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Original Article

Patients' Preferences in Anticoagulant Therapy
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Background—With proliferating treatment options for anticoagulant therapy, physicians and patients must choose among them based on their benefits and risks. Using a Discrete Choice Experiment, we elicited patients' relative preferences for specific benefits and risks of anticoagulant therapy.

Methods and Results—We selected a sample of US patients with cardiovascular disease from an online panel and elicited their preferences for benefits and risks of anticoagulant therapy: nonfatal stroke, nonfatal myocardial infarction, cardiovascular death, minor bleeding, major bleeding, bleeding death, and need for monitoring. These attributes were used to design scenarios describing hypothetical treatments that were labeled as new drug, old drug, or no drug. Latent class analysis was used to identify groups of patients with similar preferences. A total of 341 patients completed all Discrete Choice Experiment questions. On average, patients valued a 1% increased risk of a fatal bleeding event the same as a 2% increase in nonfatal myocardial infarction, a 3% increase in nonfatal stroke, a 3% increase in cardiovascular death, a 6% increase in major bleeding, and a 16% increase in minor bleeding. The odds of choosing no drug or old drug versus new drug were 0.72 (95% confidence interval, 0.61–0.84) and 0.86 (95% confidence interval, 0.81–0.93), respectively. Previous stroke or myocardial infarction was associated with membership in the class with larger negative preferences for these outcomes.

Conclusions—Patients' preferences for various outcomes of anticoagulant therapy vary and depend on their previous experiences with myocardial infarction or stroke. Incorporating these preferences into benefit risk calculation and treatment decisions can enhance patient-centered care. **(*Circ Cardiovasc Qual Outcomes*. 2014;7:00-00.)**

Key Words: benefit-risk assessment ■ choice behavior ■ patient centered outcome research ■ utility theory

Large clinical trials have demonstrated potential differences among the novel oral anticoagulants (NOACs) and warfarin with respect to both stroke reduction and increased bleeding risk.[1–6] When evaluating the overall balance between benefits and risks of treatments, physicians take into account probabilities of various beneficial and harmful treatment outcomes. However, implicit in their evaluation is the relative weights that they attach to each of those different outcomes. Inevitably, any treatment decision will be based on a subjective and implicit weighing scheme of those benefits and risks. In the case of anticoagulant therapy, perceptions about the relative effect of stroke, myocardial infarction (MI), and bleeding on a patient's quality of life may differ from physician to physician.[7,8] Moreover, it is not clear whether physicians and patients have similar valuations and preferences toward treatment outcomes and attributes.[8–11]The Discrete Choice Experiment (DCE) is a useful method to measure patients' relative preference weights for harmful or beneficial treatment outcomes. These weights reflect the trade-offs that an individual is willing to make among different treatment outcomes when choosing among treatment options. With the advent of NOACs, treatment decisions for patients with atrial fibrillation (AF) have become more complex, but no study has examined patient preferences for outcomes of different anticoagulant treatments. A handful of studies has used DCE for this purpose in Crohn disease,[12] osteoarthritis,[13] irritable bowel syndrome,[14] and multiple sclerosis.[15] Some other studies have used preference estimates from DCE studies as a common metric to compare benefits and risks of interventions.[16]

In a sample of patients with cardiovascular disease, we conducted a DCE to elicit their relative preference weights for different outcomes of anticoagulant therapy, including risk of nonfatal stroke, nonfatal MI, cardiovascular death, minor bleeding, major bleeding, bleeding death, and the need for international normalized ratio monitoring. Quantifying these preferences and incorporating them into benefit risk evaluations can promote patient-centered prescribing decisions.

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WHAT IS KNOWN

- With proliferating treatment options for anticoagulant therapy, balancing benefits and risks in treatment decisions have become more complex; yet, no study has examined patient preferences for these benefits and risks.

WHAT THE STUDY ADDS

- Using a discrete choice experiment, we elicited relative preferences for different benefits and risks of anticoagulant therapy in a sample of patients with cardiovascular disease.
- Patients in our sample valued a 1% increased risk of death from bleeding, the same as a 3% increase in nonfatal stroke, a 2% increase in nonfatal myocardial infarction, a 3% increase in cardiovascular death, a 16% increase in minor bleeding, and a 6% increase in major bleeding.
- Patients exhibited a preference for new drugs regardless of their relative benefits and risks.
- Incorporating patients' preferences into anticoagulant treatment decisions may help enhance the objectivity and patient-centeredness of those decisions.

Methods

Study Sample

Our study population, a sample of an online panel of patients across the United States with cardiovascular conditions, was recruited through the market research company Lightspeed Research (http://www.lightspeedresearch.com/). Lightspeed provides online sampling for studies in healthcare sector and other industries; their consumer populations have been used in several previous peer-reviewed research studies.[17–21] The company's approach conforms to the Council of American Survey Research Organizations code of standards and ethics for survey research, as well as local, regional, and national laws on privacy and data protection.

All panel participants in the United States, who were aged ≥18 years, were able to read English and had a self-reported history of cardiovascular disease, were eligible to participate, regardless of their sex, geographical location, and other demographic variables. Panelists first received email invitations from the company to take part in a survey that contained a unique universal resource locater to our questionnaire. This initial email did not mention the survey topic to avoid self-selection; only the survey length and incentive for participation were explained. Those who clicked on the Web link were redirected to a questionnaire located on the secure Web site on our hospital's server.

Patients who agreed to participate received small incentives in the form of a point-based reward paid by Lightspeed Research on completion of the survey. These points can be redeemed for a check mailed to the panelist. This study was reviewed and approved by the Brigham and Women's Hospital Institutional Review Board.

Study Procedure

The DCE methodology is grounded in multiattribute utility theory in economics[22] and is a technique to measure individuals' valuation of different aspects of healthcare technologies.[23] This theory is based on the assumption that first, any commodity (eg, anticoagulant drugs) can be characterized by several key attributes and their levels (eg, likelihood of various efficacy outcomes, likelihood of side effects, modality); and second, whenever individuals have options to choose from (eg, anticoagulant drugs), they make their choice by comparing those attributes and levels. The attributes that we used to characterize hypothetical treatment options were chosen based on major outcomes from NOAC trials and included the likelihood of nonfatal stroke, nonfatal heart attack, fatal heart attack or stroke, minor bleeding, major bleeding, fatal bleeding, and need for blood-test monitoring (Appendix Table I in the Data Supplement).

We asked patients to assume that they were at increased risk of cardiovascular events similar to those associated with AF and explained various potential benefits and risks associated with anticoagulant therapy. Then, we presented 14 choice questions, each containing 3 hypothetical treatment options labeled as new drug, old drug, and no drug, and asked patients to choose one of these 3 options by comparing their attributes. A sample choice question is presented in Table 1. Our design was such that if we had used noninformative labels for treatment options (eg, drug A versus drug B), on average, we would not expect to see any preference toward either of those treatment options per se. We randomly labeled treatment options as new drug and old drug to explore whether patients had a bias toward choosing new or old medications, independent of their attributes. By changing the attribute levels of treatment options (ie, new drug and old drug) in subsequent choice questions, we were able to use individuals' stated choices in different questions to estimate their underlying preference weights for different treatment attributes. The attribute levels of the no drug option reflected the baseline risks of different outcomes in the absence of treatment and thus did not change across the questionnaires.

Questionnaire Design

We defined outcome-based DCE attributes to match the major efficacy and safety clinical end points commonly used in clinical trials

Table 1. A Sample Discrete Choice Experiment Choice Question

	New Drug	Old Drug	No Drug
Risk of heart attack (remain alive)	4 of 100	6 of 100	6 of 100
Risk of stroke(remain alive)	7 of 100	4 of 100	10 of 100
Risk of death from heart attack or stroke	5 of 100	10 of 100	15 of 100
Risk of minor bleeding (remain alive)	0 of 100	30 of 100	30 of 100
Risk of major bleeding (remain alive)	10 of 100	20 of 100	10 of 100
Risk of death from bleeding	3 of 100	1 of 100	1 of 100
Need for monitoring	Every 3 mo	Every month	No monitoring
	☐	☐	☐

Suppose that you have bad chest pain and visit your doctor. Your doctor tells you that you are at increased risk of heart attack and stroke. Your doctor tells you about drugs you can take that can reduce your risk of heart attack and stroke. However, your doctor warns you that some patients have unexpected bleeding when taking these drugs. This bleeding can be minor, such as small nose or gum bleeds. The bleeding could also be major and require blood transfusions and hospital care. Some patients may die if their bleeding cannot be controlled. If new drug, old drug, or no drug were your only options, which would you choose? Make your choice by clicking on one of the 3 buttons below the table. Move the mouse over each phrase for its definition. You can always go back to another page by clicking on the back button. You can change your answers at any time.

of anticoagulants.[3–5] In accordance with methodological guidelines for designing choice experiments,[24] we minimized the number of attributes studied to avoid overly complex choice questions.

On the basis of discussion with clinical experts, we identified 7 attributes central to anticoagulant use (Appendix Table I in the Data Supplement). The first 6 were nonfatal stroke, nonfatal MI, cardiovascular death (including fatal stroke), minor bleeding, major bleeding, and bleeding death, defined so as to minimize the potential overlap among them.[25] A seventh, the need for international normalized ratio monitoring, allowed us to compare patients' preference weights for clinical outcomes (on a probability scale) to a measure of treatment modality. The ranges selected for different attribute levels were based on the observed probabilities of events in the major randomized clinical trials for warfarin and the NOACs (ie, dabigatran, rivaroxaban, and apixaban).[1,3–5] We converted annual outcome rates to rates >5 years, assuming a constant hazard rate of events. This enabled us to present all probabilities as the incidence rate for each event in 100 patients during a 5-year period. To facilitate respondents' understanding of the choice questions and to enhance interpretation of numeric presentation of risks, participants were able to access definitions of these attributes and a graphical presentation of the probabilities in real-time in pop-up windows while completing the questionnaire.

Theoretically, a large number of (hypothetical) treatment options and therefore choice questions can be generated using these 7 attributes and all various combinations of their levels (ie, full factorial design). Because presenting all possible choice questions in a DCE is not practical, we used a fractional factorial design[26] in which we selected a subsample of 140 choice questions, grouped into 10 versions of the DCE questionnaire. Each respondent was asked to complete a randomly assigned version of the DCE questionnaire that contained 14 choice tasks. Two of 14 choice questions presented in all DCE questionnaires included a treatment option that was clearly better than other options in all aspects (a dominant treatment option). This enabled us to check the rationality of responses and attentiveness of respondents to the choice questions. We also included the no drug option in each choice question to provide the possibility to opt-out whenever neither new drug nor old drug seemed adequately attractive to the respondent. Thus, we avoided forcing respondents to choose a drug.[23]

The design of the Web-based questionnaire, which facilitated direct data entry into our secure server, was performed using the Choice Based Conjoint application of Sawtooth (SSI Web version 8.2.4; Sawtooth Software Inc;). We created a fractional factorial design using Sawtooth and verified the design to be balanced and nearly orthogonal.[24] These properties ensure that each attribute level appears an equal number of times by itself (balance) and in combination with other attribute levels (orthogonality) throughout the questionnaires. This is necessary for minimizing bias and improving precision in estimation of preferences, given a fixed sample size. By varying the seed number for random number generator, we generated and compared numerous designs and then selected the final design based on efficiency (ie, highest precision for coefficient estimates) and a larger D-efficiency given a fixed sample size.[23,27] The sample size calculation was performed using simulation of responses, assuming that 20% of respondents would pick the no drug option and the rest were indifferent to the remaining 2 alternatives, the SEs of coefficients for all attribute level were <0.035 providing a sample size of 250 respondents.

Statistical Analysis

The underlying model for discrete choice experiments[28] suggests that given a set of options, the log odds ratio of choosing one of the options is proportional to a linear function of attributes of each option. We used generalized linear models to estimate coefficients, also known as relative preference weights, reflecting the average effect of attribute levels on the likelihood of choice. The ratio of any 2 coefficients can be interpreted as Maximum Acceptable Risk,[12,29] which shows the average magnitude of risk that patients are willing to accept in one of the attributes in exchange for achieving an improvement in the other attribute. We coded the choice data for all 7 attributes as continuous variables, and we defined 2 alternative specific dummy variables for old drug and no drug, treating new drug as the reference level.

Statistical models that can be used for the analysis of choice data include conditional logit models, Bayesian mixed logit models, and latent class analysis (LCA).[23] A complex correlation structure in the choice data requires methods that can account for it. For example, a strong correlation may exist among preferences of patients who choose a drug versus those who choose no drug; this can undermine the independence of irrelevant alternatives (IIA)[23,24] assumption and create bias in the estimation of preferences. Also a strong correlation within versus between patients' choices can result in a clustering of

Table 2. Baseline Characteristics of Patients in this Study

Variable	n=341
Age (SD)	51.5 (15.8)
Women	125 (37%)
Education	
Some high school	7 (2%)
High school	65 (19%)
Some college	128 (37%)
Bachelor degree	65 (19%)
Some graduate school	20 (6%)
Master degree	46 (13%)
Doctorate	10 (3%)
No. of dependent children	
None	217 (63%)
1	54 (16%)
2	43 (13%)
≥3	27 (8%)
Self-reported current health status	
Excellent	7 (2%)
Very good	43 (13%)
Good	64 (19%)
With some health problems	170 (50%)
Having serious health problems	57 (17%)
Have you seen anyone among your close family or friends who has been hospitalized for heart attack, stroke, or has died as a result of these conditions?	
Multiple	155 (45%)
1	106 (31%)
None	80 (23%)
Have you previously had any of the following health problems?	n=341
Heart attack	118 (35%)
Stroke	70 (21%)
Coronary artery disease	74 (22%)
Angina	78 (23%)
Acute coronary syndrome	16 (5%)
Arrhythmia	117 (34%)
Atrial fibrillation	78 (23%)
Heart failure	66 (19%)
Peripheral artery disease	47 (14%)
Pulmonary embolism	25 (7%)
Congenital heath disease	39 (11%)
Inflammatory heart disease	23 (7%)
Metabolic syndrome	71 (21%)

Table 3. Estimated Relative Preference Weights, MAR, and OR

	Mean Weight	*P* Value	MAR (95% CI)*	OR (95% CI)
Stroke	−0.0698	<0.0001	2.79 (2.73, 2.85)	0.933 (0.92 to 0.94)
Myocardial infarction	−0.0888	<0.0001	2.19 (2.09, 2.29)	0.915 (0.90 to 0.93)
Cardiovascular death	−0.0565	<0.0001	3.44 (3.40, 3.49)	0.945 (0.95 to 0.95)
Minor bleeding	−0.0119	<0.0001	16.35 (16.34, 16.36)	0.988 (0.99 to 0.99)
Major bleeding	−0.0309	<0.0001	6.30 (6.27, 6.33)	0.970 (0.96 to 0.97)
Bleeding death	−0.1946	<0.0001	1.00	0.823 (0.79 to 0.86)
Need for monitoring	−0.0010	0.2098	200.62 (200.61, 200.63)	0.999 (1.00 to 1.00)
No drug	−0.3283	<0.0001	0.59 (−0.22, 1.41)	0.720 (0.61 to 0.84)
Old drug	−0.1463	<0.0001	1.33 (0.97, 1.69)	0.864 (0.81 to 0.93)

MCFadden likelihood ratio index =0.1843; LL=4278; LL0=5245; log-likelihood ratio=(2×(LL−LL0))=1934. CI indicates confidence interval; LL, log-likelihood; LL0, log-likelihood null; MAR, Maximum Acceptable Risk; and OR, odds ratio.

*The 95% confidence intervals for MAR has been estimated using delta method[33]:

$$\mathrm{Var}(\mathrm{MAR}_k) = \left[\left(\frac{1}{\widehat{\beta}_r}\right)^2 \mathrm{var}\left(\widehat{\beta}_r\right) + \left(\frac{\widehat{\beta}_k}{\widehat{\beta}_r}\right)^2 \mathrm{var}\left(\widehat{\beta}_r\right) + 2\left(-\frac{1}{\widehat{\beta}_r}\right)\left(\frac{\widehat{\beta}_k}{\widehat{\beta}_r^2}\right)\mathrm{cov}\left(\widehat{\beta}_k, \widehat{\beta}_r\right)\right]$$

choice data. Nested logit models, mixed logit models, and latent class analyses can account for these types of correlations.

We conducted a LCA to identify classes of individuals with similarities in their preferences.[30–32] LCA uses a semiparametric approach to model the correlation structure of the data and is particularly useful when one is interested in examining possible heterogeneities among participants' preferences. The LCA was performed using Latent Gold Choice version 4.5.0. After identifying class membership for each patient, we conducted a post hoc logistic regression to examine how class membership was associated with patient characteristics.

Results

A total of 341 patients with cardiovascular disease provided complete responses to all questions and were included in the analysis. Initially, 6892 emails were sent out by the research company to its pool of potential respondents; 688 individuals (10%) clicked on the link and were directed to the survey, where they were asked to provide their consent for participation; 101 individuals (15%) declined to be part of this study; 132 individuals (19%) did not identify themselves to have any of 13 categories of cardiovascular diseases (disqualified); and an additional 114 patients (17%) did not complete all 14 choice questions in the survey.

The mean age in our sample was 52 (SD, 16) years; 63% were men and 141 (41%) had a Bachelor's degree or higher, consistent with national demographic data on education attainment levels across the United States (Table 2). Most respondents (n=217; 63%) reported no dependent children, 227 (67%) stated having some or serious health problems, 261 (76%) indicated that they knew of a close friend or family member with a history of stroke or MI, and 177 (52%) had had a history of stroke or MI themselves.

Among the 341 respondents, 15 (4%) chose the new drug, 3 (1%) chose the old drug, and 10 (3%) chose no drug in all 14 choice questions, regardless of the probabilities presented. In the remaining respondents, over one third (123; 36%) failed to choose the dominant treatment option in ≥1 of 2 fixed choices. This made it possible to identify a subsample of 190 patients whose responses met pre-established criteria for rationality.

We initially used a single-class conditional logit model to estimate average preferences in all patients. Estimated preference weights and associated odds ratios and Maximum Acceptable Risks and their confidence intervals[33] are reported in Table 3. A 1% increase in risk of bleeding death was used as the reference for the calculation of Maximum Acceptable Risks. Figure 1 provides a visual presentation of estimated preference weights in the full sample (n=341) and in the subsample of 190 respondents who met criteria for plausible decision making. In the full sample (n=341), the preference weight for a 1% increase in risk of nonfatal MI was −0.0888 (P<0.0001). All else equal, the odds of choosing a drug that increased risk of nonfatal MI by 1% was 0.92. The negative preference weights for nonfatal stroke (−0.0698; P<0.0001) and death related to MI or stroke (−0.0565; P<0.0001) were smaller (in absolute terms) than for nonfatal MI. Patients had larger negative preferences related to death from bleeding when compared with preference weights for nonfatal stroke, nonfatal MI, and death from stroke or MI. Patients were willing to accept a 2.8% risk of nonfatal stroke, 2.2% risk of nonfatal MI, and 3.4% increased risk of death related to MI or stroke to avoid 1% additional risk of death related to bleeding. The negative preference weight for additional visits for international normalized ratio monitoring (per year) was small (−0.0010; P=0.2098).

Overall, patients had strong negative preferences on no drug (−0.3283; P<0.0001) or an old drug (−0.1463; P<0.0001) compared with a new drug, with all other variables held constant. In other words, regardless of the actual probabilities of efficacy and side effects, patients were 14% less likely to choose an old drug (odds ratio, 0.86; 95% confidence interval, 0.81–0.93) and 28% less likely to choose no drug (odds ratio, 0.72; 95% CI, 0.61–0.84). However, when we restricted the analysis to those with rational responses (n=190), the negative preference weight for the old drug was no longer significant (−0.0380; P=0.4721).

To explore preference heterogeneities, we used a latent class conditional logistic model with the number of classes

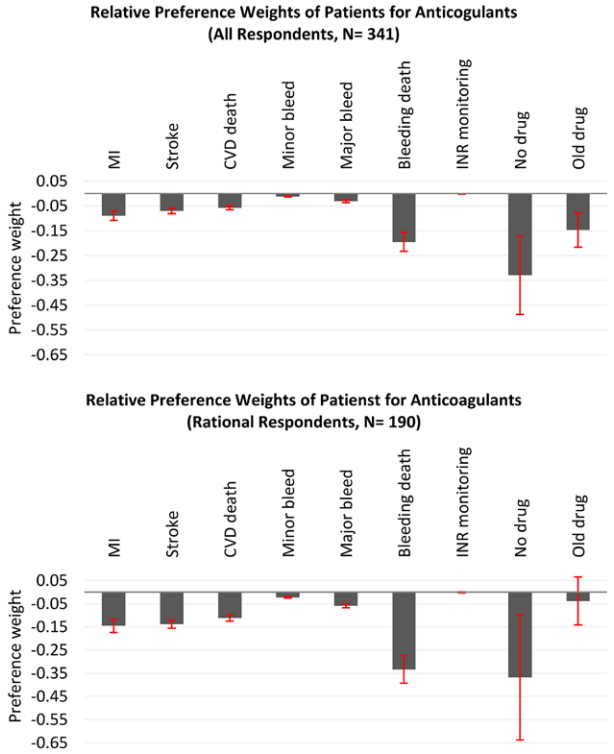

Figure 1. Relative preference weights of patients for attributes of anticoagulant therapy: (**A**) all respondents (n=341) and (**B**) rational respondents (n=190). CVD indicates cardiovascular disease; INR, international normalized ratio; and MI, myocardial infarction.

set to 2. We then increased the number of latent classes one at a time, re-estimating the model, and selected model with optimum number of classes. The optimum number of classes was determined by comparing model fit based on the changes in log-likelihood ratios, Akaike information criteria, Bayesian information criteria, Entropy R^2, and resulted class sizes. In the subsample of patients who provided rational responses (n=190), we identified 2 distinct segments (ie, classes) of patients with different preferences for treatment attributes (Figure 2). These segments were defined using LCA so that patients within each segment had more similar preferences. When compared with those in class 2, those in class 1, which consisted of 131 (68.9%) patients, had larger negative preferences toward risk of nonfatal MI, nonfatal stroke, and cardiovascular-related death, while they had smaller negative preferences for risk of minor bleeding. They also had larger negative preferences for choosing no drug or old drug when compared with class 2, but the difference was not statistically significant. The logistic regression analysis to predict class membership indicated that patients with no history of stroke or MI were 2.89 (95% CI, 1.37–6.09) times more likely to be in class 2 than in class 1 (Table 4). None of other patient characteristics predicted class membership. A 3-class model resulted in a small third class size with a modest improvement in model fit, suggesting that a 2-class model sufficiently captured preference heterogeneities given our sample size.

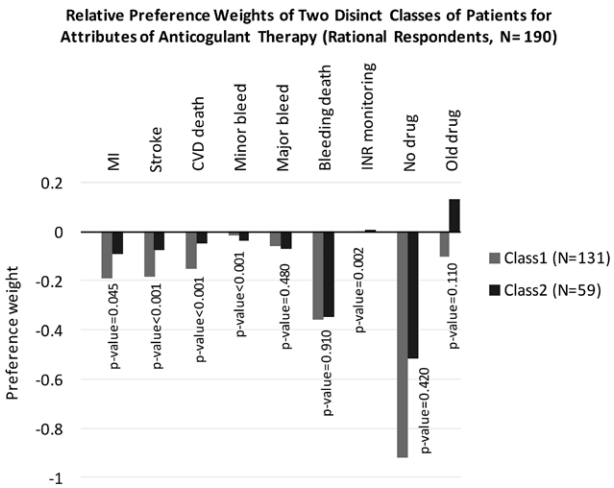

Figure 2. Relative preference weights of 2 distinct classes of patients for attributes of anticoagulant therapy (rational respondents, n= 190). *P* values show a statistically significant difference between the preference weights of 2 classes. CVD indicates cardiovascular disease; INR, international normalized ratio; and MI, myocardial infarction.

Discussion

Using a discrete choice experiment, we elicited relative preferences for different benefits and risks of anticoagulant therapy in a sample of patients with cardiovascular disease. On average, patients in our sample weighted an increased risk of fatal bleeding more heavily than thrombotic outcomes. Specifically, respondents valued a 1% increased risk of death from bleeding the same as a 3% increase in nonfatal stroke, a 2% increase in nonfatal MI, a 3% increase in cardiovascular death, a 16% increase in minor bleeding, and a 6% increase in major bleeding. The negative preference weight for bleeding death was considerably larger than the negative preference weight for cardiovascular death, which is in contrast to the

Table 4. Association Between Latent Class Membership (in Class 2 vs Class 1) and Individual Characteristics

Self-Reported Diseases	OR (95% CI)
Coronary artery disease	1.68 (0.68–4.16)
Angina	1.73 (0.74–4.06)
Arrhythmia	1.33 (0.64–2.80)
Atrial fibrillation	0.51 (0.22–1.18)
Heart failure	1.12 (0.47–2.66)
Peripheral artery disease	0.90 (0.30–2.75)
Pulmonary embolism	0.38 (0.03–4.31)
Congenital heath disease	0.96 (0.30–3.08)
Inflammatory heart disease	2.19 (0.36–13.67)
Metabolic disorder	0.94 (0.42–2.11)
Male sex	0.96 (0.45–2.07)
Age <50 y	1.23 (0.57–1.66)
Bachelor degree or higher	0.82 (0.41–1.66)
No dependent children	1.05 (0.48–2.32)
Excellent, very good, or good health status (vs having some or serious health problems)	0.84 (0.39–1.85)
No history of MI or stroke	2.89 (1.37–6.09)

Model *C*-statistics=0.688. CI indicates confidence interval; MI, myocardial infarction; and OR, odds ratio.

usual practice of assigning identical weights for all causes of death when using weights that reflect health-related quality of life. Patients clearly discriminate between different fatal events, suggesting that they have different levels of risk tolerance for those events. The observed difference between preference weights for bleeding death and cardiovascular death may be attributable to the fact that patients tend to internalize the sequence of all events that eventually lead to death rather than evaluating death as an isolated health state. They may, for example, consider the effect of differences in experiencing among causes of death and differences in consequences on family members and caregivers. Another possible explanation is that, in contracts to cardiovascular death, patients might perceive bleeding death as an avoidable adverse effect of treatment, and therefore show more aversion toward it. Assigning larger weights to risks when compared with benefits also can be related to an individual's asymmetrical preferences for losses versus gains, as has been described in Prospect theory.[34]

When we included all respondents in our analysis, the odds of choosing an option labeled as old drug was significantly lower than choosing new drug, which indicates that patients were inclined to choose the new drug rather than considering the actual benefits and risks associated with different medications. However, this preference was not observed in the subsample of patients who correctly answered 2 fixed questions that were embedded to check for rationality of responses. The effect of labeling has also been shown in a conjoint analysis by Tong et al,[35] in which the authors found that labeling the treatment options as coronary stent and coronary bypass surgery had a significant effect on patients' choice.

An important advantage to using DCE is that it allows one to measure individuals' preferences for multiple harmful and beneficial outcomes and the trade-offs that they are willing to make among those outcomes. This aspect of DCE fits well within a benefit risk framework, which can be used to help patients, providers, and other stakeholders make objective treatment decisions. For example, these preference weights can be combined with the observed probabilities of outcomes of anticoagulants in clinical trials[6] or observational studies to calculate and compare incremental net benefit of the medications. An incremental net benefit approach, combined with preference elicitation methods, provides a practical framework for incorporating patient preferences into risk benefit analyses.[16]

A systematic review by MacLean et al[36] identified 48 studies of patients' preferences for antithrombotic therapy. Most of these studies, however, used other preference elicitation methods, such as standard gamble, time trade-off, or hypothetical scenarios to derive patients' risk thresholds. Although one study used DCE to evaluate patients' preferences for different attributes of anticoagulants,[37] the focus of that study was not on benefit risk aspects of anticoagulants. Finally, Zhang et al[38] used a rating scale to determine preferences of 807 individuals for potential harmful outcomes of cardiovascular treatment and, in line with our findings, they concluded that patients rated stroke and MI worse than cardiovascular death.

Whether irrational responses should be excluded from the final analyses is debatable.[39] If we consider a normative perspective, we may conclude that those who did not pass the rationality check either did not comprehend choice questions or were not sufficiently attentive to the experiment. Another possible explanation is that their choices were influenced by other attributes of new drugs that are missing in our DCE. In contrast, descriptive utility theories such as prospect theory suggest that individuals systematically deviate from normative utility theories.[34] These theories suggest that instead of following principles of rationality as defined by expected utility theory, individuals use heuristics to simplify their decision-making process and they weigh benefits and risks asymmetrically.

Our study has other limitations. Although the most common indication for anticoagulants is AF, participants in our survey were patients with general cardiovascular diseases. This was mainly to ensure whether we would achieve a sufficient sample size. We compared the preferences of 78 patients with AF in our sample with the preferences of the remaining patients by modeling an interaction between AF and preferences. When compared with the rest of patients, patients with AF had a larger negative preference for bleeding death and no drug but were indifferent to new drug and old drug labels. Preferences of patients with AF were similar to non-AF patients in all other aspects. We modeled attributes as continuous variables to simplify interpretations of findings. This requires the assumption that the effect of attribute levels on preferences is linear, which may not always be true. However, we relaxed the linearity assumption by effect coding the choice data and found that the estimated effects were near linear, and therefore this assumption did not alter our conclusions. Our patient sample was selected from an online panel and therefore may not fully represent the actual universe of patients with cardiovascular conditions in the United States. Even though the similarity between the demographic characteristics of our sample and corresponding national statistics are reassuring, any generalization of our findings should be made with caution. It is possible that the W-based sampling strategy and the complexity of the choice tasks may have hindered patients' understanding of the questionnaire. The relatively high ratio of patients who failed the test for rational responses (36%) raises some concern about patient understanding and of the validity of our findings. However, by examining the model with effect-coded data, we observed a clear rank ordering of preferences across different levels of risk in all attributes. This suggests that patients, on average, understood the choice tasks and made their selections based on the probabilities presented to them because choice models based on random utility theory are robust to random choice variation. In addition, exclusion of irrational respondents from our analysis did not materially change the results. Furthermore, the comments that respondents provided at the end of the questionnaire suggested that, overall, they had little problem in understanding and responding to the questionnaire. All these support the validity of our findings, despite the seemingly high ratio of irrational responses. To ensure the validity of our findings, the sensitivity of our results to selection of attributes and definitions that have been provided for different attributes in the questionnaire should be explored in future studies. Missing attributes can affect proper estimation of preferences in general, and of alternative specific coefficients (ie, old drug, no drug), in particular. We assumed that

the main outcomes of clinical trials reflect the most important aspects of anticoagulant therapy. Although there is evidence that these outcomes are also important for patients,[40] it is possible that other important aspects of benefits and risks are missing from our study. Finally, patients' actual treatment choices may differ from their stated choices in our experimental setting. This is a known limitation of the DCE method because it relies on stated preferences rather than revealed preferences.[41] Collecting actual patient treatment decisions and testing those against their stated choices in experimental setting can elucidate the degree of concordance between stated and revealed preferences and should also be explored in future studies.

Despite these limitations, our findings have important clinical implications. We found that patients' preference for avoiding the inconvenience of international normalized ratio monitoring may be trivial when compared with their preference for avoiding clinical outcomes. Also, patients may prefer NOACs to warfarin solely on the basis that they are new drugs and not necessarily because of any benefits that they may confer. This suggests that labels can influence patients' medication choices and such labels should be used with caution in shared decision-making process. We also found that patients who previously experienced stroke and MI may have different relative preferences for the various treatment outcomes than patients who have not experienced these events. Understanding that these patients, on average, are more willing to accept risks in exchange for the benefits of anticoagulants can influence treatment decisions in these subpopulations. Given that physicians' concern about the risks of anticoagulants is partly responsible for underuse of these medications,[8] our results might influence physicians' viewpoints about how patients perceive and evaluate risks of anticoagulants.

Deciding on the appropriate balance between various benefits and risks is a complex task that patients and physicians face on a daily basis. In the setting of stroke prevention for AF, this task is more complicated now than ever, given the proliferation of new treatment strategies. Incorporating the preference weights that we elicited in this study into anticoagulant treatment decisions may help enhance the objectivity and patient-centeredness of those decisions.

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