Patient-Accessible Tool for Shared Decision Making in Cardiovascular Primary Prevention: Balancing Longevity Benefits Against Medication Disutility

Running title: Fontana et al.; Patient-accessible tool for shared decision making

Marianna Fontana, MD*; Perviz Asaria, MBBS, MRCP, MPH*; Michela Moraldo, BSc; Judith Finegold, MA, MBBS, MRCP; Khalil Hassanally, BSc, MBBS; Charlotte H. Manisty, MRCP, PhD; Darrel P. Francis, MA, MD, FRCP

International Centre for Circulatory Health, National Heart and lung Institute, Imperial College London, London, United Kingdom

*contributed equally

Address for Correspondence:
Mariana Fontana, MD
The Heart Hospital Imaging Center
16-18 Westmoreland Street
London, W2 1LA, United Kingdom
Tel: +44 2034563081
Fax: +44 2034563086
E-mail: marianna_fontana@yahoo.it

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Abstract

**Background**— Primary prevention guidelines focus on risk, often assuming negligible aversion to medication. Yet most subjects discontinue primary prevention statins within 3 years. We quantify real-world distribution of medication disutility, and separately calculate average utilities for a range of risk strata.

**Method and Results**—We randomly sampled 360 members of the general public in London. Medication aversion was quantified as the gain in lifespan required by each individual to offset the inconvenience (disutility) of taking an idealised daily preventative tablet. In parallel, we constructed tables of expected gain in lifespan (utility) from initiating statin therapy for each age group, sex and cardiovascular risk profile in the population. This allowed comparison of the widths of the distributions of medication disutility and of group-average expectation of longevity gain. Observed medication disutility ranged from 1 day to >10 years of life being required by subjects (median 6 months, inter-quartile range 1 to 36 months) to make daily preventative therapy worthwhile. Average expected longevity benefit from statins at ages ≥50 years ranges from 3.6 months (low-risk women) to 24.3 months (high-risk men).

**Conclusions**—We can no longer assume that medication disutility is almost zero. Over a quarter of subjects had disutility exceeding the group-average longevity gain from statins expected even for the highest-risk (i.e. highest-gain) group. Future primary prevention studies might explore medication disutility in larger populations. Patients may differ more in disutility than in prospectively-definable utility (which provides only group-average estimates). Consultations could be enriched by assessing disutility, and exploring its reasons.

**Key words:** statin, primary prevention, compliance/adherence
Introduction

Initiation of lifelong primary prevention therapy for cardiovascular disease in a high risk patient should be based on a shared decision-making process between patient and doctor following clear presentation of appropriate information, including quantification of the risks and benefits expected from treatment and the cost and inconvenience (disutility) to the patient. This ideal scenario is almost never achieved.

Currently, primary prevention practice focuses on risk stratification using population-based statistical estimates to determine which individuals would have most to gain from preventative therapy.1 Doctors are documented to view risks differently from patients, and both have difficulty in evaluating, perceiving and conveying risks and benefits in an easily understood manner.2-5 The benefits of primary prevention are thus often presented to the patient without formal quantification of the cost, harms or inconvenience they might incur. However patients do understand risks and trade-offs3 and trust doctors more when presented with numerical information than given vague interpretations of risk.6

Previous interventions, aimed at improving adherence, have used new methods to convey cardiovascular risk rather than tackling the underlying reasons why people stop medication. The focus has been on individual counselling, and on quantitative and graphical displays, or the use of imaging techniques such as coronary CT scans to improve risk perception.7-9 These are based on the principle that better risk perception will lead to higher adherence and persistence with primary prevention therapy.10-12

Patient inconvenience, or medication disutility, has rarely been taken into consideration when initiating therapy. Knowing one’s risk to be high does not necessarily mean that one will, must, or even should take a preventive step. Taking action is dependent on many factors, and a
large part of a patient’s resistance to treatment involves the reluctance to embark on a lifetime of medication. Statins are cost-effective for most persons with even modestly elevated cholesterol or any coronary heart disease risk factors if they do not mind taking a pill daily\textsuperscript{13-17}.

When medication disutility is incorporated into the risk-benefit equation, it becomes clear that cost-effectiveness of statins is extremely sensitive to medication disutility. However, in spite of its crucial importance in determining the incremental cost-effectiveness ratio (ICER), medication disutility data is very scarce\textsuperscript{14}. Owing to lack of data, guideline-writers have had to work on the basis that medication disutility is negligible. Cost-effectiveness analyses have typically used base case estimate of zero disutility, and covered up to 0.01 or 0.02 in sensitivity analyses\textsuperscript{13,14,17}. Expressed as an absolute lifespan gain, for current English life expectancy at age 50 years, this translates to covering in sensitivity analyses the possibility that patients may be willing to give up a lifespan as large as 3.6 (or at most 7.2 months) to avoid medication. The analyses highlight that conclusions are exquisitely sensitive to this value, but there is limited data on which to base an estimate.

We do not know how close to zero medication disutility is. Nor do we know whether its distribution is fairly narrow, in which case a single value may be suitable for use in disease prevention decisions for all, or whether the distribution is wide, in which case it may be advisable to assess disutility within individuals in clinical practice.

Our study is the first to attempt to quantify the spectrum of individual medication disutility for primary prevention in a sample of the general population. We juxtapose it against the spectrum of expected longevity gain from initiation of statin therapy across the same general population.
Methods

Medication disutility

Medication disutility was assessed in a random sample of the general population of London by face-to-face interview using a structured questionnaire. Medication disutility has been assumed to lie between 0 - 0.001 in Time Trade-Off studies used in previous economic calculations, which roughly translates to being willing to give up between 0 - 5 months of life to avoid taking daily medication. We designed our study to be able to estimate the proportion of subjects having medication disutility greater than 6 months, with 95% precision and a confidence interval of ±2%, even if the actual proportion of subjects in the population with this level of medication disutility was as small as 5%. Power calculations were based on the assumption that medication disutility would be normally distributed in the population. The sample size required on this basis was a minimum of 300 participants. We planned to recruit 360.

Study Population

Survey participants were approached in public thoroughfares in London, on the basis that this would potentially be the target population for cardiovascular screening and primary prevention. Participants were approached and recruited on three days in October and November 2010. Members of the public were approached until 360 agreed to participate.

Disutility Survey

In order to focus the survey on medication disutility and minimize other potential sources of low compliance such as cost, subjects were asked to imagine an idealised tablet that was available at negligible cost, with no need for prescription, nor medical supervision, nor follow up blood tests. They were also asked to assume that the tablet would have no side effects and could be started or stopped at will with no consequence other than receiving only partial benefit.
Disutility was assessed by initially asking subjects whether gaining an additional day of expected life would be sufficient benefit for them to commence lifelong therapy with the idealised tablet. If the answer was negative, then the subjects were asked if an additional 10 years of expected life would suffice. If the answer was positive, medication disutility was assumed to lie in the interval between 1 day and 10 years. This range was progressively narrowed using a binary tree (maximum 6 further steps) to reach the benefit required by each subject to offset their personal medication disutility.

The algorithm was constructed to approximately halve the time interval at each step, thus aligning the time points approximately evenly on a log scale. Speed of completion of the algorithm was confirmed by pilot testing and on average took less than 1 minute. Subjects who indicated that 10 years of longevity benefit would be insufficient were classed as having an extreme medication disutility. Demographic information on age, sex, employment status, current use of medication and previous heart attack or stroke were also sought. The full questionnaire is shown in Appendix 1.

Statistics
Survey data were summarised using simple measures of central tendency (mean and median) and spread across quartiles for each age and sex group. The distribution of medication disutility was also examined visually to assess whether it followed a normal distribution, and whether it had the same shape in each age and sex group. Differences on tablet disutility across gender and age were tested using parametric and non parametric tests for both.

The survey was indicated by the local Ethical Committee chair to not require Ethical Committee Approval, because it assessed attitudes to an imaginary medication and was carried out on members of the general public without collection of personally-identifiable information.
Paddington life expectancy gain charts

We calculated the expected average increase in life expectancy due to initiation of statin therapy for men and women with different levels of baseline risk using standard multiple decrement life table methods. Baseline life expectancy was based on all-cause and cardiovascular mortality rates for England and Wales in 2005 obtained from the Office of National Statistics UK. These were then decremented for high-risk groups according to the risk level induced by different permutations and combinations of the following risk factors: tobacco exposure, systolic blood pressure, total cholesterol, age and sex. The size of the decrement for each age-sex-risk combination was calculated by entering values into the SCORE algorithm recommended by the European Heart Association for risk stratification, and obtaining the percentage increase in mortality for each group. The SCORE algorithm compares each risk factor combination to the national average. Data on the national average mean, and the distribution of blood pressure, smoking status and cholesterol were obtained from the QRESEARCH database (2005) which includes data on over 13 million patients spread throughout the UK.

Data on diabetes has not been collected uniformly in SCORE study cohorts. Thus people with diabetes were included in the general SCORE database used for the development of risk functions. However, because of non-uniformity in the ascertainment of diabetes, diabetes was not included as a dichotomous variable into the SCORE risk function. We have followed the same method for decrementation of life expectancy in diabetics in this study.

Blood pressure, total cholesterol and smoking status above the national average level were considered to act multiplicatively to increase cardiovascular risk as per the algorithm C. All in all, 40 different age-sex-risk combination tables were calculated to obtain values of expected longevity benefit for a full spectrum of risk groups (See Appendix 2 and Supplemental Table 1)
for details). The design of the Paddington tables was kept as similar as possible to the SCORE charts, displaying, instead of 10-year risk of fatal cardiovascular disease, the average longevity benefit (in months) that a patient can expect to gain by starting lifelong therapy with statin.

Percentage reduction in cardiovascular mortality with statin therapy was obtained from a meta-analysis of trials of lipid lowering agents in primary prevention populations. For each cardiovascular risk group, life tables were then recalculated with the statin effect. The difference between baseline life expectancy, and life expectancy with the statin therapy, was taken as the average expected longevity benefit. The youngest age at which initiation of statin therapy was modelled was 50 years. The spectrum of cardiovascular risk modelled was based on the distributions of blood pressure, cholesterol and smoking in the UK population, thus the spectrum of longevity benefit represents the average distribution of life years gained from statin therapy in the UK population.

**Results**

Table 1 shows the baseline characteristics of survey respondents. 360 participants were recruited after approaching 379 members of the public. The distribution of medication disutility expressed as longevity gain desired by an individual to offset the inconvenience of taking a lifelong preventative tablet, is shown in Figures 1 and 2 and Appendix 3. Two-thirds of subjects had medication disutility greater than 1 month and 12% had extreme medication disutility (desiring ≥10 years predicted increase in life expectancy to adhere to therapy). Near-zero medication disutility (<1 month longevity benefit required) was expressed by 34% of subjects. There was no relationship between sex and disutility (31±42 months in males versus 26±38 months in females, p=0.30 by t-test, p=0.40 by Mann-Whitney U test). There was no relationship between age and
disutility: Pearson correlation with age was 0.04 (p=0.42), with sqrt(age) was -0.01 (p=0.79), Spearman rank correlation with age was -0.01 (p=0.79) (Figure 1 and 2).

Tables of expected lifespan gain according to age, sex, smoking status, blood pressure and cholesterol level of the subject are shown in Figure 3. The shading on the chart corresponds to the increase in group-average life expectancy for a notional large group of patients with that specified cardiovascular risk profile starting lifelong statin therapy. These life expectancy gains are meaningful only for the group as a whole, as is the case for risk percentages that are also sometimes displayed in this way. In practice, a small proportion of patients will gain the lion’s share of the extra lifespan, while a large proportion will gain no extra lifespan, as shown in Appendix 4. From the age, sex, smoking status, blood pressure and cholesterol, it is not possible to be more specific as to whether one particular patient will gain. Even if a trial were conducted, each individual patient could only be in one arm, and it would not be possible to pinpoint if an individual patient had personally gained or not. The value represents only the mean for patients with that particular risk factor profile.

Figure 4 shows the frequency distribution of medication disutility (top panel), juxtaposed against longevity benefit from statin therapy (bottom panel). The calculated longevity benefit with statin therapy ranges from 5.5 months to 24.3 months in males, and from 3.6 to 18.2 months in females depending on individual cardiovascular risk profile. 99% of the UK population will gain less than 24.3 months of additional life as a result of lifelong primary prevention with a statin, whilst 1% has a risk profile which allows them to gain more than this. Individual-subject medication disutility has a wide distribution in our survey population ranging from less than 1 day to more than 10 years.

Figure 5 shows the expected distribution of longevity benefit in the English population
resulting from distribution of (A) total serum cholesterol (B) systolic blood pressure (C) smoking in the general population with all other risk factors held constant and (D) the distribution of total cardiovascular risk using all 3 variables combined. For each panel (A, B, C), the distribution of longevity benefit with statin therapy was calculated allowing that particular risk factor to vary with a pre-specified distribution (the distribution of that risk factor in the population in the UK) whilst the other risk factors were held constant at the population mean. The distribution of longevity benefit for total cardiovascular risk was calculated using all 3 variables combined in an aggregate risk score using the SCORE algorithm.\textsuperscript{21}

**Discussion**

The implicit assumption in guideline development and clinical protocols for primary prevention of cardiovascular disease, namely that medication disutility is zero or near zero, may not be sound. Much more work remains to be done to develop evidence-based approaches to account for medication aversion during clinical encounters. In our simple study, even for an idealised tablet, more than a quarter of individuals have medication disutility which exceeds the group-mean lifespan gain from statin therapy calculated for a very high cardiovascular risk group.

A simple calculation of averaged expectation of benefit versus disutility might suggest that addition of even such an idealised agent would not be perceived by that individual patient to present a net gain. Whether they would judge the situation differently, if it were made clear that some patients would gain a great deal of lifespan while many gained none, is unknown and might be an important question to explore in future studies.

**Prevalence of medication disutility in the general population**

The prevalence and degree of significant medication disutility in the general population, which is
the target population of primary prevention, may often be much greater than previously assumed. The medication disutility curves (Figures 1 and 2) are not normally distributed but centrifugal, with a standard deviation 1.5 times the mean.Nearly half of the population have disutility greater than double the median or less than half the median. The shape of the medication disutility distribution curve seems similar across age groups, suggesting that its shape is genuine and that ageing with associated perceived nearness of mortality did not have a large effect (Figures 1 and 2).

Medication disutility varies dramatically from person to person, to a much greater extent than estimated cardiovascular risk between individuals. Clinical practice evaluates risk factors using statistical estimates to determine whether taking a statin is worthwhile, but the inter-individual variation in medication disutility, which appears to have a greater effect on net benefit for individuals, is rarely addressed. This variation between individuals in the size of medication disutility is greater than the effect of variation in any one of the common risk factors used to determine thresholds for treatment (Figure 5).

Even if primary prevention guidelines were revised to incorporate a non-zero value for medication disutility, there is no single value that could reasonably be entered because disutility varies to such an extent between individuals; much more so than utility. If our data is representative, then alongside assessing blood pressure, cholesterol and smoking status, it may be informative to assess individual medication disutility and explore its reasons.

Faced with a patient with high expected lifespan gain from preventative therapy but even higher medication disutility, the clinician should not simply withhold therapy. Equally, however, they should not simply prescribe and assume the medication will be taken. High disutility could instead initiate exploration of its underlying reasons.
Use of an idealised tablet to assess medication disutility

We were keen to determine the lower limit of medication disutility and therefore used a hypothetical intervention to assess disutility rather than a real one that might have an adverse reputation. The hypothetical medication enhanced lifespan without having the four principal drawbacks of primary prevention medications: cost to the patient, inconvenience of obtaining a prescription, perceived loss of autonomy to stop and start at will, and adverse symptoms. Removal of these barriers improves compliance with medical therapy for chronic diseases.24

With real drugs, the possibility of side effects, the inconvenience of having to obtain prescriptions and the non-zero cost mean that the distribution of disutility is likely to be greater than the values we obtained, and the spectrum of values might be wider.

Our study should therefore be considered only a lower limit on medication disutility. Nevertheless it identifies that disutility is not near zero, and is not trivial in comparison to the benefits offered by a medication such as a statin. In order to translate this concept into clinical practice further studies with questionnaires specifically designed to investigate real medications used in primary prevention would be needed. Such a design, specific to the individual agent, and a particular cost and arrangement for prescription, will give a more complete picture of real-life medication disutility in a given particular clinical context.

Study limitations and future study design

We did not collect individualised risk factor data on the subjects in our survey and therefore are unable to plot a joint utility–versus–disutility distribution at an individual level. This would only have been possible with detailed background information (including measurement of blood pressure and measurement of blood lipids). We did not impose this step because we wanted this survey to be broadly representative of the general population and not only those willing to
undergo these for a research study. Thus it is important to note that the longevity benefit distributions in Figure 5 describe the general population and not the particular subjects in this survey. We cannot exclude the possibility that our sample of subjects might be unrepresentative of the general population. Furthermore, comparing the individual medication disutility with expected life year gain can be problematic as the difference becomes significant especially at individual level. When used in real life a physician should make clear that a calculated increase of 1 year in life expectancy is an estimated based on an average of lifespan gain between subjects. To make this difficult concept easy to understand for every individual the physician could offer a page with 3 examples of how, amongst a group of 10 people with an average increase of 1 year, individual gain may vary from the mean (Appendix 4).

Our questionnaire was a very simple form of the time trade-off method. This was aimed to be brief to allow us to sample the general population and minimise the possibility of examining only an unrepresentative subset biased towards interest in health. Our choice of survey design achieved a 95% participation rate. In ultimate clinical practice, with a patient voluntarily engaging in a consultation and therefore already showing some level of commitment to the questioner, a more comprehensive tool would be appropriate.

We assessed medication disutility without assessing the individualised expected lifespan. It is possible that people who are formally told that their remaining expected lifespan is short, might have less medication disutility. However, in our dataset, age – known to the public to be the most powerful determinant of mortality risk - did not affect medication disutility. Future studies using individualised utility calculations would be able to test this hypothesis.

It is likely that a participant’s personal disutility may be influenced by context and situation25. For example, if we had questioned patients within a GP surgery or a hospital
outpatient department, then their response may have been influenced by the many health related
cues nearby. We cannot assume that disutility assessed in a public space is equivalent to
disutility that would be assessed in a primary prevention scenario. Future studies are needed to
assess medication disutility in patients attending a primary care service for screening and being
considered for preventative treatment.

Despite our request to imagine an ideal medication accessible without effort and causing
no side effects, participants’ responses may nevertheless have been coloured by an expectation of
a high rate and magnitude of side effects, for example through non-placebo-controlled reports in
the mass media.

Our survey had an upper limit on medication disutility of “>10 years”, which prevents us
from being able to sub-classify subjects beyond this ceiling. However, from a practical point of
view knowing exact disutility numerically when it is already above the maximum achievable
longevity benefit may not be so important as recognising that subjects with such strong
medication disutility do exist.

Since mortality rates change over time, the survival depicted in any period life table will
not perfectly reflect the true survival experience of a cohort. For example, secular improvements
in health mean that actual life expectancy of cohorts is often longer than that predicted using
period life tables constructed by applying present-day survival rates across age groups.
Furthermore, life expectancy varies from country to country and cohort to cohort, so that
Paddington tables might need to be reconstructed for different countries and cohorts.

Our sample is limited to North West London, which may not be representative of other
areas in the UK. However survey participants were drawn from the general population, which is
the target population of primary prevention therapy. To minimise intrusiveness we did not ask
subjects their ethnicity, but we did approach subjects without regard to their apparent ethnicity. Census data show that the general population of London is more ethnically diverse than most of the rest of the UK, with 58% being white British; 11.3% other white, 13.3% South Asian, 10.6% black, 1.5% Chinese, and 5.5% mixed or other. The consistently large variation in medication disutility in both sexes across all age groups suggests that distribution is genuinely wide. Interviewing subjects in other cities is likely to make the distribution not narrower but wider.

Individual medication disutility may be fluid over time, for example being influenced by a personal ‘heart scare’ or a cardiovascular event in a friend or family member. Mass media reports may also be unhelpful because, without the benefit of placebo control comparison, the extent of genuine incremental side effects can easily be overestimated.

Finally, our data reflect medication disutility in a primary prevention cohort and we did not assess the impact of cardiovascular events on medication disutility in secondary prevention. Only one individual in the survey had a previous cardiovascular event. Further studies are needed to investigate the longitudinal behaviour of medication disutility in order to determine how often medication disutility should be re-assessed.

Conclusions

The tables presented in this study are designed to allow both patient and doctor to compare risk and benefit of preventative tablet therapy to determine an average expected net benefit for a notional group of similar patients, using a mutually understood metric of lifespan gain. High disutility in an individual might prompt exploration of the underlying reasons, and enhancing the interaction between patient and clinician in this way might strengthen the consultation.

Guidelines specifying a risk threshold for treatment may have been derived from a tacit
assumption of near-zero medication disutility, which may not be representative for many
subjects. Future public health research could explore more advanced methodologies, since our
simple medication disutility assessment takes only a minute - less than the time taken to measure
cholesterol and blood pressure.

Although still at an early stage, individualised quantification and discussion of
medication disutility, and parallel methods of describing group-average preventative benefits,
might bring us closer to primary prevention that is truly personalised.

Conflict of Interest Disclosures: None.

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**Table 1.** Baseline Survey population characteristics.

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**Figure Legends:**

**Figure 1.** Distribution of medication disutility by sex. This figure illustrates the distribution of medication disutility for an idealised tablet, expressed as lifespan gain in months needed to offset taking daily therapy.
**Figure 2.** Distribution of medication disutility by age. The distribution of medication disutility for an idealised tablet, expressed as number of months needed to make therapy worthwhile.

**Figure 3.** Paddington tables. Months of longevity benefit obtained from statin therapy. Each chart can be read by looking up the patient age, sex, blood pressure, cholesterol level and smoking status. The shading corresponds to the increase in group-average life expectancy for a notional large group of patients with that specified cardiovascular risk profile starting lifelong statin therapy.

**Figure 4.** Disutility versus utility. Frequency distribution of disutility, longevity benefit that subjects expressed a desire for in order to make tablet therapy worthwhile (top panel), and the frequency distribution of utility, actual expected gain in lifespan from statin therapy in the English population (bottom panel). The difference between the two values is the net benefit of tablet therapy. Because utility has a very much narrower spectrum than disutility, for those with a high disutility, regardless of utility statins are a net harm; for those with low disutility, regardless of utility statins are a net benefit. It is only for those in the middle grey zone of the top panel that sex, smoking status, blood pressure and cholesterol are the deciding factors.

**Figure 5.** Expected distribution of longevity benefit in the English population. Distribution of longevity benefit with statin therapy resulting from distribution of a) total serum cholesterol b) systolic blood pressure c) smoking in the general population with all other risk factors held constant. d) shows the distribution of longevity benefit for total cardiovascular risk using all 3 variables combined in an aggregate risk score using the SCORE algorithm.
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**Figure 3**

Cholesterol (mmol/l) [4 5 6 7 8] 160 200 240 280 320 (mg/dl)
**Disutility**
Additional lifespan desired in order to offset inconvenience of having to take a daily tablet.

**Utility**
Additional lifespan gained with statin therapy.

Figure 4
Figure 5

(a) Cholesterol

(b) Blood pressure

(c) Smoking status

(d) Total risk
Patient-Accessible Tool for Shared Decision Making in Cardiovascular Primary Prevention: Balancing Longevity Benefits Against Medication Disutility
Marianna Fontana, Perviz Asaria, Michela Moraldo, Judith Finegold, Khalil Hassanally, Charlotte H. Manisty and Darrel P. Francis

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SUPPLEMENTAL MATERIAL

APPENDICES

Appendix 1 – Sample of Structured Survey

We are doing a survey on whether people think it is worth taking tablets to prevent heart disease and stroke – even if they do not have those conditions already.

This survey is about an imaginary tablet which does not exist.

Please imagine a tablet which:
- Has no side effects
- Costs you next to nothing to obtain (you may be able to buy it cheaply at the supermarket)
- You do not need a prescription for it
- There is no problem if you stop it at any time or if you stop and start – except that you might not get the full benefit

We are trying to see whether people think it is worth taking this tablet every day. It might depend on how much it increases your life expectancy?

Q1. If this tablet gives you one extra day of life on average, so you think you would take it? (Proceed to algorithm on page 2 to define longevity benefit required to offset disutility of taking tablets)

Now some questions about you which will help us analyse the results. If there are any questions now you would rather not answer – please tell us, and we can just skip them.

Q2. Are you on any regular tablets?
Q3. Have ever had a heart attack or a stroke?
Q4. How old are you?
Q5. Male or Female?
Q6. Are you working at the moment?
Q7. If yes, what you do for a living?
Q8. If not, are you a student?

Chart of durations and algorithm
Offer first “1 day” and then “10 years”. If the answers are “no” and “yes” respectively for those first two dates, offer the date at the midpoint (on this chart) between the longest date to which the participant has responded “no” and the shortest date to which the participant has responded “yes”.

1 day
  1 week
  2 weeks
  1 month

2 months
  3 months
  4 months
  6 months

9 months
  10 months
  1 year
  2 years

3 years
  4 years
  5 years
  8 years

10 years
Appendix 2 – calculation of longevity benefit with statin therapy

Baseline life expectancy and increase in life expectancy with statin use were calculated separately for males and females using standard multiple decrement life table methods. A sample life table used to calculate period life expectancy for males is shown in Webtable 1.

Baseline life expectancy for each 5 year age band can be derived from the “control arm” table.

All-cause mortality was calculated for each age group in the population using 2005 data from Office of National Statistics¹,² using the following formula:

\[ nM_x = \frac{nD_x}{nP_x} \]  
*(Equation 1)*

where:

\( n = \) number of years in the age interval  
\( nM_x(\text{all cause}) = \) mortality rate for \( x \)-year age group beginning at age \( x \), i.e. \( x \leq \text{age} < x+n \)  
\( nD_x(\text{all cause}) = \) all cause deaths in \( x \)-year age group beginning at age \( x \)  
\( nP_x(\text{all cause}) = \) mid-year population for \( x \)-year age group beginning at age \( x \)

CVD and non CVD mortality in the population were calculated in a similar fashion using data on CVD and non CVD deaths to give \( nM_x(\text{CVD}) \) and \( nM_x(\text{NCVD}) \)

The conditional probability of all-cause death in 5-year age interval was then calculated to take account of the life years at risk at the beginning of the interval as follows:

\[ nq_x (\text{all cause}) = 2 \times n \times nM_x/(2+n \times nM_x) \]  
*(Equation 2)*

The conditional probability of CVD and non-CVD death are then given by:

\[ nq_x(\text{CVD}) = nM_x(\text{CVD})/nM_x(\text{all cause}) \]

\[ nq_x(\text{NCVD}) = nM_x(\text{NCVD})/nM_x(\text{all cause}) \]
and \[ nq_x^{(all\ cause)} = nq_x^{(CVD)} + nq_x^{(NCVD)} \] 

*Equation 3*

where:

\[ nq_x^{(CVD)} = \text{conditional probability of CVD death in the 5 year age interval} \]

\[ nq_x^{(NCVD)} = \text{conditional probability of non-CVD death in the 5 year age interval} \]

These inputs were then fed into the life table by the standard approach to derive period life expectancy remaining for each age group, \( e^0 \).  

Life expectancy with statin use is shown in the adjacent “statin arm” table. The effects of statin commencement were studied for ages of commencement 50 years and above. The relative risk reduction in the probability of a CVD death at each age over 50 years is given in (Column12) \( RR_{(CVD)} \). These risk reductions were obtained from a meta-analysis of randomised controlled trials of lipid lowering agents. The conditional probability of CVD death \( (nq_x^{(CVD)}) \) was considered to be reduced in that proportion, in people taking statins. The conditional probability of non-CVD deaths \( (nq_x^{(NCVD)}) \) was held constant. Remaining period life expectancy for each age group, \( e^{\text{statin}} \), was recalculated after applying these reductions to derive life expectancy with statins (column 20). Life expectancy gained from statin therapy was defined as the difference in life expectancy from the control arm table to the statin arm table.  

**High and low CVD risk groups:**

The national distribution of systolic blood pressure (SBP), total cholesterol (TC) and smoking were taken from the QRESEARCH database and were as follows:

- **SBP:** 135.7 (sd 19.6) mmHg males, 132.6 (sd 21.5) mmHg females
- **TC:** 5.7 (sd 1.1) mmol/l males, 5.9 (sd 1.1) mmol/l females
- **Smoking:** prevalence 28.1% males, 23.1% females
We generated 40 different combinations (R) of these risk factors. SBP and TC levels above the national average in combination with smoking were assumed to decrease the probability of survival from CVD respectively. The magnitude of the effect on CVD survival probability for each risk factor combination was taken from the SCORE risk algorithm, which estimated the beta coefficients for the effects of each risk factor on CVD survival from a number of large European population cohort studies with 2.7 million person years of follow up. The SCORE algorithm was calculated separately for the effects of risk factors on survival from coronary heart disease (CHD) and stroke. We modified this to get and effect for all CVD by taking an average of the beta coefficients for CHD and stroke. We also updated the population average values of TC and SBP in the SCORE algorithm to reflect the national average values for England. The effects of the combined risk factor combinations on CVD survival were thus calculated as follows:

\[ w = \beta_{TC}(TC_R - TC_{national}) + \beta_{SBP}(SBP_R - SBP_{national}) + \beta_{smoker} \text{ (current)} \quad (Equation 4) \]

where:

\( w \) = weighted sum of all risk factors

\( TC_R \) = total cholesterol of individual at risk

\( TC_{national} \) = national average value for total cholesterol

\( SBP_R \) = SBP of individual at risk

\( SBP_{national} \) = national average value of SBP

\( \beta_{TC} \) = \( \beta \) coefficient of the effect of a 1 mmol/L increase in cholesterol on CVD survival

\( \beta_{SBP} \) = \( \beta \) coefficient of the effect of a 1 mmHg increase in SBP on CVD survival

\( \beta_{smoking} \) = \( \beta \) coefficient of the effect smoking on CVD survival
and:

$$\pi p_{RCVD} = \pi p_{CVD} \exp(w)$$

where:

$$\pi p_{RCVD} = \text{probability of CVD survival for an individual with risk factor combination } R$$

$$\pi p_{1-CVD} = 1 - \pi q_{CVD} \text{ baseline probability of CVD survival in English population}$$

Baseline life expectancy in the “control arm” for each risk group (R) can then be calculated by feeding these values into the “control” life table. Conditional probabilities of non CVD death were assumed to remain constant. Life expectancy with statin use can correspondingly be calculated by feeding these values into the “statin arm” table and applying the relative reductions in CVD mortality. The difference between these two tables in life expectancy remaining at each age is taken to be the average life expectancy gain with statin therapy in each risk group (R).

The frequency distribution for the 40 risk combinations of (R) in the English population was estimated by simulation by drawing a value for SBP, TC and smoking status 10,000 times, randomly and independently from the distributions SP, TC and smoking in the English population in the QRESEARCH database.
Appendix 3 – Distribution of medication disutility for being on other medication and working status.

**Supplemental figure 1.** Proportion of all survey respondents divided according to the use of regular medications expressing various levels of medication aversion, given as number of months longevity benefit desired by the subjects to make therapy worthwhile.

**Supplemental figure 2.** Proportion of all survey respondents divided according to the working status expressing various levels of medication aversion, given as number of months longevity benefit desired by the subjects to make therapy worthwhile.
Appendix 4 – Three examples of how, amongst a group of 10 people with an average increase of 1 year, individual gains may be very different from the mean.

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Average 1 yr gained

Average 1 year gained
# SUPPLEMENTAL TABLE

Supplemental Table 1. Life tables used to calculate period life expectancy for males.

$n =$ number of years in the age interval; $l_x =$ number of people alive at age $x$; $q_x^{(CVD)} =$ probability of dying of cardiovascular disease for $x$-year age group beginning at age $x$, i.e. $x \leq age < x+1$; $q_x^{(NCVD)} =$ probability of dying of non cardiovascular cause for $x$-year age group beginning at age $x$; $d_x =$ all cause deaths in $x$-year age group beginning at age $x$. $\mu L_x =$ person years lived in this age interval; $T_x =$ future years of life remaining at age $x$; $\epsilon_x =$ baseline life expectancy at age $x$; RR$_{CVD} =$ relative risk reduction with statin; $\epsilon_{\text{statin}} =$ life expectancy with statin at age $x$.

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<th>Number of deaths in this age interval</th>
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<th>Average age in life experience when starting at birth $x$</th>
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SUPPLEMENTAL REFERENCES


