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Medical Decision Making and the Counting of Uncertainty

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In economic theory, *homo economicus* is a concept used to explain decision-making as a rational exercise.[1] The "economic man", to use the term often associated with the work of the utilitarian philosopher John Stuart Mills, is someone who makes decisions by carefully weighing the benefits and costs of his options, then deciding on a course of action that maximizes his utility. Although now considered overly simplistic, this idea is often implicit in how we as clinicians have traditionally approached medical decision-making. In the case of statins for the primary prevention of cardiovascular diseases, the choice is frequently framed in terms of the trade-off between the potential benefit of preventing a future heart attack or stroke (i.e., utility) versus the side effects and inconveniences of taking a medication (i.e., disutility). Thus the recently released 2013 American Heart Association / American College of Cardiology Guideline on the Treatment of Blood Cholesterol reminds us that, in addition to calculating estimated atherosclerotic cardiovascular disease (ASCVD) risk to determine statin eligibility, we should engage with patients "in a discussion… to consider the potential for ASCVD benefit and for adverse effects, for drug-drug interactions, and patient preferences for treatment."[2] Yet, while much of the debate over the current guidelines has focused on the accuracy of risk estimation,[3, 4] the evidence base is limited for how to engage with patients during the decision making process to assess their disutility for taking statin therapy.

This is in part because although the proportion of patients who report side effects can be measured, it is difficult to assign a numeric value to the aspect of disutility resulting from having to take a medication daily. In this issue of *Circulation*, Fontana and Asaria and colleagues address this issue by surveying a random sample of 360 individuals encountered on London throughfares.[5] Describing a hypothetical medication that has negligible costs and no side effects, the investigators used a time-trade off approach to ask the participants how much this medication must add to their lifespan before they are willing to take it daily. Medication disutility, measured in this way, was found to have a bimodal distribution. While a third of the individuals surveyed had minimal medication disutility and were willing to

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take the hypothetical medication even if the benefit was less than a month, 12% of participants reported the highest level of medication disutility that the survey was able to measure, and would refuse the hypothetical medication even if they could gain more than 10 years of life.

These findings should not surprise most clinicians, who often encounter patients resistant to the very idea of taking medications. Nonetheless, as the authors note, all too often disutility is assumed to be nearly zero for statins, for example in published cost-effective analyses that have drawn favorable conclusions for broadening statin use.[6, 7] The basis for this assumption is unclear, though it appears to have been extrapolated from very low level of disutility for warfarin and aspirin observed in previous studies of patients with atrial fibrillation.[8, 9] The present study by Fontana and Asaria and colleagues is therefore an important step forward, both for its development of a tool to quantify medication disutility and for its provocative finding that a significant minority of individuals in the general population may have high levels of medication disutility.

How might these results influence the day-to-day decision of whether to recommend primary prevention statin therapy to individual patients? The authors provide some guidance by using the SCORE algorithm[10] to calculate the distribution of estimated longevity benefit from statin therapy for various demographic and cardiovascular risk subgroups of the general UK population. The estimated longevity benefit for taking statins, when calculated in this way, ranges from 5.5 months to 24.3 months of added lifespan for men, and 3.6 to 18.2 months for women. Although these findings suggest that many individuals will have medication disutility that are numerically higher than their estimated longevity benefit, the authors are appropriately cautious to infer that this comparison should determine eligibility for statins at the individual level, for several reasons. Since cardiovascular risk factors were not collected during the survey, estimated longevity benefit could not be calculated at the individual level for this study. However, even if the data collection was complete, a direct comparison of estimated longevity benefit against medication disutility would be problematic. To see this, consider the hypothetical example of two individuals, A and B, both of whom are 60 years-old men, don't smoke, have systolic blood pressure of 140 mmHg and total cholesterol of 5 mmol/L, and have medication disutility quantified as 5 years. Using Figure 3 provided by the authors, the longevity benefit associated with statin therapy is 7.4 months for both of these men, and is much lower than their medication disutility. Individual A stays off statins, never experiences a cardiovascular event, and is happy that he was able to avoid a lifelong course of preventive medications. Individual B, however, has a fatal heart attack at age 65 that could have been prevented by taking a statin, and loses an extra 15 years of lifespan. In his case, it would be hard to justify the decision to not offer him statin therapy on the grounds that his medication disutility greatly outweighed his *estimated* longevity benefit.

The point of this example is not that medication disutility should not be a part of the decision making process for statin therapy, but that, due to the inherent uncertainty for estimating any particular individual's cardiovascular risk, a direct comparison of medication disutility and estimated longevity benefit can be misleading. At an epistemological level, regression based methods such as the SCORE algorithm[10] and the Pooled Cohorts Equation

recommended by the recent guidelines[2] can only arrive at an averaged risk for all individuals who share the same risk profile, and therefore can not predict with certainty whether any given individual will go on to have a cardiovascular event.[11] Furthermore, there has been recent recognition that uncertainty in cardiovascular risk estimation can be caused by the poor concordance between different risk equations,[12] and by variability in the factors used to estimate risk, such as the variability in systolic blood pressure[13] or the level of C-reactive protein.[14]

On the other side of the utility equation, the determination of patient preferences such as medication disutility is also fraught with uncertainty. Just as framing and cognitive biases affect perceptions of risks,[15] medication disutility is also likely to be fluid and context dependent.[16] The substantial differences between the level of medication utility described here compared with those expressed by atrial fibrillation patients in previous studies[8, 9] could in part be due to differences in how the questions were asked (concerning a hypothetical tablet versus familiar medications, aspirin or warfarin) and the settings in which participants were interviewed (in public space versus a research office). Finally, the mere quantification of medication disutility does not address the deeper question of *why*. When faced with a patient who is resistant to taking medications that could have important health benefits, a truly patient-centered approach would require the insightful physician to explore the reasons, such as whether the concerns are justified misgivings for our overreliance on medications to treat lifestyle diseases,[17] or whether the disutility represent fears about side effects that are misperceived or misattributed.[18]

In the social and behavioral sciences, it has been increasingly recognized that rational decision-making is more nuanced than the simple weighing of utility and disutility, and is bounded by incomplete information, uncertainty, and the cognitive limits of the mind.[19] This perspective of bounded rationality could also improve how we approach medical decision-making at the level of the individual patient. Increasingly, shared decision making is emphasized to ensure that individual patients can make “informed, evidence-based decisions that are consistent with their values and preferences”.[15, 20] While the science of shared decision making has advanced our understanding of how to communicate quantitative risk,[15] the work by Fontana and Asaria and colleagues in this issue of *Circulation* reminds us that we still lack evidence-based approaches to incorporate patient preferences such as medication disutility into the shared decision making process. As our understanding of cardiovascular risk continues to be refined, how to account for the uncertain calculus of risk, benefits, and preferences at the individual level will be a central challenge for the practice of personalized cardiovascular medicine.

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