective.

Results: The probability that the intervention was cost-effective depended on the duration of the effect of the intervention. The intervention was cost-effective with high probability if effects persisted over the lifetime of intervention recipients. The probability of cost-effectiveness was lower for shorter durations of effect.

Conclusions: The intervention was likely to be cost-effective under a lifetime perspective.

Trial registration: ISRCTN27508731, prospectively registered 05/07/2012

Strengths and limitations

- The Healthlines trial was one of the largest RCTs designed to evaluate a telehealth-based complex intervention for the management of cardiovascular disease risk.
- This study complements and extends the findings of a within-trial evaluation carried out on outcomes at 12 months from randomisation by evaluating the cost-effectiveness of the telehealth intervention over the lifetime of trial participants using a cohort simulation model
- The intervention is likely to be cost-effective from a health system perspective, but we cannot identify the most plausible duration of intervention effect

Introduction

Cardiovascular disease (CVD) is a prevalent long-term condition associated with substantial morbidity and mortality.[1] Effective care for patients with raised CVD risk requires attention to, and management of, underlying risk factors such as high blood pressure and obesity.[2] A challenge in estimating the cost-effectiveness of interventions intended to reduce CVD risk is that randomised controlled trials (RCTs) may have follow-up periods that are shorter than the period over which an intervention may affect CVD risk. This is in spite of the impact that interventions to reduce CVD risk – such as blood pressure management and weight management programmes – might have in reducing the future occurrence of debilitating events such as acute myocardial infarction and stroke.

Telehealth is one form of condition management that may be relevant to long-term conditions in general and to CVD in particular.[3] However, there is a lack of high-

quality evidence regarding the cost-effectiveness of telehealth. [4 5 6 7] To estimate the clinical and cost-effectiveness of a de novo telehealth intervention, the Healthlines CVD risk RCT individually randomised 641 participants to receive either usual care or a theory-based telehealth intervention that encouraged participants to engage in beneficial behaviour change. The primary clinical outcome of the trial was 10-year CVD risk, measured using the QRISK2 risk prediction algorithm[8], at the end of 12-months of follow-up.

In the absence of data from long-term follow-up, there is no means of assessing the enduring impact on cost-effectiveness of the changes in modifiable risk factors that the intervention may have wrought. For example, it is plausible that some patients who managed to reduce their blood pressure (BP), body mass index (BMI) or whose medication adherence was improved as a result of the intervention may continue with newly acquired beneficial behaviours after the end of the 12 months of trial follow-up. Indeed, it is implausible that all trial participants would immediately revert to their pre-intervention BP or BMI immediately on trial completion.

This paper describes the development and analysis of a state transition cohort simulation cost-effectiveness model intended to estimate the expected net benefits of the Healthlines telehealth intervention over the lifetime of trial participants. This approach is consistent with the principles of economic evaluation,[9] guidance from the National Institute for Health and Care Excellence (NICE)[10], and ISPOR guidelines [11] which recommend that cost-effectiveness analyses be undertaken over a time period that reflects differences in cost and effect attributable to an intervention or treatment. The long-term cost-effectiveness analysis complements the analysis of cost-effectiveness of the intervention at 12 months post-randomisation published in a companion paper.[12]

The Healthlines RCT

The trial protocol, methods, results and cost-effectiveness analyses have been reported elsewhere.[3 13] Briefly, patients aged between 40 and 74 with ten-year CVD risk ≥20% (measured by the QRISK2 algorithm) and at least one modifiable risk factor (for example, weight management or smoking) were recruited from 42 GP practices in England. Individuals were not considered if they had a confirmed diagnosis of CVD, were pregnant, did not have access to the internet and telephones or were unable to communicate verbally. More detail on these and other exclusion criteria is available in Salisbury et al.[3] In total, 641 patients were randomised, and received either unmodified usual care (n=316), or a telehealth intervention in addition to usual care (n=325), for a follow-up period of 12 months.

Participants in the intervention arm could receive up to 13 responsive, tailored telehealth encounters with trained Health Information Advisors (HIAs). Participants were encouraged to access and use online material and apps related to CVD risk. Participants with systolic blood pressure ≥140 mmHg and without atrial fibrillation were offered a blood pressure monitor to use at home, and could upload readings to a portal to monitor progress. Telephone calls focused on goal setting, stimulus control and the management of CVD risk in a way that was relevant to the circumstances of each individual participant and which was in line with NICE guidelines. This included ensuring that patients were taking appropriate drug treatment, and addressing problems with medication adherence.

The within-trial economic evaluation at the end of 12 months of follow-up adopted an NHS perspective. The cost-effectiveness of the intervention was estimated against NICE thresholds using NHS cost data collected from medical records and questionnaires during the trial, and using data on quality-adjusted life years (QALYs) estimated from responses to the EQ-5D-5L[14] generic quality-of-life measure at

baseline, and six and 12 months from randomisation. Mean incremental NHS costs in 2012/13 prices were estimated to be £138 per patient (i.e. the intervention was more expensive), and mean incremental QALY gains were estimated to be 0.012. The estimated ICER was £10,859, and the estimated net benefit at a threshold of £20,000 was estimated to be £116 (95% confidence interval: -£58 to £291). The probability that the intervention was cost-effective at this threshold value was 0.77.

Methods

Model structure

Cohorts of 1,000 patients were simulated. These cohorts were based on the characteristics of the 641 trial participants. Cohorts differed according to age at randomisation, sex and trial allocation of the patient groups modelled. A set of discrete, mutually exclusive states were created and defined by the presence (or absence) of a CVD-related condition, or with death (Figure 1). Sequences of states experienced by the simulated cohort members defined clinical pathways in which QALYs (associated with utilities and mortality) and costs were accumulated. Cost-effectiveness, as measured by the averages of costs and QALYs in each arm, was the primary outcome. These averages were calculated and allowed for the construction of net benefit statistics. Costs were expressed in 2012/13 sterling prices.

The model is based on adapted updated versions of models used in previous health technology assessments in the area of CVD risk.[15 16] A National Health System perspective was adopted. The model cycled annually. Both costs and outcomes were subject to a half-cycle correction.[17] Consistent with the inclusion criteria of the trial, and the construction of the QRISK2 algorithm,[8] patients were assumed to be free of CVD when they entered the model – this corresponds to the 'event free' state. Subsequent states correspond to the occurrence of the events used in the QRISK2

algorithm – acute myocardial infarction (AMI), angina, transient ischaemic attack (TIA) and stroke – and to post-event states, e.g. a 'post-stroke' state (Figure 1).

Patients cycled the model until death, or age 100, at which point they were assumed to die. A total of 1,000 iterations of the model were simulated, in which values of input parameters were varied simultaneously. Each iteration used a value drawn from probability distributions assigned to particular input parameters of the model as described below, in the supplementary material and in Salisbury et al.[3] Probabilistic sensitivity analysis was used to quantify uncertainty around point estimates of net benefit. The model was implemented in Excel 2013 (Microsoft: Redmond, Washington).

Probability of transitioning to primary and secondary states

The probability of entering a particular state is determined by CVD risk. Initial risk scores of patients at the beginning of the model, corresponding to the event-free state, were based on information collected in the RCT (Table 1). CVD risk in the initial year (year 0) is thus average participant baseline QRISK2 score. Change in CVD risk at the end of this year/start of the next year (year 1) is measured by QRISK2 score calculated at 12-month follow-up and adjusted for baseline risk, details of which are provided in Salisbury et al.[3] CVD risk in subsequent years was obtained by adding percentage increases obtained from growth rates in annual risk in males when all input values to the QRISK2 algorithm other than age were held constant.

Growth rates from males were used because the level of CVD risk is higher for males than for females at all ages, other variables being constant. Using the relatively more rapid growth rates observed in female risk levels as a basis for extrapolation would

have meant that at some ages female risk was much higher than male risk. The use of male risk growth rates constrains female risk levels to be below male levels at all ages, ensures that risk does not rise above 100%, better reflects estimated prevalence of risk in males and females, and more generally ensures that the cost-effectiveness results are based on plausible risk profiles.[3]

The QRISK2 algorithm is not validated for ages beyond 84. Risk for patients surviving to 85 and above was obtained by extrapolating 10-year risk by 1% per annum, which corresponds to the coefficient obtained from an ordinary least squares regression of QRISK2 scores on age.

Ten-year risk scores were converted into an annual risk of any event to reflect the annual cycles of the model. Annual risk scores of *any* defined CVD event were then disaggregated into the risk of a *specific* event – AMI, angina, TIA and stroke – using data on the incidence of these conditions by age and sex. The sources for these data and the input values used are described in the online supplementary material. Further detail on their calculation is available in Salisbury et al.[3]

These incidence rates establish the probability of moving from the event-free state to a specific CVD-related event state; that is, they establish the risk of a primary event. Transitions to secondary events (any event after the primary event) are determined by the age and sex-specific transition probabilities given in Ara et al,[15] who describe in detail the data sources and methods used in their construction. Permitted transitions between states are listed in the online supplementary material (Table A1).

The probability of death due to causes not related to CVD risk was based on standardised mortality ratios calculated from the most recently available (2012) Office of National Statistics Interim Life Tables.[18] This mortality ratio excluded CVD-related

ICD-10 codes (I20-I25 and I60-I69). The risks of mortality used in each iteration of the model were based on draws from a univariate normal distribution.

Simulated participants were constrained to experience no more than three CVD events, an assumption that reflected data availability and model tractability. The same assumption was used in Ara et al.[15] However, few of the 1,000 simulated participants approached experiencing three events, and therefore the assumption is unlikely to have influenced cost-effectiveness conclusions.

Duration of effect of intervention

The duration of the effect of the Healthlines intervention on CVD risk beyond the end of trial follow-up is unknown, but the modelling thereof is the principal motivation for undertaking the simulation modelling described here. Four different scenarios based on different durations of effect were modelled, and their implications for cost-effectiveness compared. This is similar to the approach of Mistry et al.[19]

The scenarios modelled are of durations of intervention effect of one, two, and five years from baseline, and for remaining lifetime. If, for example, the duration effect is two years, then participants in the intervention arm receive the benefit of lower risk for two years, after which they are modelled as having the same sex- and age-adjusted risk as participants in the control arm. Similar logic applies to the other scenarios. In the case of a lifetime duration of effect, risk is permanently lower in the intervention arm. To avoid sudden 'jumps' in risk at the point at which the intervention ends, the model uses a smoothing adjustment which calculates the average score of intervention arm risk and usual care risk for the year after which the modelled duration of effect expires.

Data on utility

QALYs in year zero of the model were obtained from participant responses to the EQ-5D-5L measure at baseline, six and 12 months of RCT follow-up, and were 'cross-walked' to UK EQ-5D-3L instrument and valued using the Euroqol UK value set.[20] QALYs were adjusted to account for between-arm differences observed at the end of trial follow-up. For other years of the model, age- and sex-adjusted population EQ-5D norms were estimated from Ara and Brazier[21] to provide baseline utility scores that applied to the event-free state. These EQ-5D data were used to calculate QALYs.

Multiplicative adjustments, which assume a constant proportional effect on baseline utility,[21] were made to reflect the decremental impact of experiencing CVD-related health states. Ara and Brazier[21] was used as the source of state-specific utilities other than TIA, which were drawn from Luengo-Fernandez et al,[22] and for unstable angina. It was assumed that the utility estimates for angina in Ara and Brazier related to stable angina; it was further assumed that utility associated with the unstable angina health state would be 90% of the stable angina values, as in Ara et al.[15]

Condition-specific utility values were drawn from univariate normal distributions, as recommended by Ara and Wailoo,[23] to reflect uncertainty in mean values. Utilities corresponding to post-event states were never lower than for the event state itself. This means, for example, that utilities of the "post-stroke" event state were higher than or equal to the "stroke" state, implying that experiencing a stroke had a greater negative impact on average on patient utility than did experiencing the "post-stroke" state.

It was assumed that the second and third events (such as second and third non-fatal strokes) had the same impact on utility as the first event. This rules out multiplicative

impacts of events on quality of life. The utility values associated with different states are presented in the online supplementary material (Table A2).

Data on cost

A health-system perspective was adopted for the analysis, and hence only NHS costs were considered. This excluded consideration of any personal or societal costs associated with, for example, incapacity and exit from the labour force connected with a debilitating but non-fatal stroke

The costs of health states were based, in most cases, on Ward et al[24] and Ara et al.[15] The first year of the model also included costs of the intervention, and NHS costs incurred in each arm. The costs of each health state is described in the online supplementary material.

The cost estimates in Ward et al[24] and Ara et al[15], derived from systematic reviews, were updated where appropriate and possible with new data, as described in more detail in Salisbury et al.[3] Mean costs enter the simulation model at each iteration as draws from a gamma distribution.

Cost effectiveness analysis

The simulation model uses information on the NHS costs and QALYs observed during the 12-months of trial follow-up in the initial year (year 0). All subsequent costs and QALYs are simulated by the model as a function of QRISK2 scores using the methods described above. Costs and outcomes were both discounted at 3.5% per year, in line with NICE recommendations.[10] Cumulative costs and QALYs were obtained for the lifetime of cohort members by calculating probability-weighted averages of the number of patients in each state, the length of time patients have

been in particular states, and the costs, mortality and quality of life associated with each state.

Results

The mean age of males (females) in the trial was 67 (69), and males comprised 80% of trial participants. Table 1 contains baseline and adjusted 12 month QRISK2 scores – higher scores indicate higher CVD risk.

Table 2 provides the results of the cost-effectiveness analysis for different durations of intervention effect. The longer the assumed duration of effect, the more likely it is that the intervention is cost-effective at cost effectiveness thresholds conventionally employed (i.e. £20,000 per QALY). It is notable that, even if the beneficial effects of the intervention on CVD risk last only one year, the intervention is likely to be cost-effective. This is also apparent in the cost-effectiveness acceptability curves, where a monotonic relationship between duration of the probability of cost-effectiveness is evident (

Figure 2). The corresponding cost-effectiveness planes for each scenario illustrate this point in a different way (Figure 3). At longer durations of effect, almost all of the 1,000 simulated incremental cost/incremental pairs are in the northeast or southeast quadrants. At shorter durations, an increasing but still modest number of these pairs are in the northwest or southwest quadrants.

The small QRISK2 difference between arms means that the control and intervention groups have very similar risk profiles once the assumed duration of effect expires. The lifetime cost-effectiveness results are therefore influenced, especially at short

durations of effect, by the inclusion of costs and QALYs observed during the 12-month period of trial follow-up. The between-arm cost and QALY differences in the initial 12 months are propagated forward over the remaining lifetime of trial participants, and are more influential than the subsequent minor differences in costs and QALYs associated with different levels of simulated QRISK2. Nevertheless, the differences in QRISK2 are consequential at longer durations of effect, since they are associated with fewer CVD events in the intervention arm.

Discussion

Cost-effectiveness over the lifetime of participants in the Healthlines telehealth trial was estimated using a cohort simulation model. The probability of cost-effectiveness increased with longer durations of effect, but even with the shortest duration of effect the intervention was estimated to be cost-effective. These results reflect the cost-effectiveness analysis at 12 months: because of the small difference in QRISK2 between arms, the QALY difference observed at the end of trial follow-up has a major influence on lifetime cost-effectiveness.

The model is subject to a number of limitations. The quality of the output reflects the assumptions and data used to construct and populate the model. The QRISK2 algorithm is not validated for ages beyond 84, and we made an assumption as to growth in risk for the small number of simulated trial participants who lived to 85 and beyond.

As in all modelling exercises of this type, the results may be sensitive to structural assumptions, such as the number of health states modelled.[11] We cannot eliminate the possibility that alternative representations of clinical pathways may produce different conclusions. However, we have relied on a representation of health states

that is consistent with the QRISK2 algorithm, the defined events (e.g. stroke) of which are represented as distinct states in the model.

The model understates uncertainty associated with QRISK2 because the variance structures underlying the algorithm are not published or otherwise available, and the consequence of this is to narrow confidence intervals around net monetary benefit statistics. This may have implications, in particular, for the probability of cost-effectiveness.

We have not accounted for non-health service costs, which may have consequences for carers and the wider economy for some of the conditions modelled, such as stroke.[25] However, it is not clear if accounting for these costs would necessarily alter the between-arm comparison of cost-effectiveness, since slightly fewer fatal and non-fatal strokes would be experienced in the intervention arm.

Finally, the analysis does not identify the most plausible duration of effect. Evidence from long-term follow-up is necessary to conclusively answer this question, although synthesis of evidence from similar trials and relevant observational studies may also offer a useful complementary approach to long-term follow-up.

Comparison with other literature

Comparison of the findings of this study with other literature assessing the long-term cost-effectiveness of interventions directed at managing CVD risk is complicated by differences in the study design used to inform the modelling, patient profiles, and the nature of the interventions examined. However, the approach of using different assumed durations of effect, or different effect sizes, is encountered in similar studies.

For example, the evaluations of CVD interventions from a long-term perspective undertaken by Mistry et al[19], Asaria et al[26] and Penaloza-Ramos et al[27] are all sensitive to some degree to assumptions made concerning the duration of intervention effect. This is in spite of differences between these studies in population characteristics, CVD risk equation used and interventions studied, which preclude a comparison of the findings of the present study and these other analyses.

Studies also differ in the study design used to inform long-term cost-effectiveness modelling. The effect estimates used as the basis of modelling in our study are those of the 'intention to treat' analysis of the Healthlines RCT. This is a source of difference between the present paper and, for example, the economic modelling undertaken in support of the routine use of "health checks" in the NHS in England.[28] The economic model developed to analyse the consequences of these health checks was based on a much more extensive simulation involving synthesis of various model parameters, compliance rates and effect estimates from a variety of sources.

Ultimately, although modelling and evidence synthesis will continue to be important sources of evidence in this area, definitive evidence on the long-term consequences for CVD risk of Healthlines (and similar interventions) will require RCTs with long-term follow-up.

CONCLUSION

The Healthlines telehealth service is likely to be cost-effective for individuals with raised CVD risk when a lifetime perspective is adopted. Results are somewhat sensitive to the assumed duration of intervention effect. When considering the deployment of large scale telehealth programmes in this area, decision makers may need to consider the longevity of the behavioural and other changes rendered by the

type of telehealth service studied in the Healthlines RCT, alongside other evidence concerning the long-term cost effectiveness of similar interventions for CVD risk.

Tables and figures

Table 1 QRISK2 scores at baseline and after 12-months of follow-up

	Control arm		Intervention arm	
	Baseline	12 month follow-up, adjusted for baseline	Baseline	12 month follow-up, adjusted for baseline
QRISK2 score for males	31.59	32.00	31.83	31.60
QRISK2 score for females	27.73	28.24	27.86	27.84

Note: The data are presented as levels of QRISK2 as it is the level of risk that determines the probability of events such as stroke or acute myocardial infarction.
These data are based on imputed QRISK2 scores – multiply imputed data are used in the base case economic evaluation at 12 months from randomisation.[3] These data are based on CVD risk of all of those randomised (n=641) in the RCT. The methods used for multiple imputation are described in further detail in the companion 12 month economic evaluation paper. [12]

Table 2 Base case cost-effectiveness results for different durations of effect: per-patient average costs and effects

	Modelled duration of effect			
	1 year	**2 years**	**5 years**	**Lifetime (permanent) effect**
Control arm NHS costs	£6,595	£6,617	£6,608	£6,602
Intervention arm NHS costs	£6,726	£6,741	£6,714	£6,657
Control arm QALYs	8.573	8.573	8.573	8.572
Intervention arm QALYs	8.584	8.586	8.589	8.598
Incremental costs (95% CI)	£131 (£125 to 138)	£124 (£118 to 130)	£107 (101 to 112)	£55 (49 to 61)
Incremental QALYs (95% CI)	0.011 (0 .011 to 0 .011)	0.013 (0 .012 to 0 .013)	0.016 (0.016 to 0.017)	0.026 (0.026 to 0.027)
ICER	£11,776	£9,886	£6,477	£2,091
Probability cost effective at £20,000 threshold	0.74	0.84	0.95	0.99
Probability cost effective at £30,000 threshold	0.87	0.93	0.99	1.00
NMB at threshold of £20,000 (95% CI)	£92 (-172 to 352)	£127 (-144 to 382)	£223 (-153 to 468)	£472 (197 to 728)

SD: Standard deviation; CI = Confidence interval; QALYs = Quality-adjusted life years; ICER = Incremental cost-effectiveness ratio; CE = Cost-effectiveness; NMB = Net monetary benefit

Figure 1 Simulated model states

This figure based is on Figure 27 of Ward et al[24]

Figure 2 CEACs from lifetime simulation assuming different durations of effect

Figure 3 Cost-effectiveness planes from lifetime simulation assuming different durations of effect

Contributorship statemement: PD and SH: Conducted economic analysis. RA: Led development of original simulation model, which was updated and modified by PD for the Healthlines study. Provided advice on model development and adaptation. LE: Acted as trial manager. Undertook participant recruitment and follow-up, data collection and data entry. AF: Participant recruitment and follow-up, data collection and data entry for the RCT. CS: Led protocol development and the funding application for the programme grant, acted as chief investigator with overall responsibility for conduct of the RCT. All authors had a role in interpreting the data. PD wrote the first draft of this article, and all authors contributed to subsequent revisions. All authors approved the final version for submission.

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Data sharing: The data used in the paper are based on the sources described in the main text and supplementary material, also on summarised data from the Healthlines RCT. Requests for the sharing of the patient-level data from the Healthlines RCT that underlies summarised data presented here may be made to CS. Consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low.

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Ethics: The Healthlines trial was approved by the National Research Ethics Service Committee South West – Frenchay (Reference 12/SW/0009). All participants provided informed consent to take part in the trial.

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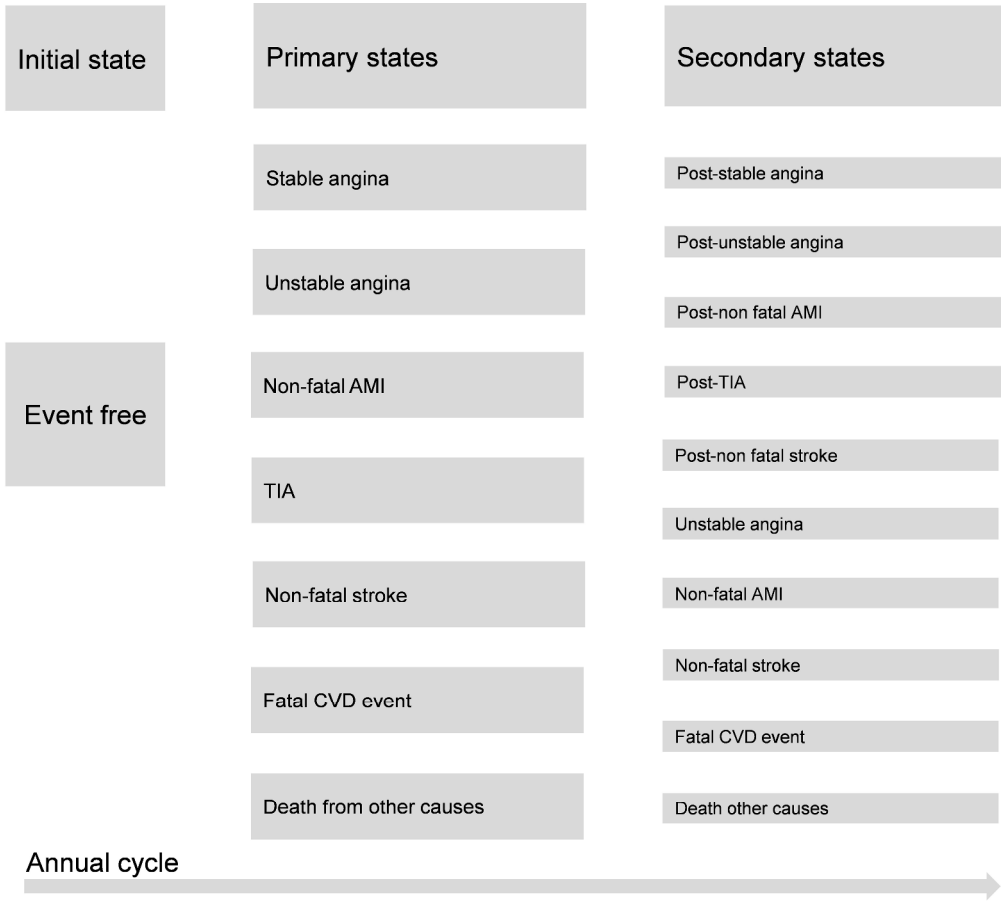

Simulated model states‼ ┼ ‼ ┼ Note to figure: This figure based is on Figure 27 of Ward et al[24]

Figure 1
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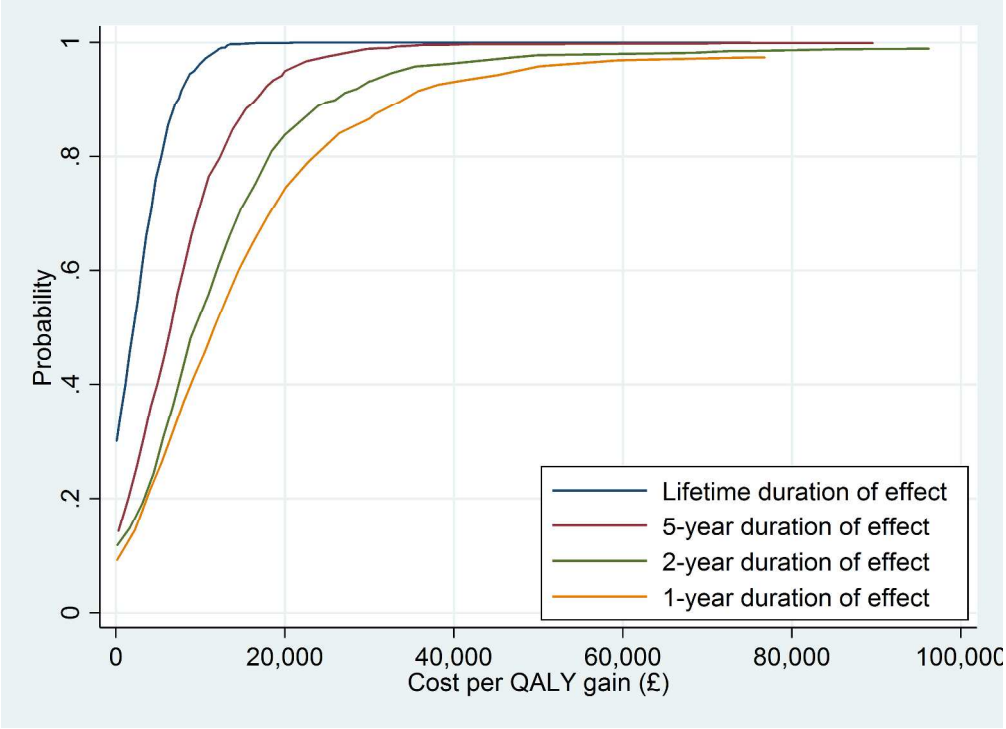
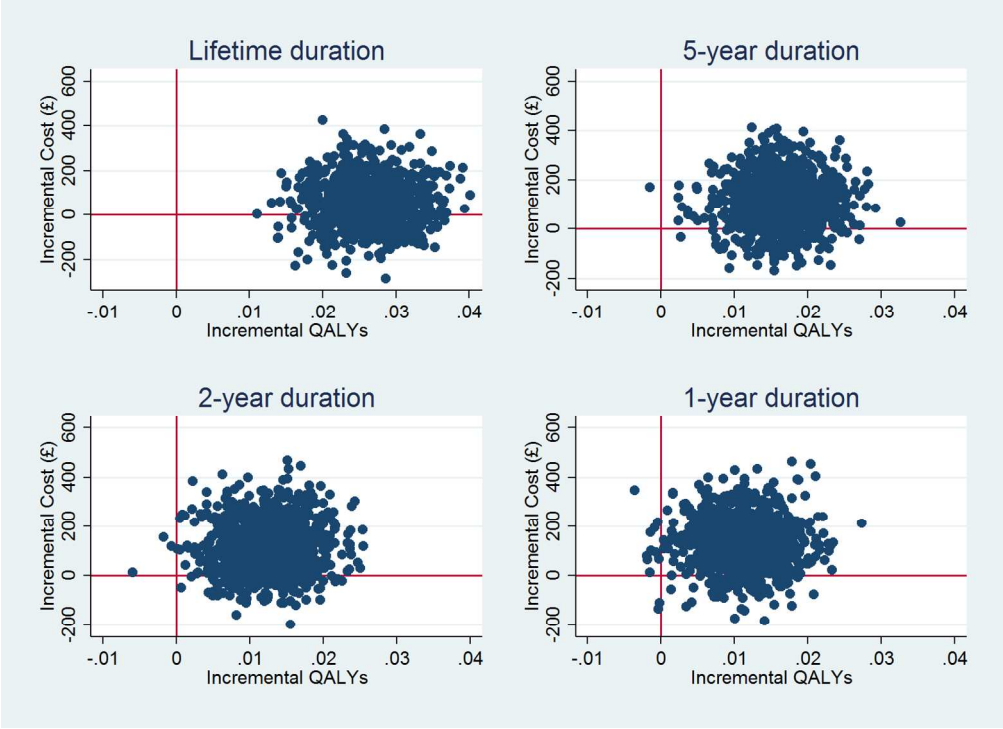


CEACs from lifetime simulation assuming different durations of effect
Figure 2



Cost-effectiveness planes from lifetime simulation assuming different durations of effect
Figure 3

Appendix – online supplementary information

A1 Permitted transitions in simulation model

Event free state to primary states

Event free to Primary Stable Angina (SA)

Event free to Primary Unstable Angina (USA)

Event free to Primary AMI

Event free to Primary TIA

Event free to Primary Stroke

Event free to Fatal CVD event (FCVD)

Event free to Death other causes (DOC)

Primary states to subsequent states

PRIMARY_SA to SECONDARY_(USA or 1st AMI or 1st Stroke or FCVD or DOC) else post SA

PRIMARY_USA to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post USA

PRIMARY_AMI to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post AMI

PRIMARY_TIA to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post TIA

PRIMARY_Stroke to SECONDARY_(1st Stroke or FCVD or DOC) else post Stroke

Post-primary states to subsequent states

Post PRIMARY_SA to SECONDARY_(USA or 1st AMI or 1st Stroke or FCVD or DOC) else post SA

Post PRIMARY_USA to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post USA

Post PRIMARY_AMI to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post AMI

Post PRIMARY_TIA to SECONDARY_(1st AMI or 1st Stroke or FCVD or DOC) else post TIA

Post PRIMARY_Stroke to SECONDARY_(1st Stroke or FCVD or DOC) else post Stroke

Secondary state transitions

SECONDARY_SA to SECONDARY_((USA or 2nd AMI or 2nd Stroke or FCVD or DOC) else post SA

SECONDARY_USA to SECONDARY_((2nd AMI or 2nd Stroke or FCVD or DOC) else post USA

SECONDARY_AMI to SECONDARY_((2nd AMI or 2nd Stroke or FCVD or DOC) else post AMI

SECONDARY_TIA to SECONDARY_((2nd AMI or 2nd Stroke or FCVD or DOC) else post TIA

SECONDARY_Stroke to SECONDARY_((2nd Stroke or FCVD or DOC) else post Stroke

Post SECONDARY_SA to SECONDARY_(USA or 2nd AMI or 2nd Stroke or FCVD or DOC) else post SA

Post SECONDARY_USA to SECONDARY_(2nd AMI or 2nd Stroke or FCVD or DOC) else post USA

Post SECONDARY_AMI to SECONDARY_(2nd AMI or 2nd Stroke or FCVD or DOC) else post AMI

Post SECONDARY_TIA to SECONDARY_(2nd AMI or 2nd Stroke or FCVD or DOC) else post TIA

Post SECONDARY_Stroke to SECONDARY_(2nd Stroke or FCVD or DOC) else post Stroke

Notes to A1: SA = Stable angina; USA = Unstable angina; AMI = Acute myocardial infarction; TIA = Transient ischaemic attack; FCVD = Fatal cardiovascular disease event; DOC = Death other causes
This is the same list of permitted transitions described as in Ara et al [1] and Ara et al [2]. A1 contains the same information as Table 82 in Ara et al [1].

INPUT VALUES, REFERENCES AND PROBABILITY DISTRIBUTIONS FOR MODEL PARAMETERS

Table A2 provides a map to the various model parameters, input values, and associated probability distributions from which input values for specific model runs were drawn, and which are presented in more detail where applicable.

A2 Key input parameters and associated probability distributions

Parameter	Input values	Probability distribution	Comments
Health state utility values	Various; listed in Table A3	Normal	Ara and Wailoo[3] recommend the use of normal distributions to characterise the uncertainty in mean utilities
Health state costs	Various, listed in Table A4	Gamma	A number of sources, eg Gray et al [4], recommend using gamma distributions in characterising uncertainty in cost variables
Incidence rates for primary CVD events	Various, listed in Table A5 and Table A6	N/A	We follow Ward et al[5] and Ara et al[2] in using the mean values of published incidence rates in each model run
CVD Risk	Based on age and sex adjusted QRISK2 scores from baseline and 12m follow-up that are	N/A	The variance structures underlying the QRISK2 algorithm are not published and hence we

	presented in Table 1 in the main text, and then adjusted subsequently using the QRISK2 algorithm		could not characterise uncertainty in this measure. See Discussion in main paper.
Risk of death from non-CVD causes	Based on standardised mortality ratios published by the ONS	Normal distribution	We follow Ara et al[2] in using a normal distribution for model draws

UTILITIES

Ara and Brazier[6] was used as the source of state-specific utilities other than TIA, which are based on Luengo-Fernandez et al[7]. It was assumed that the utility estimates for angina in Ara and Brazier related to stable angina, and that unstable angina health utilities would be 90% of the stable angina values, as in Ara et al.[2]

As further noted in the main text, any 'third' events, i.e. those occurring after a secondary event, have the same utility as the 'second' event.

A3 Health state utility values

Health state	Mean utility value
Primary stable angina	0.615
Primary unstable angina	0.556
Primary AMI	0.721
Primary TIA	0.760
Primary stroke	0.626
Post-primary angina	0.775
Post-primary unstable angina	0.701
Post-primary AMI	0.742
Post-primary TIA	0.78
Post-primary stroke	0.668
Secondary stable angina	0.541
Secondary unstable angina	0.489
Secondary AMI	0.431
Secondary TIA	0.760
Secondary stroke	0.479
Post-secondary stable angina	0.715
Post-secondary unstable angina	0.647
Post-secondary AMI	0.685
Post-secondary TIA	0.78
Post-secondary stroke	0.641

Costs

A detailed discussion of the cost data used to model each state is provided in Salisbury et al.[8] Briefly, the costs of stable and unstable angina, of non-fatal acute myocardial infarction a are based on Ward et al[5] and Ara et al.[2] The cost of fatal

acute myocardial infarction are based on Clarke et al.[9] The costs of non-fatal stroke and of transient ischaemic attack are based on Luengo-Fernadez et al.[7] The cost of fatal stroke is based on Youman et al.[10] In all cases, costs were adjusted to 2012/13 sterling prices as described in Salisbury et al.[8]

A4 Health state costs

Health state	Mean cost in 2012/13 £ prices
Stable angina	606
Stable angina in subsequent years	356
Unstable angina	4,324
Unstable angina in subsequent years	453
Non-fatal acute myocardial infarction	3,362
Post non-fatal acute myocardial infarction	356
Fatal acute myocardial infarction	1,846
Transient ischaemic attack	3,963
Transient ischaemic attack in subsequent years	1,380
Non-fatal stroke	8,989
Non-fatal stroke in subsequent years	1,976
Fatal stroke	9,493

INCIDENCE RATES FOR PRIMARY EVENTS

Incidence rates for primary events are used to calculate the probability of one of stable angina, unstable angina, acute myocardial infarction (AMI), stroke, and transient ischaemic attack (TIA). These incidence rates are then used to disaggregate the risk of any such event, measured by the QRISK2 score, into the risk of a single event.

The data sources and adjustments made to data are described in more detail in Salisbury et al. [8] Here, we briefly describe these sources, and present in A5 and A6 the incidence data used in the simulation model.

The incidence of angina was taken from data for England reported British Heart Foundation Coronary Heart Disease Statistics 2012,[11] using the data reported for England. This was split into incidences of stable and unstable angina using incidences reported in Sutcliffe et al. [12] Incidence of fatal and non-fatal AMI was also taken from British Heart Foundation Coronary Heart Disease Statistics 2012.[11] Incidence of first ever stroke was based on Wang et al, [13] and incidence on mortality from strokes was based on Lee et al. [14]

Incidence of TIA is taken from British Heart Foundation Stroke Statistics 2009. [15]

A5 Incidence rates of CVD events per 1,000 males per year

Age band	Stable angina	Unstable angina	Non-fatal AMI	Fatal AMI	TIA	Non-fatal stroke	Fatal stroke
55-64	0.84	0.25	0.28	0.04	0.74	0.65	0.08
65-74	1.16	0.35	0.42	0.11	1.45	1.27	0.16
75-84	0.75	0.23	0.73	0.29	3.27	2.73	0.35
85+	0.75	0.23	1.23	0.76	7.94	5.12	0.65

A6 Incidence rates of CVD events per 1,000 females per year

Age band	Stable angina	Unstable angina	Non-fatal AMI	Fatal AMI	TIA	Non-fatal stroke	Fatal stroke
55-64	0.35	0.11	0.07	0.02	1.05	0.63	0.14
65-74	0.74	0.22	0.18	0.06	2.18	1.23	0.28
75-84	0.57	0.17	0.38	0.22	5.61	2.64	0.6
85+	0.57	0.17	0.75	0.64	9.14	4.95	1.13

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CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Lines 60-87
		Present the study question and its relevance for health policy or practice decisions.	Lines 88-97
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Lines 99-108
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Lines 99-103
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Lines 119-120
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Lines 109-118
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Lines 88-97
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Lines 262-263
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Line 139-140
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Estimates are based on effectiveness data from the Healthlines RCT (Lines 109-129)
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Not applicable
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Lines 220-226
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable

Section/item	Item No	Recommendation	Reported on page No/ line No
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Lines 246-257 in main text, and page5-6 of supplementary material
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Line 141
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Lines 132-140 and Figure 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Lines 142-202
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Lines 132-218
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 in main text, and Tables A2, A3, A4, A5and A6 in the appendix
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2 in main text
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Not applicable
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Table 2 and Figure 2 in the main text
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Lines 291 to 347

Section/item	Item No	Recommendation	Reported on page No/ line No
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 1
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 2

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist