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Effects of Benefits and Harms on Older Persons' Willingness to Take Medication for Primary Cardiovascular Prevention

Terri R. Fried, MD; Mary E. Tinetti, MD; Virginia Towle, MPhil; John R. O'Leary, MA; Lynne Iannone, MA

Background: Quality-assurance initiatives encourage adherence to evidenced-based guidelines based on a consideration of treatment benefit. We examined older persons' willingness to take medication for primary cardiovascular disease prevention according to benefits and harms.

Methods: In-person interviews were performed with 356 community-living older persons. Participants were asked about their willingness to take medication for primary prevention of myocardial infarction (MI) with varying benefits in terms of absolute 5-year risk reduction and varying harms in terms of type and severity of adverse effects.

Results: Most (88%) would take medication, providing an absolute benefit of 6 fewer persons with MI out of 100, approximating the average risk reduction of currently available medications. Of participants who would not take it, 17% changed their preference if the absolute benefit was increased to 10 fewer persons with MI, and, of participants who would take it, 82% remained willing if the absolute benefit was decreased to 3 fewer persons with MI. In contrast, large proportions (48%-69%) were unwilling or uncertain about taking medication with average benefit causing mild fatigue, nausea, or fuzzy thinking, and only 3% would take medication with adverse effects severe enough to affect functioning.

Conclusions: Older persons' willingness to take medication for primary cardiovascular disease prevention is relatively insensitive to its benefit but highly sensitive to its adverse effects. These results suggest that clinical guidelines and decisions about prescribing these medications to older persons need to place emphasis on both benefits and harms.

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Author Affiliations:
Department of Medicine (Drs Fried and Tinetti), School of Epidemiology and Public Health (Dr Tinetti), and Program on Aging (Mss Towle and Iannone and Mr O'Leary), Yale University School of Medicine, New Haven, Connecticut; and Clinical Epidemiology Research Center (CERC), VA Connecticut Healthcare System (Dr Fried), West Haven, Connecticut.

QUALITY-ASSURANCE AND pay-for-performance initiatives increasingly encourage adherence to evidence-based guidelines for the prevention or management of particular diseases. However, guideline-directed therapy may be at odds with the preferences of the patients who are targeted by the guidelines. For example, many patients with atrial fibrillation would prefer a different therapy for reduction of stroke risk from that recommended by treatment guidelines.[1,2]

Guidelines for primary disease prevention are based on the goal of reduced risk of disease-specific outcomes, such as myocardial infarction (MI) or stroke. Implicit in these guidelines is the judgment that these benefits outweigh any potential harms of intervention, a view shared by many clinicians.[3,4] However, there is evidence that these judgments may not agree with the way in which patients view benefits and harms. Qualitative studies demonstrate that, for many persons considering primary prevention interventions, there is a "cost" associated with the very act of taking a medication.[5] In addition, adverse medication effects are viewed by patients as unacceptable outcomes in their own right.[6-8] Several small quantitative studies have shown considerable variability in the amount of benefit that a primary prevention therapy would need to provide in order for a patient to be willing to take the medication.[9,10] These studies leave unanswered the question of the relative importance of benefits and harms of medications and how patients weigh these against one another. Disagreements between how guidelines and patients value the benefits and harms of medications may be particularly relevant for older adults who have multiple risk factors for chronic disease and meet criteria for many guideline-directed medications for primary prevention. The purpose of the current study was to examine how the willingness of older adults to take medica-

tion for primary cardiovascular disease prevention is affected by the likelihood of reduction in MI and the type and severity of adverse medication effects. It also sought to determine how well they understood the probabilistic information about the benefits of therapy.

PARTICIPANTS

Participants were recruited from sites selected to promote access to a population of older persons of diverse race/ethnicity and socioeconomic and health status and to represent patients who are eligible for preventive cardiac medications in actual clinical practice. Participants were recruited from 3 senior centers; 1 serving an urban, predominantly African American population and 2 serving a suburban, predominantly white population; and 1 independent/assisted-living facility providing both market-rate and subsidized apartments. Within these facilities, recruitment consisted of solicitation for participation at influenza clinics and other events such as exercise classes, congregate meals, discussion groups, and presentations by the investigators. Because of the study objective to determine how well participants could understand the numerical information regarding medication benefits, all volunteers were included in the study without exclusion. The only exception was the exclusion of potential participants recruited from the assisted-living facility if they had a formal diagnosis of dementia as provided by the social worker in the facility. A single participant, who failed to complete the interview and did not answer any of the outcome measures, was excluded from the analyses. The protocol was approved by the Yale University School of Medicine human investigations committee.

DATA

All data were collected by self-report. Participants underwent a face-to-face interview with a trained research associate. Interviews were conducted either at the recruitment site, or, for persons who had difficulty traveling, in their home.

Sociodemographic variables included age, sex, race/ethnicity, education, sufficiency of monthly income,[11] and marital status. Health variables included chronic conditions; medications; functional status, assessed using instrumental activities of daily living (ADLs),[12] and self-rated health.

The outcome was participants' willingness to take a medication for primary prevention of MI. The medication was described as reducing the participant's risk of having an MI over the next 5 years, being taken 1 time per day, and being covered by insurance.

The benefits of the medication were described in terms of the patient's risk of MI with and without the medication. Participants were shown a pictograph illustrating the number of people out of 100 who would and would not have an MI, in order to improve understanding and minimize framing bias.[13,14]

In an initial scenario, participants were asked to consider that their risk for an MI over the next 5 years was 20 in 100 and that this risk would be reduced to 14 in 100 with the medication. This baseline risk is a conservatively large estimate of the average risk in the study population, based on an average 10-year risk in the Framingham cohort for 70- to 74-year-olds of 25% for men and 11% for women.[15] We wanted to show participants sufficiently high enough absolute risks such that risk reduction would be meaningful.[16] However, we desired a time frame that would be relevant for persons at more advanced ages, and thus elected to use 5 years rather than 10 years. The 30% relative risk reduc-

tion represents the average absolute risk reduction achieved in primary prevention trials of statins and antihypertensives.[17,18]

In subsequent scenarios, we changed risks with and without the medication in order to vary the absolute reduction in cardiovascular risk: (1) relative risk reduction increased to 50% (risk without medication: 20 in 100; risk with medication: 10 in 100); (2) baseline risk and relative risk reduction both increased (risk without medication: 50 in 100; risk with medication: 25 in 100); and (3) baseline risk decreased (risk without medication: 10 in 100; risk with medication: 7 in 100).

We then returned to the benefit as presented in the initial scenario but described the medication as having different adverse effects: (1) mild daily fatigue and dizziness not severe enough to interfere with ADLs; (2) fatigue and dizziness severe enough to interfere with ADLs; (3) mild nausea not severe enough to interfere with ADLs; (4) nausea severe enough to interfere with ADLs; (5) fuzzy or slowed thinking not severe enough to interfere with ADLs; and (6) fuzzy or slowed thinking severe enough to interfere with ADLs.

In each scenario participants were asked whether they would take the medication. The response categories included: "Yes," "No," "Not sure," and "Do not understand the question." Participants who responded "Do not understand the question" were not included in the main analysis but rather were included in an analysis of participants' understanding of the questions. We calculated the proportion of participants who provided discrepant answers as an additional measure of participants' understanding. A discrepant answer was defined as the willingness to take medication with a given absolute risk reduction but unwillingness to take medication with greater absolute risk reduction *or* unwillingness to take medication with a given absolute risk reduction but willingness to take medication with lower absolute risk reduction.

Participants were also asked in each scenario why they would or would not take the medication. Two of us (T.R.F. and J.R.O.) collaboratively developed a set of categories representing the open-ended responses. We used the categories to code each of the open-ended responses independently and then met to resolve differences.

STATISTICAL ANALYSIS

Descriptive statistics (proportions, means [SDs]) were used to describe the cohort and their willingness to take medication in the different scenarios. We examined sociodemographic, health, and psychosocial factors associated with willingness to take medication in the initial scenario and in the scenario presenting a medication with mild fatigue and dizziness. These factors were examined in bivariate analyses using χ^2 or Fisher exact tests.

A description of the 356 participants is provided in **Table 1**. Only 4 participants (<1%) responded that they did not understand 1 or more of the scenarios. An additional 4 participants provided 7 discrepant responses.

EFFECT OF BENEFITS ON WILLINGNESS TO TAKE MEDICATION

In the initial scenario depicting a medication without adverse effects offering a 30% relative reduction in risk of MI to an older person at approximately "average" baseline risk (absolute risk reduction of 6 fewer persons with MI), most participants (88%) indicated they would take

the medication (**Figure 1**). As the absolute benefit offered by the medication increased, so did the proportion willing to take the medication. However, sizeable numbers of those who would not take the medication in the initial scenario continued to indicate that they would not do so. For example, with an increase in the relative risk reduction to 50% (absolute risk reduction of 10 fewer persons with MI), 83% of those who initially would not take or were not sure about taking the medication continued to express this view. When the absolute risk reduction of the medication was reduced to 3 fewer persons with MI, most participants who were willing to take the medication in the initial scenario (82%) continued to be willing.

The reasons given by the 42 participants who would not take the medication in the initial scenario included dislike of medications (n=7), belief that the benefit was too small (n=13), belief that medication would have adverse effects (n=13), and belief that outcomes are "up to fate" (n=3) (**Table 2**). Participants who became willing to take the medication as the absolute benefit increased all referred to the benefits becoming sufficiently large.

Few sociodemographic or health characteristics were associated with willingness to take the medication. In the initial scenario, white participants, participants with higher self-rated health, and participants with fewer chronic health conditions were significantly more likely to be unwilling to take the medication (**Table 3**). Age, sex, education, income, marital status, health literacy, depression, functional status, number of prescription medicines, and quality of life were not associated with willingness to take the medication.

EFFECT OF HARMS ON WILLINGNESS TO TAKE THE MEDICATION

Of the participants willing to take the medication in the initial scenario, large proportions indicated they were not willing to take the medication with equivalent benefit if it was associated with adverse effects (**Figure 2**). Almost one-half (48%) would not take or were not sure about taking a medication associated with fatigue and dizziness mild enough not to interfere with ADLs, and larger proportions would not take or were not sure about taking a medication associated with mild nausea or fuzzy thinking. Of participants willing to experience these adverse effects, only 11% to 12% remained willing if the symptoms were severe enough to interfere with ADLs.

The most common reason given by the 149 participants who were willing to take the medication in the original scenario but unwilling to take a medication associated with mild fatigue and dizziness was not wanting to experience these symptoms (n=82). Other reasons included the belief that the benefit was not worth the symptoms (n=26), belief that symptoms would interfere with ability to function (n=21), and effects on quality of life (n=5) (Table 2).

The only factor associated with willingness to take the medication in this scenario was self-rated health (Table 3). Of note, equal proportions of those who had (53%) or who had not experienced dizziness (54%) in the previous week were unwilling to take the medication. Similarly, equal proportions of those who had (54%) or who had not (54%) experienced fatigue were unwilling to take the medication.

Table 1. Description of 356 Participants	
Characteristic	**No. (%)**
Female	267 (75)
Race	
White	267 (75)
Black	81 (23)
Other	8 (2)
Age, mean (SD), y	76 (7)
Education, mean (SD), y	13 (2)
Married	116 (33)
Just enough/not enough money at the end of the month	127 (36)
≥1 Instrumental activity of daily living disability	93 (26)
Self-rated health	
Excellent	42 (12)
Very good/good	260 (73)
Fair/poor	54 (15)
Chronic conditions, No.	
0-3	110 (31)
4-6	153 (43)
≥7	93 (26)
Takes ≥1 prescription medication	329 (92)
Prescription medications, mean (SD), No.	4 (3)

COMMENT

Among this diverse cohort of older persons, individuals were able to understand numerical information regarding the benefit associated with a medication for primary prevention of cardiovascular disease. Most (88%) would want to take a medication providing an absolute benefit of 6 fewer persons experiencing an MI over a 5-year period and having no adverse effects. This absolute benefit represents the amount of relative risk reduction commonly afforded by such medications (30%) and approximately average baseline risk for cardiovascular disease. Relatively small proportions of participants changed their willingness to take the medication with changes in the absolute risk reduction provided by the medication. In contrast, large proportions (48%-69%) of those willing to take the medication with average risk reduction would be unwilling to take a medication with the same benefit if it was associated with a variety of different symptoms mild enough not to interfere with ADLs. Few sociodemographic or health characteristics were associated with participants' willingness to take medication.

The central finding of this study was the large influence exerted by the presence of adverse effects on older persons' decisions about whether to take a medication. A prior study[19] using adaptive conjoint analysis to measure preferences for treatment of knee osteoarthritis demonstrated that patients placed greater importance on the presence of common adverse effects and risk of rare effects than on the benefits associated with the therapy. The current study, by asking participants directly whether they would choose to take a medication, further illustrates the extent to which older persons' willingness to take medication is influenced by its adverse effects. The findings in this study regarding variability in willingness to take medication according to its benefit are consistent with the results of earlier investigations.[9,10] This study further demonstrated that
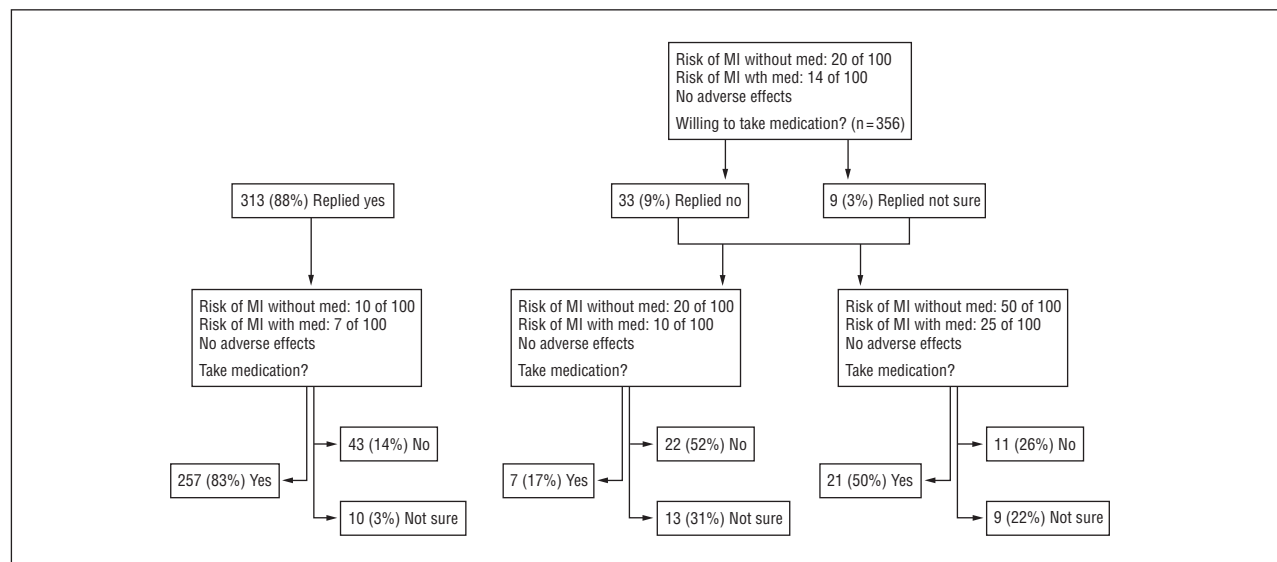
Figure 1. Willingness to take medication (med) for primary cardiovascular prevention according to the benefits of the medication. The medication was described as being taken once daily and covered by insurance. Included in the "no" responses were participants who indicated they were not sure if they would take the medication. Responses do not add up to 100% owing to the exclusion of participants who indicated they did not understand the question. MI indicates myocardial infarction.

Table 2. Reasons for Unwillingness to Take Medication (Med)

Reason	No. (%)
Risk of MI Without Med: 20 of 100; Risk of MI With Med 14 of 100; No Adverse Effects (n=42)	
Benefit too small	13 (31)
Do not believe there would be no adverse effects	13 (31)
Dislike of medications	7 (17)
Belief that outcomes are a function of fate	3 (7)
Other	6 (14)
Risk of MI Without Med: 20 of 100; Risk of MI With Med 14 of 100; Mild Fatigue and Dizziness (n=149)[a]	
Desire to avoid these symptoms	82 (55)
Symptoms not worth benefit	26 (17)
Belief that independence or function would be affected	21 (14)
Would diminish quality of life	5 (3)
Other	15 (10)

Abbreviation: MI, myocardial infarction.
[a] Percentages do not add up to 100% due to rounding.

Table 3. Patient Characteristics Associated With Unwillingness to Take Medication (Med)

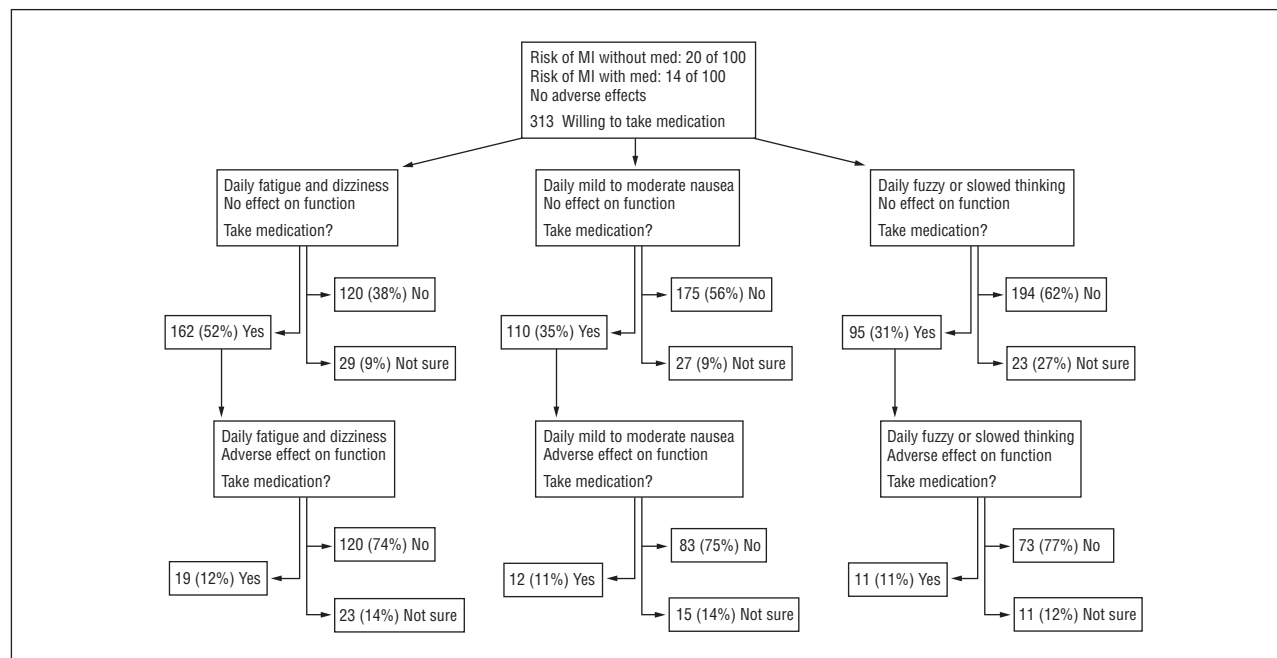|	Unwilling to Take Med	
Characteristic	No. (%)	P Value
Risk of MI Without Med: 20 of 100; Risk of MI With Med 14 of 100; No Adverse Effects		
Race		
Nonwhite (n=88)	5 (6)	.05
White (n=267)	37 (14)	
Self-rated health		
Good/fair/poor (n=199)	17 (9)	.03
Excellent/very good (n=156)	25 (16)	
Number of chronic conditions		
≥5 (n=196)	17 (9)	.05
<5 (n=159)	25 (16)	
Risk of MI Without Med: 20 of 100; Risk of MI With Med 14 of 100; Mild Fatigue and Dizziness[a]		
Self-rated health		
Good/fair/poor (n=197)	96 (49)	.03
Excellent/very good (n=157)	95 (61)	

Abbreviation: MI, myocardial infarction.
[a] Includes 42 participants who were unwilling to take medication without adverse effects and 149 participants who were willing to take medication without adverse effects.

changing the absolute benefit provided by the medication affected the willingness only of a small proportion of people unless the change in absolute benefit was substantial. The relative lack of sensitivity of preferences to small changes in benefit supports the theory of decision making postulating that people generally make health care decisions based on the gist of information, or its bottom-line meaning, rather than the details of numerical risk.[16] The unwillingness of some participants to take medication in the initial scenario, in which the medication provided benefit without harm, might be seen as evidence that participants did not understand the scenarios. However, many of the participants who were unwilling to take the medication in the initial scenario assigned a meaning of "too low" to the baseline risk and/or risk reduction, and this meaning did not change for them as the numbers were altered. These findings provide quantitative confirma-

tion for qualitative research demonstrating the ways in which patients weigh medication benefits against highly individual concerns they have about taking medications that go beyond adverse effects.[5]

These findings have several implications for the development and implementation of practice guidelines. It is notable that, even when told that medication would not have an adverse effect or that this effect would not affect their function, a number of participants indicated they did not believe this would be the case. Although the scenario could be faulted for failing to acknowledge that all medications have the potential for adverse events, it

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                         ┌─────────────────────────────────┐
                         │ Risk of MI without med: 20 of 100│
                         │ Risk of MI with med: 14 of 100   │
                         │ No adverse effects               │
                         │                                  │
                         │ 313  Willing to take medication  │
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Figure 2. Willingness to take medication (med) for primary cardiovascular prevention according to the harms of the medication. Included in the "no" responses were participants who indicated they were not sure if they would take the medication. Responses do not add up to 100% owing to the exclusion of participants who indicated they did not understand the question. MI indicates myocardial infarction.

represents the actual manner in which medications are often discussed by clinicians in outpatient care. A number of studies audiotaping physician-patient visits have documented the low frequency with which physicians describe medication adverse effects, in contrast to a much higher prevalence of discussion about the purpose of taking the medication.[20-22] Moreover, patients' reports of adverse events are frequently discounted by clinicians,[23,24] and nonspecific symptoms such as fatigue and dizziness are viewed as unlikely to be attributed to medication,[25] despite emerging evidence from observational data of an association of nonspecific symptoms with both individual and total number of medications.[26,27] This clinical approach is reinforced by current disease management guidelines. In primary prevention, when the benefit of intervention reaches a certain threshold as determined by the patient's baseline risk and magnitude of risk reduction, all but the most serious adverse effects related to the medication are labeled as "side effects." This term relegates these effects as secondary to the achievement of the disease-specific outcome, resulting in an indication to provide the intervention. The focus on the disease-specific outcome has resulted in multiple calculators to provide patients with individualized estimates of their disease-specific risks[28] and precise knowledge regarding the risk reduction associated with various therapies from randomized trials. In contrast, ascertainment of medication adverse effects is much less complete.[29]

The results of this study support ongoing efforts to delineate the extent to which symptoms can be ascribed to medication effects. This delineation is important because, in the absence of better evidence, patients do ascribe these symptoms to medications and make decisions about taking medications based on this assumption.[30,31] Guidelines need to recognize that adverse effects of medi-

cations, even when mild, are not "side effects" but rather competing outcomes important in their own right. The decision about whether to take a medication should not be predicated on magnitude of benefit alone but rather on the balance of benefits and harms. When a symptom is attributable to a medication, patients need to be allowed to determine when, in their individual calculation, the benefits of a medication are not worth this harm, and to be supported in decisions not to take a medication, even if, as may frequently be the case, the clinician disagrees.[4]

One study limitation is that we do not know the proportion of persons at each recruitment site who participated in our study. In addition, our study participants were overall of higher educational status[32] and better health[33] than nationally representative populations of older persons, which may affect the generalizability of our results. A second limitation is that, to enhance participants' understanding of the medication scenarios, we presented them in a fixed order, with each subsequent scenario building on the last. We therefore cannot know whether responses were subject to an ordering effect. It is unknown whether the results would generalize to primary prevention for other diseases or to decisions regarding secondary prevention.

Perhaps the most important limitation, given the findings of this study regarding adverse effects, is that we presented the benefit of the medication in terms of disease risk reduction rather than in terms of the effect of this reduction on global outcomes, such as survival, function, and symptoms. These are the outcome domains that have been shown to be particularly important to older persons' treatment decision making. Participants may have, for example, been more willing to take medication if they understood it to reduce their risk of functional decline as a consequence of MI. However, there

are currently limited data available to characterize the outcomes of MI according to these domains. The results of this study support the need for these data in order to be able to present the benefits of intervention to patients in the most meaningful manner possible.

When presented with the average benefit achievable by current medications for primary cardiovascular prevention for persons at average risk, many of the older persons in this study were willing to take such a medication in the absence of adverse effects. Although willingness was relatively insensitive to the amount of absolute benefit that a medication would provide, a substantial minority of participants changed their willingness depending upon this benefit. Conversely, the majority of persons would not take a medication with average benefit if it had mild adverse effects, and an even smaller proportion was willing to take a medication with adverse effects severe enough to interfere with ADLs. These results suggest that clinical guidelines and decisions about prescribing these medications to older persons need to place emphasis on both their benefits and harms.

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