Are preventive drugs preventive enough? A study of patients' expectation of benefit from preventive drugs

PN Trewby, AV Reddy, CS Trewby, VJ Ashton, G Brennan, J Inglis

ABSTRACT

Objectives **– The study aimed to find the threshold of benefit for a hypothetical cholesterol-lowering drug below which the subject would not be prepared to take the drug. We also looked at whether proximity to the target event (myocardial infarction) and the subjects' views on drug taking affected this threshold.**

Design **– We studied 307 subjects using a written questionnaire and interview. Group 1 (102 subjects) had just been discharged from the coronary care unit. Group 2 (105 subjects) were taking cardio-protective drugs but had no recent history of myocardial infarction. Group 3 (100 subjects) had no history of myocardial infarction and were taking no cardio-protective drugs.**

Results **– Median values for the threshold of benefit below which the subject would not take the preventive drug were 20%, 20%, and 30% absolute risk reduction for Groups 1, 2 and 3 respectively. Median values for expectation of average prolongation of life were 12, 12 and 18 months respectively. Only 27% of subjects would take a drug offering 5% or less absolute risk reduction over five years. Subjects' views on medicinal drug taking in general and proximity to the target event were predictors of the acceptance of preventive drugs. Eighty percent of subjects wished to be told the numerical benefit of a preventive drug before starting on it.**

Conclusion **– For the majority, the expectation of benefit from a preventive drug is higher than the actual benefit provided by current drug strategies. There is a tension between the patient's right to know about the chance of benefiting from a preventive drug and the likely reduction in uptake if they are so informed.**

KEY WORDS: absolute risk reduction, atrial fibrillation, cholesterol, evidence-based medicine, hypertension, myocardial infarction, National Service Framework, patient expectations, preventive drugs,

Preventive drug strategies presume that it is the wish of the individual to avoid the target event for which the preventive drug is designed. But they also assume that the reduction in morbidity or mortality is sufficient to offset the inconvenience of having to take a drug long-term whose effect on the individual can only be expressed in terms of benefit to a population. For the average individual the chance of benefit is small – normally less than 5% over five years (Table 1). Doctors seldom share these figures with patients, whose acceptance of a preventive drug may be determined not only by the efficacy of the drug but also by their proximity to the target event, their perception of its gravity and their view on drugs in general.

In this study we looked at subjects' views on the limit of benefit below which they would not accept a preventive drug. We used as our model a hypothetical cholesterol-lowering drug in the prevention of myocardial infarction (MI). We looked at whether proximity to the target event (myocardial infarction) and the subject's opinion on prescribed drugs in general influenced their views. Those taking cardio-protective drugs were asked to give their estimate of the chance that they would benefit from taking them.

Patients and methods

In total, 550 subjects were approached and given an outline of the study; 308 agreed to participate. One was excluded because of poor understanding of the written questionnaire. Subjects were randomly selected from three groups: Group 1 (n =102) had just been discharged from the coronary care unit (CCU) with a diagnosis of definite (n = 45) or suspected (n = 57) myocardial infarction. Group 2 (n = 105) had no recent history of actual or suspected myocardial infarction but were all taking preventive cardiovascular drugs. Group 3 subjects (n = 100) had no known cardiovascular disease and were on no preventive cardiovascular drugs.

Subjects were given an explanation of the study and a questionnaire to return in person or by post. In the questionnaire, subjects were asked to imagine that their blood cholesterol level was higher than normal for them, putting them at increased risk of a

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Key Points

Even high risk patients have less than 5% chance of benefiting from a cardioprotective drug taken for 5 years; 95% of patients will take the drug for 5 years without benefit

These statistics are seldom shared with patients

In this study we found the median value for the lower limit of benefit below which subjects would not wish to embark on a preventive drug strategy was 20% over 5 years. This included patients just discharged from the Coronary Care Unit

The study suggests that informing patients of the percentage chance of benefit from preventive drug strategies will substantially reduce the uptake of such drugs. For the individual, this is unlikely to be detrimental. For the population at large, reduced uptake of the drug will lead to an increased prevalence of the target event

The study points to the need for discussion as to whether and when and how information on preventive drug effectiveness is presented to subjects before they are started on long term treatment from which statistically they have little chance of benefit

heart attack during the next five years. They were told a new safe drug was available which in previous studies had been found to reduce this risk. The drug did not benefit everyone. Some would not benefit because they would not have a heart attack anyway; some would not benefit because the drug was not strong enough to prevent a heart attack in them. Subjects were asked to mark a visual analogue chart (Fig 1) which expressed benefit in a semi-logarithmic fashion to focus attention on the lower orders of benefit. They were also asked by how many months on average they would wish a new drug to have been shown to extend life for them to wish to take it for the rest of their lives.

Subjects taking preventive drugs were asked to give an estimate of the benefit they thought these drugs would be to them in the coming five years in protecting them against having a heart attack.

Subjects were interviewed within one week of return of their questionnaire in person (10 subjects) or by telephone (297 subjects) by one of two research nurses. The interviewer first assessed understanding of the questionnaire and then attempted to test and lower their threshold for taking the drug. If, for example, they had stated they would take the new drug if there was a 10% chance of benefiting over five years (90% chance of not benefiting), they were asked what they would do if the doctor told them there was in fact only a 5% (1 in 20) chance of benefit. Would they take the drug? If not, would they take it if there was a 7% chance of benefit? By progressively reducing the hypothetical percentage level of benefit of the drug, a level of benefit below which the subject would not consider taking the drug was established. This was recorded as the threshold of benefit for that subject.

The same process was carried out for the prolongation of life that the subject would expect to see from the drug before being prepared to take it for the rest of their life.

Subjects recording a threshold of benefit above 5% were asked if they would take a drug that only had a 5% chance of bene-

Table 1. Examples of absolute and relative risk reduction for commonly used cardiovascular and cerebrovascular preventive drug strategies.

Study	Mean treatment duration	Number of subjects	Outcome	Control untreated event rate (%)	Relative risk reduction with treatment (%)	Absolute risk reduction with treatment (%)
Pravastatin post MI or unstable angina; median cholesterol 5.6 mmol/l[1]	6.1 years	9014	All deaths	14.1	22	3.1
			Any MI	10.3	28	2.9
Primary prevention with pravastatin in men; mean cholesterol 7.0 mmol/l[2]	4.9 years	6595	All deaths	4.1	22	0.9
			Coronary events	7.9	30	2.3
Ramipril in high-risk patients (HOPE study)[3]	5 years	9297	All deaths	12.2	15	1.8
			Any MI	12.3	20	2.4
Enalapril post MI; EF <35%[4]	37 months	4228	All deaths	15.8	6	1.0
Carvedilol post MI; EF ≤40%[5]	1.3 years	1959	All deaths	15.0	20	3.0
Aspirin or other anti-platelet drug post MI[6]	27 months	20,006	Any vascular event	17	21	3.5
Aspirin or other anti-platelet drug post stroke[6]	29 months	23,020	Any vascular event	21	17	3.6
Hypertension; diastolic BP 90–109 mm[7]	4.9 years	17354	All deaths	2.9	2	0.06
			Stroke	1.3	45	0.6
Hypertension; diastolic BP 115–129[8]	18 months	143	Death, stroke or heart failure	39	93	36.3
Warfarin in non-rheumatic atrial fibrillation[9]	1.8 years	571	Cerebral infarction	7.2	78	5.6

EF = ejection fraction; BP = blood pressure.

fiting them over five years *if it was recommended by their doctor*.

Statistical analyses were carried out using the Kruskal Wallis test for comparing median values, Chi-squared test for comparing proportions and Student's *t*-test for comparing means.

Results

Subjects' views on the minimum acceptable benefit for the preventive drug ranged from 0.5% in four patients to one patient who would only take a drug if there was a 100% chance of benefit over five years. Median values following interview were 20%, 20% and 30% in Groups 1, 2 and 3 respectively (p <0.001 for difference between Group 3 and Groups 1 and 2; see Table 2 and Fig 2).

Taking 5% benefit over five years as an estimate of the effectiveness of current cardio-protective drugs (Table 1), we found that 68% of Group 1 patients, 72% of Group 2 patients and 80% of Group 3 patients would *not* take such a drug if it offered 5% or less benefit to them over five years (Fig 2). However, when asked at interview whether they would take a drug of 5% benefit

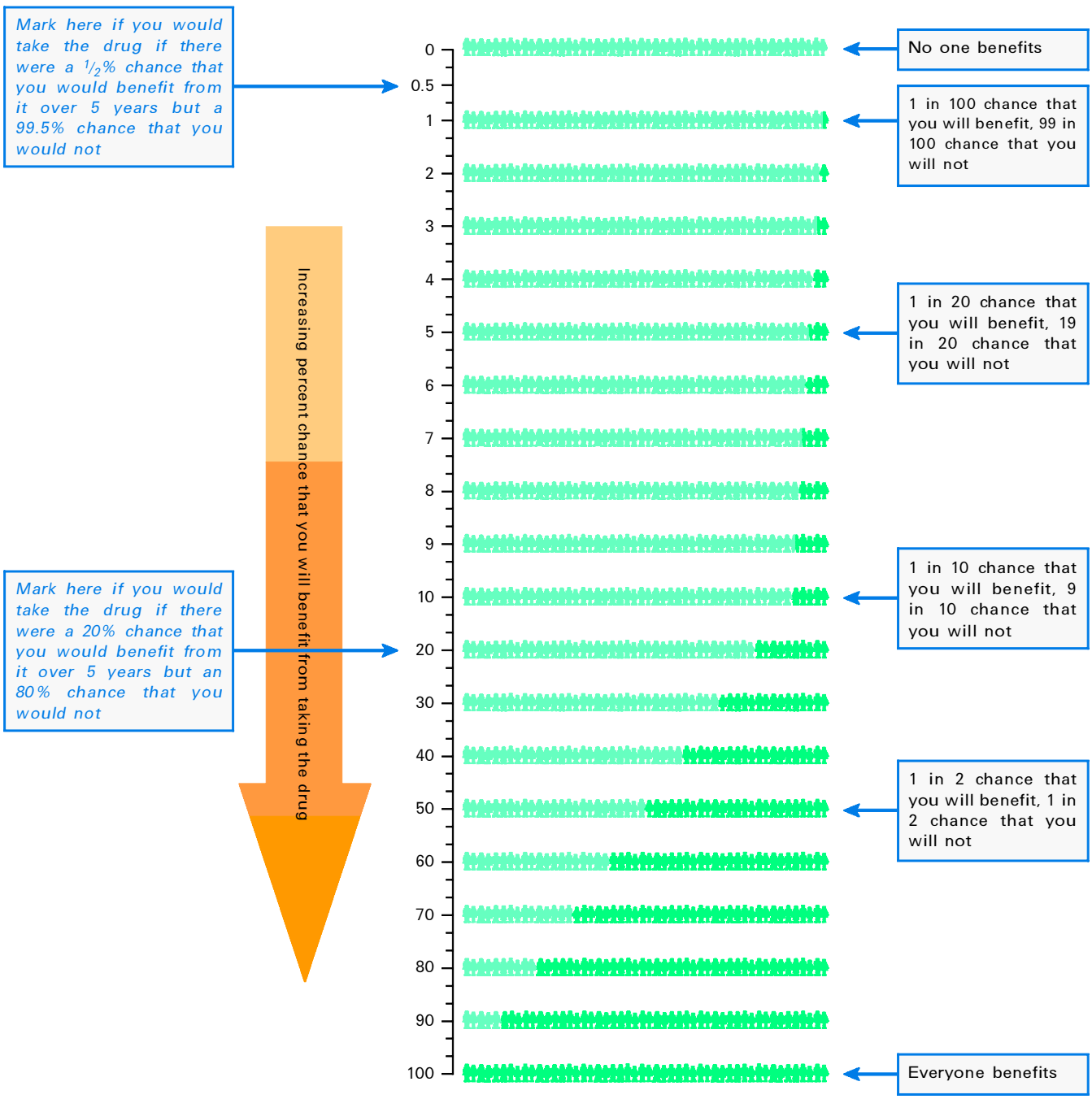

Fig 1. Detail from the visual analogue scale showing, for different hypothetical risk reductions, how many subjects will benefit (shown in light green) and how many will not benefit (shown in dark green).

to them *if their doctor recommended it*, these figures fell to 31%, 26% and 42% in Groups 1, 2 and 3 respectively. Of the 58 patients in Groups 1 and 2 who would not take a drug which only offered 5% benefit *even if recommended by their doctor*, 55 were taking preventive drugs at the time of the study, and 16 had just had a myocardial infarction.

There was also a wide variation in patients' minimum expectation of prolongation of life from a drug before they would take it for the rest of their lives, ranging from 30 years in one patient who described numerous side effects from the preventive drugs he had received, to three patients who would take a drug for the rest of their lives if it offered just one day of extra life. Median values were 12, 12 and 18 months respectively in Groups 1, 2 and 3 (Fig 3). There was no significant difference in the median values between the three groups. There was a significant positive correlation between the subjects' threshold of benefit for a drug and expectation of prolongation of life ($r = 0.39$, $p < 0.01$).

Subjects' views on taking drugs was an important factor in determining their threshold of benefit and their expectation of prolongation of life from a drug. The median threshold of benefit in those stating they were happy to take drugs ($n = 162$), those with no strong feelings ($n = 84$) and those against taking drugs ($n = 61$) were 15%, 30% and 50% respectively ($p < 0.001$ between groups) and the corresponding figures for median

Table 2. Details of subjects.

		Group 1 (n = 102)	Group 2 (n = 105)	Group 3 (n = 100)
Characteristics		**Just discharged from CCU**	**On preventive drugs but no recent MI**	**No preventive drugs, no MI**
Age (mean – SD)		62 – 11.4	64.1 – 9.4	57.7 – 15 *1,2
Male (%)		75.5*2,3	53.3	45.0
Perceived current health:	Very poor	4	1	2
	Poor	16	24	12
	Average	46	38	28
	Good	36	42	58*1,2
Current smoker (%)		19.6%	21%	24%
Percentage of subjects with relative or close friend with MI during past 12 months		9.7%	17.1%	9.0%
Willingness to take medical drugs:				
Happy to take drugs		59	61	42*1,2
Neutral		31	31	22
Against taking drugs		12	13	36*1,2
Subjects wishing to know chance of benefiting from preventive drug before starting treatment (%)		79.2%	72.4%	83.8%
Median acceptable threshold of benefit of proposed hypothetical preventive drug:				
Before interview		20%	20%	50%*1,2
After interview		20%	20%	30% *1,2
Prolongation of life (months) from preventive drug before subjects prepared to take it				
Before interview		12.5	21	24
After interview		12	12	18
(Median values)				
Percentage of subjects prepared to take a preventive drug from which there was a ≤5% chance of benefiting over 5 years		32.4%	28.6%	21%
Percentage of subjects prepared to take a preventive drug from which there was a ≤5% chance of benefiting over 5 years *if the drug was recommended by their doctor*		69.3%	74.3%	56% *1,2
Subjects' views of the % chance of benefiting from their own regular cardio-protective drugs over the next 5 years. Mean – SD (median)		65.8 – 21.3 (70.0)	63.1 – 24.6 (67.5)	–

*1statistically different from Group 1; *1,2statistically different from Groups 1 and 2; *2,3statistically different from Groups 2 and 3 (p = <0.05). SD = standard deviation.

expected prolongation of life from the drug were 12, 24 and 24 months respectively (p <0.001 between Group 1 and Groups 2 and 3).

In their free text comments, 66 patients expressed positive views on preventive medicines, 131 patients expressed negative or qualified views on preventive drugs, and 110 patients had no comment (Table 3). There was a significant difference in the median threshold of benefit and the median expected life extension between those patients expressing positive views about drugs and those expressing negative views (median threshold of benefit 12% *v* 24%, p <0.001; median life extension 10 months *v* 50 months, p <0.001).

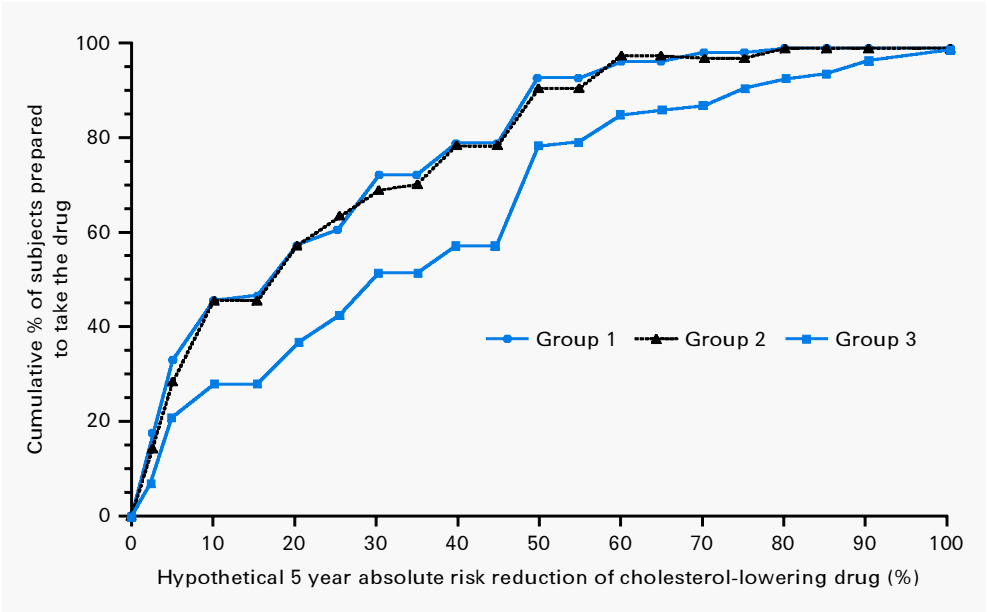

Fig 2. Cumulative number of subjects prepared to take a cholesterol lowering drug offering different hypothetical levels of absolute risk reduction for myocardial infarction.

In Groups 1,2 and 3, 79%, 72% and 84% respectively wished to be told of the percentage chance of benefiting from a preventive drug before starting on it.

There was no significant difference in median threshold of benefit or expected prolongation of life from preventive drugs between males and females, smokers and non-smokers, or between subjects when divided into four self-reported health categories or between those recruited from secondary or primary care. Those subjects who had had a myocardial infarction at any time in the past reported lower thresholds of benefit than those who had not (median values 20% v 25%, $p = 0.042$) as did those with a family history of myocardial infarction (median values 20% *v* 25%, $p = 0.050$), but there was no difference in the expected prolongation of life from preventive drugs between these groups.

Subjects in Group 3 were significantly younger than those in Groups 1 and 2 (Table 2), but in each group there was no significant correlation between age and threshold of benefit or expected prolongation of life. Indeed, taking all subjects together there was a weak *negative* correlation between age and threshold of benefit ($r = –0.14$, $p = 0.03$): the older the patient the less benefit they wished to see from a preventive drug before taking it. When asked to estimate the percentage risk reduction of their preventive drugs, subjects in Groups 1 and 2 gave a mean value of 64.5 ± 23% (median 70%). Only 3.8% of subjects gave the correct answer of a less than 10% chance of benefiting over five years.

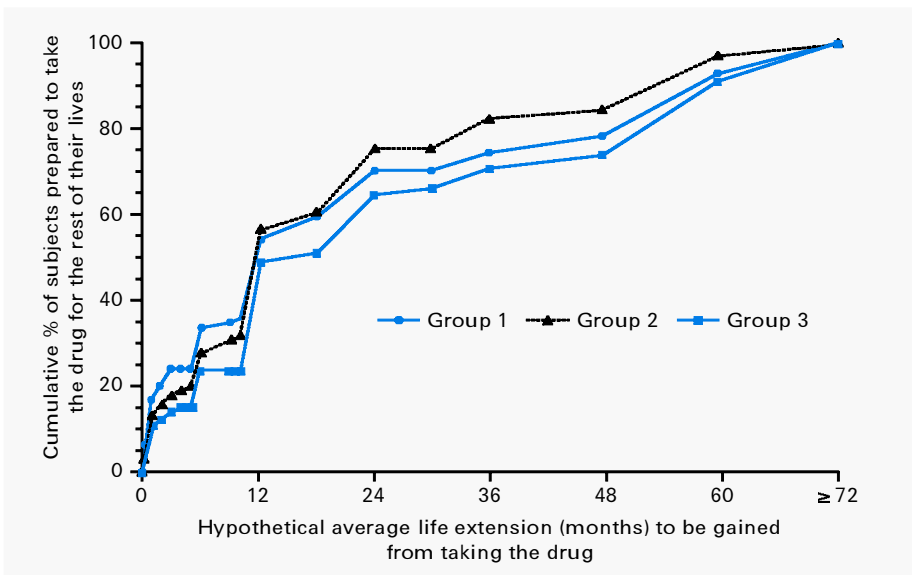

Fig 3. Cumulative percentage of subjects prepared to take a cholesterol lowering drug offering different hypothetical average increases in life expectancy.

Discussion

Our results are at odds with the UK National Service Framework vision of treating all subjects at 30% risk of myocardial infarction over 10 years with cardio-protective drugs[10]. We calculate that, taking a relative risk reduction of 30% for statins (Table 1) and even assuming this risk reduction holds constant for 10 years, only 10% of these high-risk patients will benefit from a statin. This level of benefit was only acceptable to 45% of subjects just discharged from the CCU and just 28% of those not currently taking cardio-protective drugs (Fig 2).

It is likely that the discrepancy

between our subjects' expectations of a 20% absolute risk reduction from a drug and the 5% benefit that preventive drugs actually provide is due to the low probability of subjects incurring the target event rather than the lack of efficacy of current preventive drugs. However, if as argued by Glasziou[11], relative risk reduction remains constant in groups with different pre-treatment risks, more than 5% of those in higher-risk groups might benefit from taking lipid-lowering drugs. Although subgroup analysis could help identify such high-risk patients, the numerical precision with which this risk can be expressed inevitably decreases with decreasing numbers in each group. Furthermore, taking a relative risk reduction of 30% as the average for lipid-lowering trials (Table 1), the patient's five-year risk of myocardial infarction would need to be 60% to satisfy their wish to take a preventive drug only when there is a 20% or greater chance of benefiting from the drug. There will be very few patients at such high risk; and from the population's perspective the impact of preventive strategies will be considerably weakened if only high-risk patients are targeted.

At interview, we felt that subjects found increase in life expectancy as a measure of drug benefit more difficult to grasp than absolute risk reduction and many assumed that an increase in life expectancy would be enjoyed by all. This misconception may arise from using a continuum (time) to represent a quantum or binary outcome (myocardial infarction or death do or do not occur). It is difficult to convey the idea of a gain being stochastic or probabilistic throughout the remainder of the patient's life, often maximal soon after intervention, rather than a certain gain at the end of life[12]. Tsevat *et al* estimated average gains in life expectancy of 0.4 to 6.3 years resulting from lipid lowering in high-risk 35-year-olds; and long-term follow-up of patients treated with ACE inhibitors showed a median life extension of 15.3 months for trandalopril post myocardial infarction and nine months for enalapril in severe heart failure[13–15]. Our subjects' overall median expectation of life extension of 12 months is therefore within the range that cardio-protective drugs can offer. However, even in Group 1 patients, 40% expressed unwillingness to take a drug for the rest of their lives if the expected average increase in life expectancy was less than 18 months.

The way benefit is framed and in particular whether benefit is expressed in relation to the population or to the individual is likely to colour doctors' and patients' views on preventive drugs. Much misunderstanding of the benefits of preventive drug strategies arises from using population statistics and in particular from the use of relative risk reduction in the medical literature, drug advertisements and the press[16,17]. The use of relative risk reduction figures gives no way of assessing the individual's chance that they personally will benefit from the drug as it does not take into account the control event rate. Absolute risk reduction takes into account both the control event rate and drug efficacy and answers the individual's main questions, ie what is the chance that I will benefit if I take this drug for a period of years? What is the chance that I will take it without benefit? The very unrealistic expectations of benefit expressed by our patients on preventive drugs suggest at best a lack of discussion and patient education and at worst a degree of misinformation on the benefits of these drugs. However, informing patients of the statistical chance of benefiting from their preventive drugs should not be undertaken lightly. Patients' and doctors' numeracy skills may not allow full understanding of the implications of accepting or refusing treatment[18]. Also, Redelmeier showed how patients' intuitive decisions may not correspond with scientific analyses[19] and the doctor's own advice will be governed by his or her previous personal experience[20]. Nevertheless, while medical paternalism and enforcement of evidence-based guidelines are the way forward to lower disease prevalence in the community, 80% of our subjects wished to be informed of the numerical benefit of a preventive drugs before starting.

The UK National Institute for Clinical Excellence guidelines on coronary prevention also encourages clinicians to share information with patients so they are informed and involved but interestingly gives no figures for absolute benefit to assist patients in making these decisions[21], and the UK National Service Framework for Coronary Heart Disease with its

Table 3. Examples of subjects' free text comments.

Positive views

- *...life is very sweet even for one month longer.*
- *I need to stay alive. My wife has MS.*
- *...in my nervous nineties, I wish to reach my century.*
- *I have had three heart attacks; preventive drugs have helped me tremendously.*
- *Without preventive medicines I would not have survived.*
- *Taking preventive medicines gives me a psychological boost as they give me some sort of control.*
- *...taking them gives me peace of mind.*

Negative views

- *I would not be interested in taking drugs if I had less than a 50% chance of benefiting from them.*
- *Surely diet, exercise and alternative treatment would give me more benefit; I would always seek to find out if a condition could be changed by these methods before considering a drug regime.*
- *Why take preventive medicines if your body does not need them? I believe your own body tells itself whether it needs medicines.*
- *...it would be a last resort after diet, lifestyle, prayer and homeopathy.*
- *I am concerned that as we get older we become more dependent on medication, I am wary of any drug.*
- *I have been on numerous preventive tablets since my myocardial infarction. I have had awful side effects which I am convinced contributed to my general feeling of ill health over the years.*
- *It never crossed my mind that preventive drugs would not be effective in the majority of cases otherwise they would not be supplied.*
- *Any drug less than 10% benefit is not worth taking,*

hard targets does not give the option for informed patient dissent[10]. Consent or informed dissent must lie at the heart of implementation of preventive strategies[22]. The disappointing uptake of secondary prevention[22–25], the reported 30% discontinuation rate for statins[26], and the results of detailed patient-based decision-making analysis in atrial fibrillation[27] and hypertension[19,28] suggest that individual patients' views are often at odds with population-based recommendations and that patients do wish to be more involved in decision making about their medical care. There are dissenting doctors as well, summarised in McGouran's moving personal view of a patient dying following treatment with streptokinase[29]. An analogue diagram as used in this study (Fig 1) might be an easy way to express the benefit of a preventive drug to a patient and could be included with the drug literature enclosed with drugs. A study to look at the effect on compliance of sharing this information in a real setting would be the logical follow-on from the study reported here.

In summary, our enthusiasm to lower disease prevalence in the community needs to be tempered by respect for the individual's expectation of drug benefit and a realisation that many are reluctant to take drugs long-term from which they have little chance of benefit. Doctors, as treatment brokers, must inform their patients of the quite small percentage chance that they will benefit from preventive drugs. They must take their views into account when prescribing, even if this leads to a decrease in the uptake of preventive drugs in the community.

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