

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

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Background—Primary prevention guidelines focus on risk, often assuming negligible aversion to medication, yet most patients discontinue primary prevention statins within 3 years. We quantify real-world distribution of medication disutility and separately calculate the 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 idealized 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; interquartile range, 1–36 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).

Conclusion—We can no longer assume that medication disutility is almost zero. Over one-quarter of subjects had disutility exceeding the group-average longevity gain from statins expected even for the highest-risk (ie, 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. (*Circulation*. 2014;129:2539-2546.)

Key Words: compliance ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ primary prevention.

The 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 the clear presentation of appropriate information, including the 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.

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Currently, primary prevention practice focuses on risk stratification by 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 numeric information than when 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 counseling, 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 depends on many factors, and a large part of a patient's resistance to treatment involves the reluctance to embark on a

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lifetime of medication. Statins are cost-effective for most persons with coronary heart disease risk factors if they do not mind taking a pill daily.^{13–17}

When medication disutility is incorporated into the risk-benefit equation, it becomes clear that the cost-effectiveness of statins is extremely sensitive to medication disutility. However, despite its crucial importance in determining the incremental cost-effectiveness ratio, medication disutility data are scarce.¹⁴ Because of the 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 estimates of zero disutility and covered up to 0.01 or 0.02 in sensitivity analyses.^{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 the data on which to base an estimate are limited.

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 the 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 interviews with the use of a structured questionnaire. Medication disutility has been assumed to lie between 0 and 0.001 in the time trade-off studies used in previous economic calculations,^{15–17} which roughly translates to being willing to give up between 0 and 5 months of life to avoid taking a daily medication. We designed our study to be able to estimate the proportion of subjects having medication disutility of >6 months, with 95% precision and a confidence interval of $\pm 2\%$, 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 they would potentially be the target population for cardiovascular screening and primary prevention. Participants were approached and recruited on 3 days in October and November 2010. Members of the public were approached until 360 agreed to participate.

Disutility Survey

To focus the survey on medication disutility and minimize other potential sources of low compliance such as cost, subjects were asked to imagine an idealized 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 have sufficient benefit for them to commence lifelong therapy with the idealized 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 by 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. The speed of completion of the algorithm was confirmed by pilot testing and, on average, took <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 Appendix I in the online-only Data Supplement.

Statistics

Survey data were summarized by 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 sex and age were tested by using parametric and nonparametric 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 performed 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 the initiation of statin therapy for men and women with different levels of baseline risk with the use of standard multiple-decrement life table methods.¹⁸ Baseline life expectancy was based on all-cause and cardiovascular mortality rates for England and Wales in 2005^{19,20} obtained from the Office of National Statistics UK. These rates 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 Systematic Coronary Risk Evaluation (SCORE) algorithm²¹ 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 with 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) that includes data on >13 million patients spread throughout the United Kingdom.²²

Data on diabetes mellitus have not been collected uniformly in SCORE study cohorts. Thus, people with diabetes mellitus were included in the general SCORE database used for the development of risk functions. However, because of nonuniformity in the ascertainment

Table. Baseline Survey Population Characteristics

	Population (n=360)
Male sex, %	50
Age, y, mean \pm SD	38 \pm 17
Regular use of any medication, %	22
Previous CVD history, %	1

CVD indicates cardiovascular disease.

of diabetes mellitus, diabetes mellitus was not included as a dichotomous variable into the SCORE risk function.²¹ We have followed the same method for the decrementation of life expectancy in diabetic subjects 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 SCORE algorithm. 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 II and Table I in the online-only Data Supplement for details). The design of the Paddington tables was kept as similar as possible to the SCORE charts, displaying, instead of a 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 statins.

The percentage reduction in cardiovascular mortality with statin therapy was obtained from a meta-analysis of trials of lipid-lowering agents in primary prevention populations.²³ 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 the initiation of statin therapy was modeled was 50 years. The spectrum of cardiovascular risk modeled 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

The Table shows the baseline characteristics of survey respondents. Three hundred sixty participants were recruited after 379 members of the public were approached. 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 III in the online-only Data Supplement. Two-thirds of subjects had medication disutility >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 square root of the age, it was -0.01 (*P*=0.79); and Spearman rank correlation with age was -0.01 (*P*=0.79; Figures 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, whereas a large proportion will gain no extra lifespan, as shown in Appendix IV in the online-only Data Supplement. From the age, sex, smoking status, blood pressure, and cholesterol, it is not possible to be more specific as to whether a particular patient will gain. Even if a trial were conducted, each individual patient could only be in 1 arm, and it would not be possible to pinpoint whether 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 (Figure 4, Top), juxtaposed against longevity benefit from statin therapy (Figure 4, Bottom). 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 the individual cardiovascular risk profile. Ninety-nine percent of the UK population will gain <24.3 months of additional life as a result of lifelong primary

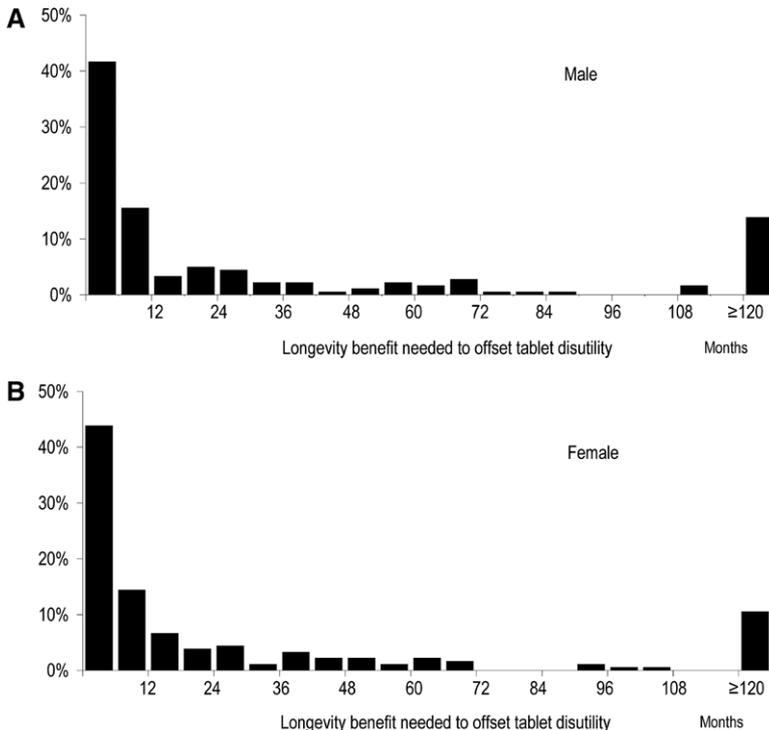


Figure 1. Distribution of medication disutility by sex: **A**, male; **B**, female. This figure illustrates the distribution of medication disutility for an idealized tablet, expressed as the lifespan gain in months needed to offset taking daily therapy.

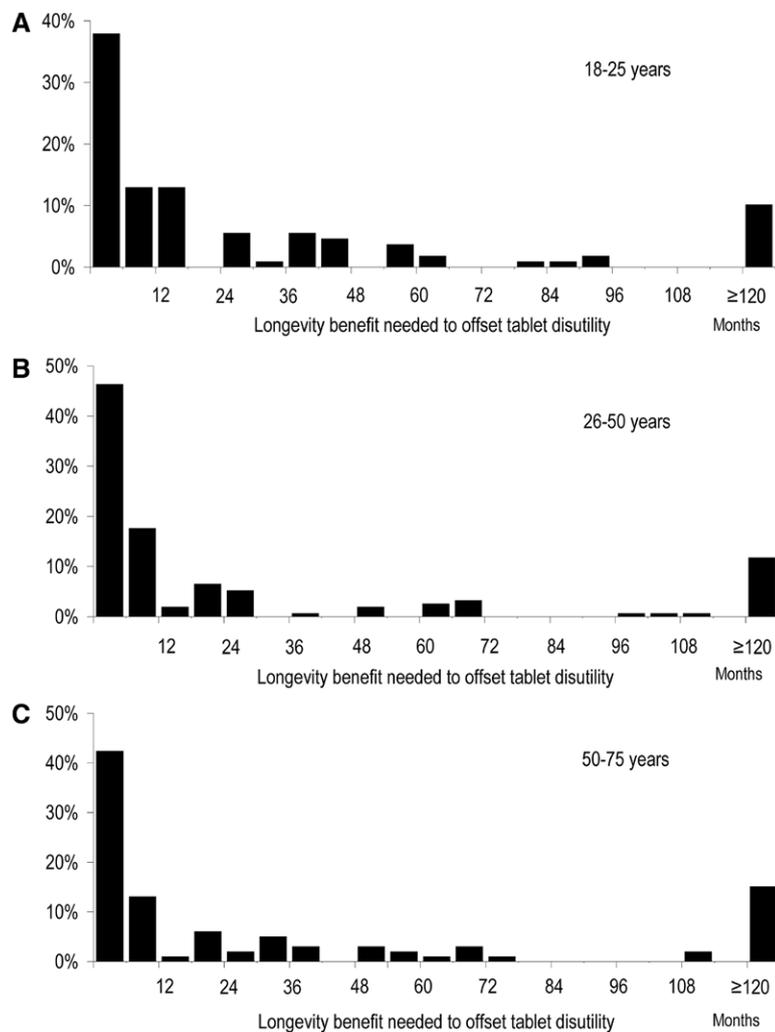


Figure 2. Distribution of medication disutility by age: **A**, 18 to 25 years; **B**, 26 to 50 years; **C**, 50 to 75 years. The distribution of medication disutility for an idealized tablet, expressed as the number of months needed to make therapy worthwhile.

prevention with a statin, whereas 1% has a risk profile that allows them to gain more than this. Individual-subject medication disutility has a wide distribution in our survey population, ranging from <1 day to >10 years.

Figure 5 shows the expected distribution of longevity benefit in the English population resulting from distribution of total serum cholesterol (Figure 5A), systolic blood pressure (Figure 5B), smoking in the general population with all other risk factors held constant (Figure 5C), and the distribution of total cardiovascular risk using all 3 variables combined (Figure 5D). For Figure 5A through 5C, the distribution of longevity benefit with statin therapy was calculated allowing a particular risk factor (cholesterol, blood pressure, or smoking status, respectively) to vary with a prespecified distribution (the distribution of that risk factor in the population in the United Kingdom), while the other risk factors were held constant at the population mean. The distribution of longevity benefit for total cardiovascular risk was calculated by using all 3 variables combined in an aggregate risk score with the use of the SCORE algorithm.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 idealized tablet, more than one-quarter of individuals have medication disutility that 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 the addition of even such an idealized 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 has disutility greater than double the median or less than half the median. The shape of the medication disutility distribution

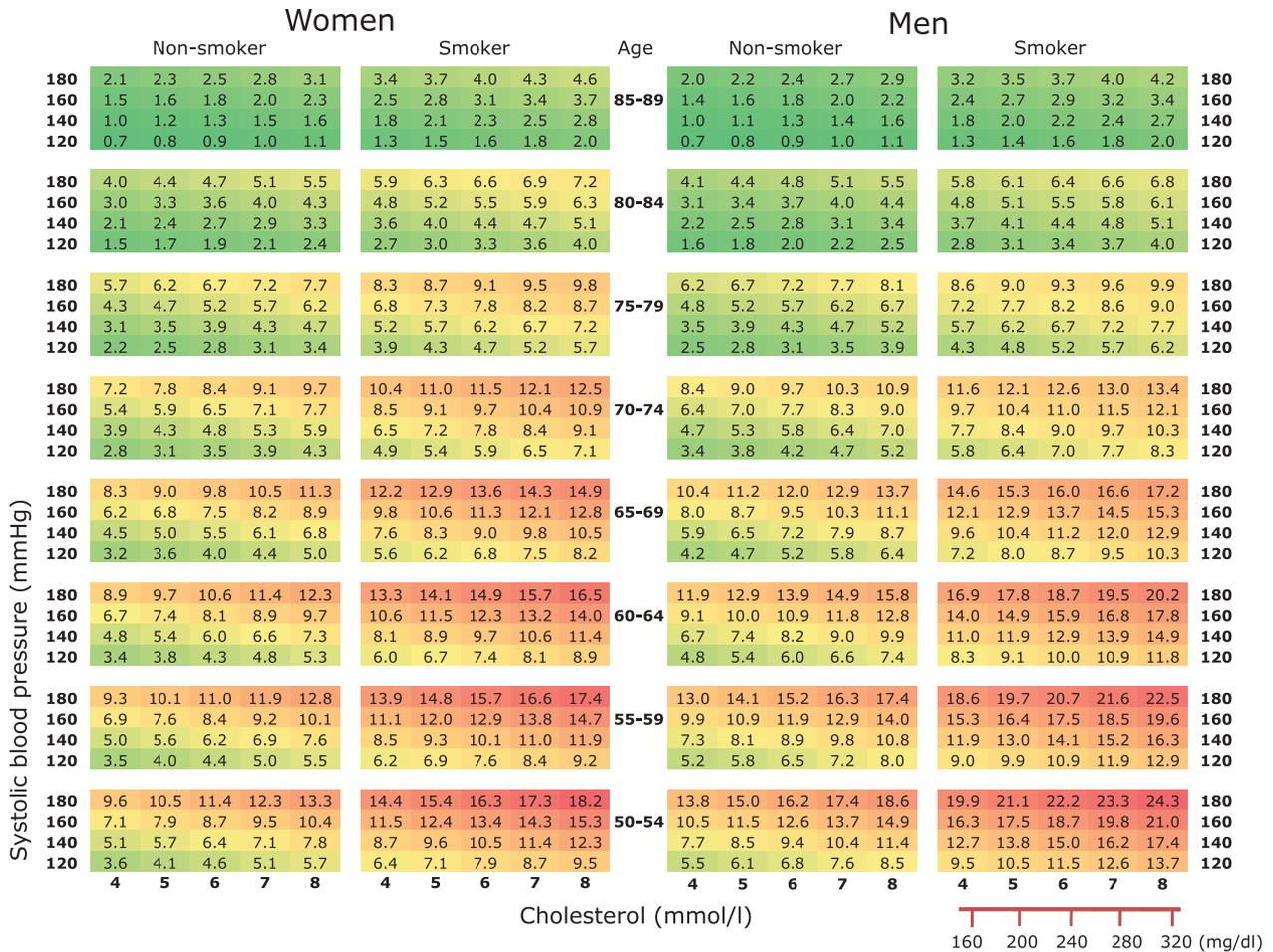


Figure 3. Paddington tables. Months of life expectancy benefit obtained from statin therapy. Each chart can be read by looking up the patient age, sex, blood pressure, cholesterol level, and smoking status. The shading corresponds to the increase in group-average life expectancy for a notional large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

curve seems similar across age groups, suggesting that its shape is genuine and that ageing with the 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 by using statistical estimates to determine whether taking a statin is worthwhile, but the interindividual 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 nonzero 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 are 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, clinicians should not simply prescribe and assume that

the medication will be taken. High disutility could instead initiate the exploration of its underlying reasons.

Use of an Idealized 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 intervention that might have an adverse reputation. The hypothetical medication enhanced lifespan without having the 4 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. The 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 nonzero 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 with the benefits offered by a medication such as a statin. To translate this concept into clinical practice, further studies with questionnaires specifically designed to investigate real medications used

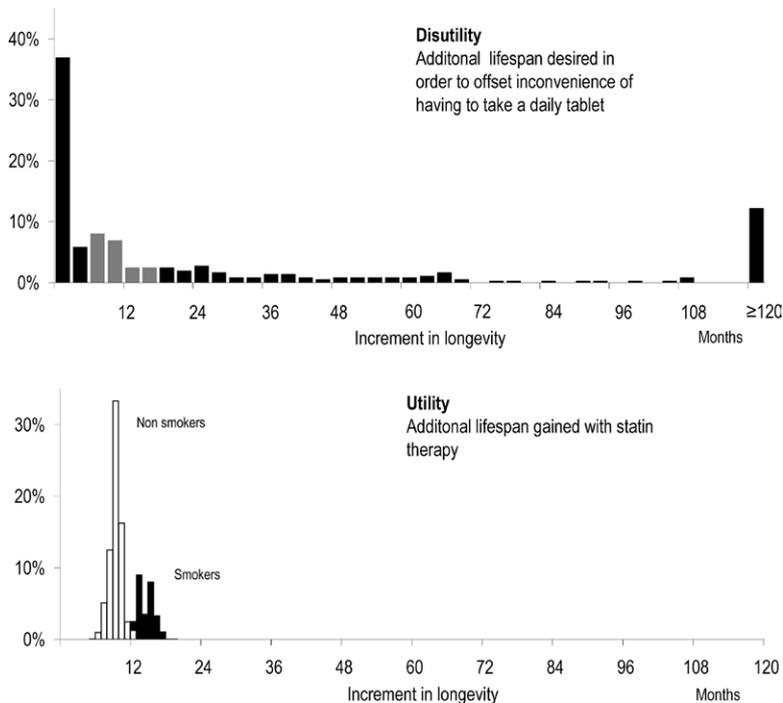


Figure 4. Disutility vs utility. Frequency distribution of disutility, longevity benefit that subjects expressed a desire to make tablet therapy worthwhile (**top**), and the frequency distribution of utility, actual expected gain in lifespan from statin therapy in the English population (**bottom**). The difference between the 2 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 gray zone (**top**) that sex, smoking status, blood pressure, and cholesterol are the deciding factors.

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 particular clinical context.

Study Limitations and Future Study Design

We did not collect individualized 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 the 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 participate in 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 not be representative 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 the individual level. When using this questionnaire in real life, a physician should make clear that a calculated increase of 1 year in life expectancy is an estimate that is based on an average of lifespan gain among subjects. To make this difficult concept easy to understand for every individual, the physician could offer a page with 3 examples of how, among a group of 10 people with an average increase of 1 year, individual gain may vary from the mean (Appendix IV in the online-only Data Supplement).

Our questionnaire was a very simple form of the time trade-off method. It was aimed to be brief to allow us to sample the general population and minimize the possibility of examining only an unrepresentative subset biased toward an 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 individualized 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 data set, age – known to the public to be the most powerful determinant of mortality risk – did not affect medication disutility. Future studies using individualized utility calculations would be able to test this hypothesis.

It is likely that a participant's personal disutility may be influenced by context and situation.²⁵ For example, if we had questioned patients within a general medical practice or a hospital outpatient department, then their response may have been influenced by the many health-related cues nearby. We cannot assume that the disutility assessed in a public space is equivalent to the 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 colored 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 subclassify 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 recognizing that subjects with such strong medication disutility do exist.

Because mortality rates change over time, the survival depicted in any period life table will not perfectly reflect the

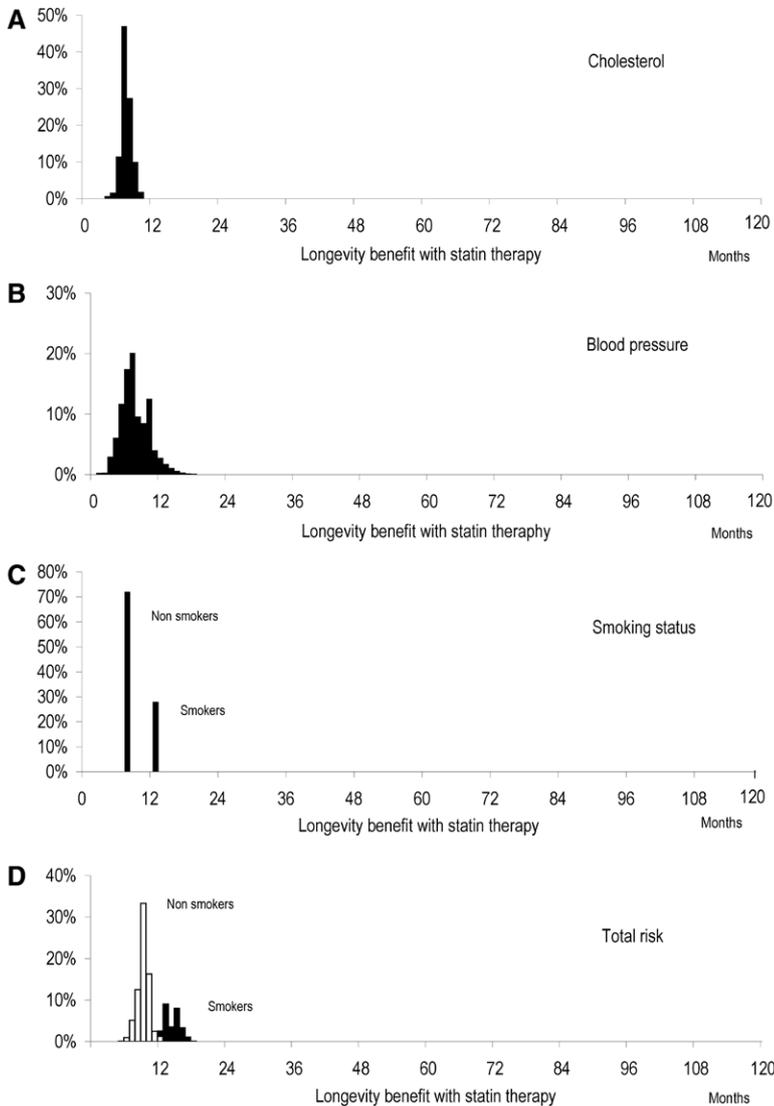


Figure 5. Expected distribution of longevity benefit in the English population. Distribution of longevity benefit with statin therapy resulting from distribution of total serum cholesterol (A), systolic blood pressure (B), and smoking (C) in the general population with all other risk factors held constant. D, The distribution of longevity benefit for total cardiovascular risk with the use of all 3 variables combined in an aggregate risk score by using the SCORE algorithm.²¹

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 by 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 United Kingdom. However, survey participants were drawn from the general population, which is the target population of primary prevention therapy. To minimize 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 United Kingdom, 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.²⁶ 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,²⁷ 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 1 individual in the survey had a previous cardiovascular event. Further studies are needed to investigate the longitudinal behavior of medication disutility to determine how often medication disutility should be reassessed.

Conclusions

The tables presented in this study are designed to allow both patient and doctor to compare the risk and benefit of preventative tablet therapy to determine an average expected net benefit for a notional group of similar patients with the use of a mutually understood metric of lifespan gain. High disutility in an individual might prompt an 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, because 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, individualized 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 personalized.

Disclosures

None.

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CLINICAL PERSPECTIVE

When we recommend that patients start primary prevention medications, we typically focus on risk as the deciding factor, with no discussion of aversion to taking medication. We rarely estimate the benefit from therapy in tangible terms. In this study, we produced tables of group-mean expectation of lifespan gain from taking a primary prevention therapy such as a statin. This is similar to a risk table, with the exception that younger patients show greater lifespan gain (despite lower short-term risk). We also surveyed 360 members of the general public, asking what level of lifespan gain would make it worth their while taking an imaginary tablet with ideal characteristics. Surprisingly, many demanded an expected lifespan gain larger than that available to any risk stratum of patients. Too little is known about how much patients dislike being on primary prevention medication or why this might be. Future research might explore this more formally. Ultimately, it may help to express to patients the size of the expected survival gain in a manner that can be easily understood. They, too, need a way to express the size of their dislike of being on preventative medication. Both could be expressed on a common scale, in terms of extra lifespan obtained or willing to be given up. If a patient expresses strong dislike of medication, it might trigger further discussion. Ultimately, these steps may help primary prevention becoming more truly personalized medicine.

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 Wehtable 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 Statistics ^{1,2} using the following formula:

$${}_nM_x = {}_nD_x / {}_nP_x \quad (\text{Equation 1})$$

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:

$${}_nq_x (\text{all cause}) = 2 \times n \times {}_nM_x / (2+n \times {}_nM_x) \quad (\text{Equation 2})$$

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 ${}_nq_{x(\text{all cause})} = {}_nq_{x(\text{CVD})} + {}_nq_{x(\text{NCVD})}$ (Equation 3)

where:

${}_nq_{x(\text{CVD})}$ = conditional probability of CVD death in the 5 year age interval

${}_nq_{x(\text{NCVD})}$ = 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_x .³

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) $RR_{(\text{CVD})}$. These risk reduction were obtained from a meta-analysis of randomised controlled trials of lipid lowering agents.⁴ The conditional probability of CVD death (${}_nq_{x(\text{CVD})}$) was considered to be reduced in that proportion, in people taking statins. The conditional probability of non-CVD deaths (${}_nq_{x(\text{NCVD})}$) was held constant. Remaining period life expectancy for each age group, e^{statin}_x , was recalculated after applying these reductions to derive life expectancy with statin (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 database⁵ 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 an 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:

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

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

current = 1 if current smoker and 0 otherwise

β_{TC} = β coefficient of the effect of a 1 mmol/L increase in cholesterol on CVD survival

β_{SBP} = β coefficient of the effect of a 1 mmHg increase in SBP on CVD survival

β_{smoking} = β coefficient of the effect smoking on CVD survival

and:

$${}_n p_{xRCVD} = {}_n p_{xCVD}^{\exp(w)}$$

where:

${}_n p_{xRCVD}$ = probability of CVD survival for an individual with risk factor combination R

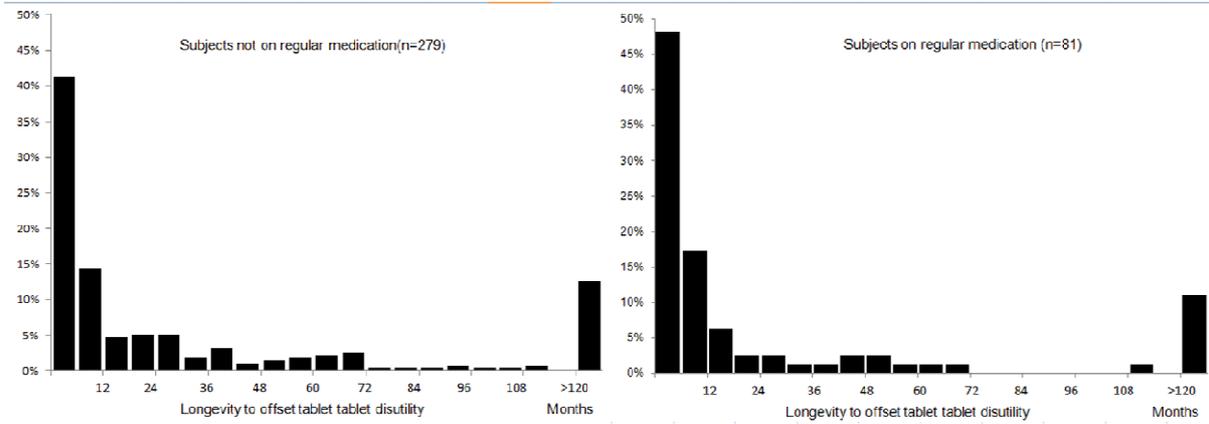
${}_n p_x = 1 - {}_n q_{xCVD}$ baseline probability of CVD survival in English population

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).

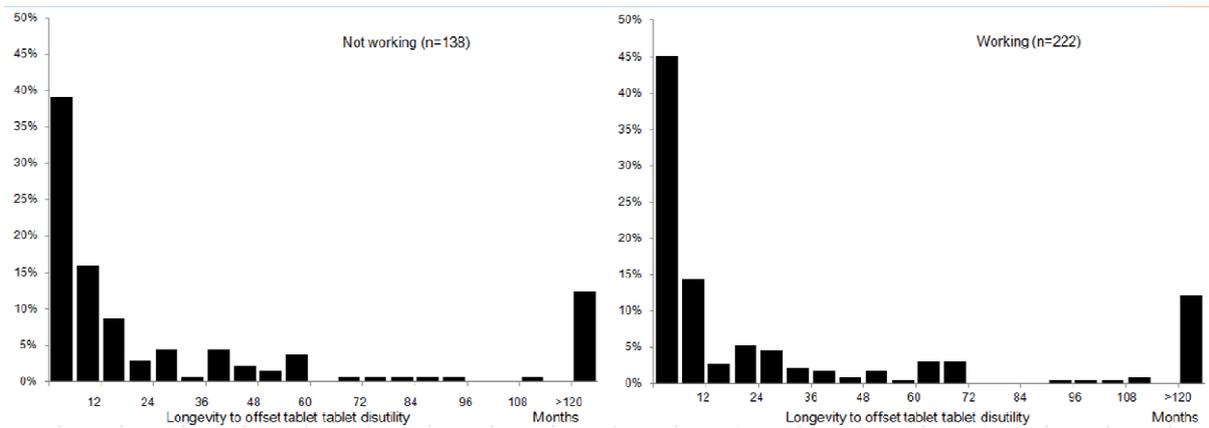
The frequency distribution for the 40 risk combinations of (R) in the English population was estimated by simulation by drawing a value for SBP, TC and smoking status 10,000 times, randomly and independently from the distributions SP, TC and smoking in the English population in the QRESEARCH database.

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.

Patient 1	1 yr gained
Patient 2	1 yr gained
Patient 3	1 yr gained
Patient 4	1 yr gained
Patient 5	1 yr gained
Patient 6	1 yr gained
Patient 7	1 yr gained
Patient 8	1 yr gained
Patient 9	1 yr gained
Patient 10	1 yr gained
Average	1 yr gained

Patient 1	0 yr gained
Patient 2	0 yr gained
Patient 3	0 yr gained
Patient 4	0 yr gained
Patient 5	0 yr gained
Patient 6	0 yr gained
Patient 7	0 yr gained
Patient 8	0 yr gained
Patient 9	0 yr gained
Patient 10	10 yr gained
Average	1 year gained

Patient 1	2 yr gained
Patient 2	2 yr gained
Patient 3	2 yr gained
Patient 4	2 yr gained
Patient 5	2 yr gained
Patient 6	0 yr gained
Patient 7	0 yr gained
Patient 8	0 yr gained
Patient 9	0 yr gained
Patient 10	0 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 ; ${}_nq_{x(CVD)}$ = probability of dying of cardiovascular disease for x -year age group beginning at age x , i.e. $x \leq \text{age} < x+n$; ${}_nq_{x(NCVD)}$ = probability of dying of non cardiovascular cause for x -year age group beginning at age x ; ${}_nd_x$ = all cause deaths in x -year age group beginning at age x . ${}_nL_x$ = person years lived in this age interval; T_x = future years of life remaining at age x ; e^0_x = baseline life expectancy at age x ; $RR_{(CVD)}$ = relative risk reduction with statin; e^{statin}_x = life expectancy with statin at age x .

Control Arm									Statin Arm										
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)
Age interval inclusive	Number alive at age x	Probability of dying of CVD during this age interval	Probability of dying of non-CVD cause in this age interval	Total number of deaths in this age interval	Number alive at end of age interval	Person years lived in this age interval	Future years of life remaining at age x	Baseline life expectancy at age x	Age interval inclusive	Number alive at age x	Relative risk reduction with statin use starting at age 50	Probability of dying of CVD during this age interval	Probability of dying of non-CVD cause in this age interval	Total number of deaths in this age interval	Number alive at end of age interval	Person years lived in this age interval	Future years of life remaining at age x	Life expectancy with statins at age x	Average gain in life expectancy when starting statin at age x
	l_x	${}_nq_{x(CVD)}$	${}_nq_{x(NCVD)}$	${}_nd_x$		${}_nL_x$	T_x	e^0_x		l_x	$RR_{(CVD)}$	${}_nq_{x(CVD)}$	${}_nq_{x(NCVD)}$			${}_nL_x$	T_x	e^{statin}_x	
<1	100000	0.000045	0.001646	169	99831	99915	7824694	78.25	<1	100000	0%	0.000045	0.001646	169	99831	99915	7906598	79	0.82
1-4	99831	0.000020	0.000697	72	99759	399180	7724778	77.38	1-4	99831	0%	0.000020	0.000697	72	99759	399180	7806683	78	0.82
5-9	99759	0.000010	0.000465	47	99712	498678	7325598	73.43	5-9	99759	0%	0.000010	0.000465	47	99712	498678	7407502	74	0.82
10-14	99712	0.000037	0.000559	59	99653	498411	6826920	68.47	10-14	99712	0%	0.000037	0.000559	59	99653	498411	6908824	69	0.82
15-19	99653	0.000116	0.002037	215	99438	497726	6328509	63.51	15-19	99653	0%	0.000116	0.002037	215	99438	497726	6410413	64	0.82
20-24	99438	0.000150	0.002757	289	99149	496467	5830783	58.64	20-24	99438	0%	0.000150	0.002757	289	99149	496467	5912687	59	0.82
25-29	99149	0.000260	0.003382	361	98788	494841	5334316	53.80	25-29	99149	0%	0.000260	0.003382	361	98788	494841	5416221	55	0.83
30-34	98788	0.000544	0.004093	458	98330	492793	4839475	48.99	30-34	98788	0%	0.000544	0.004093	458	98330	492793	4921379	50	0.83
35-39	98330	0.001123	0.005630	664	97666	489888	4346681	44.21	35-39	98330	0%	0.001123	0.005630	664	97666	489888	4428586	45	0.83
40-44	97666	0.001980	0.007349	911	96755	486051	3856693	39.49	40-44	97666	0%	0.001980	0.007349	911	96755	486051	3938597	40	0.84
45-49	96755	0.003510	0.009577	1266	95488	480607	3370642	34.84	45-49	96755	0%	0.003510	0.009577	1266	95488	480607	3452547	36	0.85
50-54	95488	0.005816	0.014230	1914	93574	472656	2890035	30.27	50-54	95488	30%	0.004071	0.014230	1748	93741	473073	2971940	31	0.86
55-59	93574	0.009718	0.023073	3068	90506	460200	2417379	25.83	55-59	93741	30%	0.006803	0.023073	2801	90940	461703	2488867	27	0.82
60-64	90506	0.014424	0.034433	4422	86084	441474	1957179	21.62	60-64	90940	30%	0.010097	0.034433	4050	86891	444577	2037164	22	0.78
65-69	86084	0.023837	0.054610	6753	79331	413537	1515704	17.61	65-69	86891	30%	0.016886	0.054610	6195	80696	418966	1592587	18	0.72
70-74	79331	0.040256	0.084028	9860	69471	372006	1102167	13.89	70-74	80696	25%	0.030192	0.084028	9217	71479	380436	1173621	15	0.65
75-79	69471	0.069029	0.132910	14029	55442	312285	730161	10.51	75-79	71479	20%	0.055233	0.132910	13448	58031	323775	793185	11	0.59
80-84	55442	0.118177	0.210112	18201	37241	231709	417876	7.54	80-84	58031	15%	0.100450	0.210112	18022	40009	245100	469410	8	0.55
85-89	37241	0.188403	0.311810	18629	18613	139635	186167	5.00	85-89	40009	10%	0.169563	0.311810	19259	20750	151897	224309	6	0.61
90+	18613	0.358276	0.641724	18613	0	46532	46532	2.50	90+	20750	0%	0.358276	0.641724	20750	0	72413	72413	3	0.99

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