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ORIGINAL RESEARCH ARTICLE

General Population vs. Patient Preferences in Anticoagulant Therapy: A Discrete Choice Experiment

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Abstract

Objectives Preference weights derived from general population samples are often used for therapeutic decision making. In contrast, patients with cardiovascular disease may have different preferences concerning the benefits and risks of anticoagulant therapy. Using a discrete choice experiment, we compared preferences for anticoagulant treatment outcomes between the general population and patients with cardiovascular disease.

Methods A sample of the general US population and a sample of patients with cardiovascular disease were selected from online panels. We used a discrete choice experiment questionnaire to elicit preferences in both populations concerning treatment benefits and risks. Seven attributes described hypothetical treatments: non-fatal stroke, non-fatal myocardial infarction, cardiovascular death, minor bleeding, major bleeding, fatal bleeding, and the need for monitoring. We measured preference weights and maximum acceptable risks in both populations.

Results A total of 352 individuals from the general population and 341 patients completed the questionnaire. After propensity score matching, 284 from each group were included in the analysis. On average, the general population members valued a 1% increased risk of fatal bleeding as being the same as a 4.2% increase in a non-fatal myocardial infarction, a 2.8% increase in cardiovascular death, or a 14.1% increase in minor bleeding. Patients, in contrast, perceived a 1% increased risk of fatal bleeding as being the same as a 2.0% increase in a non-fatal myocardial infarction, a 3.2% increase in cardiovascular death, and a 16.7% increase in minor bleeding.

Conclusions The general population and patients with cardiovascular disease had slightly different preferences for treatment outcomes. The differences can potentially influence estimated benefits and risks and patient-centered treatment decisions.

Key Points for Decision Makers

Using a discrete choice experiment, we elicited preferences concerning the benefits and risks of anticoagulant therapy in a sample of the general US population and a sample of patients with cardiovascular disease

We estimated and compared maximum acceptable risks in a propensity-matched sample of both populations and found they had slightly different preferences for treatment outcomes

The differences in benefit-risk trade-offs can potentially influence estimated benefits and risks and patient-centered treatment decisions

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1 Background

Different anticoagulants used for the prevention of thromboembolic events in patients with atrial fibrillation (AF) have different effects on thromboembolic and bleeding outcomes [1–4]. As compared to warfarin, all of the novel oral anticoagulants reduce the risk of stroke and systemic embolism and death but vary in their risk of major bleeding [5]. Optimal treatment decisions involving these agents must account for not only the probabilities of these outcomes under various treatment options, but also the weights that reflect patients' preferences for the outcomes. Ideally, in shared treatment decisions, individual patient preferences would be used to tailor treatment selection to maximize the value of treatment for patients. However, when shared decision making is not feasible or some prior knowledge about average patients' preferences is needed, previously obtained preference weights can serve as proxies for patient preferences. Average preferences of patients or patient sub-groups can also inform benefit-risk trade-offs in regulatory decisions and priority setting in resource allocations.

Nevertheless, when previously obtained preference weights exist, they are often based on the preferences of the population as a whole rather than relevant patient samples. For example, health-state values used in benefit-risk analyses and cost-effectiveness analyses are often derived from members of the general population by asking them to imagine health states associated with the disease [6, 7]. However, it is not usually known how preferences of the general population compare to those of patients with specific medical conditions, who have thought about these health outcomes more personally, and may even have experienced some of them. Differences in preferences can result in very different trade-offs and, therefore, can directly influence choices and decisions that are made. For example, in decisions about anticoagulant therapy for the treatment of AF, physicians tend to place a larger weight on avoiding bleeding events and a smaller weight on avoiding stroke as compared with their patients [8, 9].

We conducted a discrete choice experiment (DCE) to elicit and compare preferences of the general population to those of patients with cardiovascular disease (CVD) for various outcomes of anticoagulation therapy. The estimated weights reflect the trade-offs that members of the general population and patients are willing to make among different treatment outcomes when comparing various treatment options for AF.

2 Methods

2.1 Study Sample

Our study population consisted of two samples derived from online panels across USA: (1) a panel of individuals from the general population, and (2) a panel of patients with self-reported cardiovascular conditions (Table 1). Our study participants were recruited through the market research company Lightspeed Research (http://www.lightspeedresearch.com/). Lightspeed Research provides online sampling for studies in the healthcare sector and in other industries; their consumer populations have been used in several, previous peer-reviewed research studies including ours [10–12]. 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 regulations regarding privacy and data protection.

All panel participants in USA who were at least 18 years old and were able to read English were eligible to participate, regardless of their sex, geographical location, and other demographic variables. Panelists first received e-mail invitations from the company to take part in a survey that contained a unique universal resource locater to our questionnaire. This initial e-mail 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 re-directed to a questionnaire located on a secure website on our hospital's server. Individuals who agreed to participate received small incentives in the form of a points-based reward paid by Lightspeed Research upon completion of the survey. These points could be redeemed for money. This study was reviewed and approved by the Brigham and Women's Hospital Institutional Review Board.

2.2 Study Procedure

The study design and procedure were similar to our previously published study [11]. We asked participants to imagine that they had AF and that their physician determined that they are at an increased risk of experiencing a thromboembolic event. We described to the participants the benefits and harms associated with anticoagulant therapy, similar to explanations that physicians provide to patients with AF (see below). We then presented a questionnaire consisting of 14 choice questions. In each question, we presented three hypothetical treatment options and asked participants to compare the benefit-risk profile of the options and to indicate which option they preferred. Both the patient group and the members of the general population completed the same DCE questionnaire.

2.3 Questionnaire Design

Outcomes of the hypothetical treatment options were characterized using seven attributes (Appendix, Table 4). The first six attributes described the risk of clinical events: non-fatal stroke, non-fatal myocardial infarction (MI), cardiovascular death (including fatal stroke and fatal MI),

Table 1 Baseline characteristics of the sample of patients and the general population

Variable	Before matching				After matching			
	General population $N=352$	Patients $N=341$	p value for difference	Standardized difference	General population $N=284$	Patients $N=284$	p value for difference	Standardized difference
Age (SD)	46.4 (15.9)	51.5 (15.8)	<0.01	0.32	49.6 (15.9)	48.4 (16.1)	0.38	0.09
Male, *n* (%)	175 (50)	215 (63)	<0.01	0.27	158 (56)	162 (57.0)	0.73	0.04
Education, *n* (%)			0.26	0.23			0.96	0.08
Some high school	3 (1)	7 (2)			3 (1)	5 (2)		
High school	57 (16)	65 (19)			52 (18)	51 (18)		
Some college	113 (32)	128 (37)			99 (35)	96 (34)		
Bachelor degree	90 (26)	65 (19)			64 (22)	62 (22)		
Some graduate school	22 (6)	20 (6)			14 (5)	19 (7)		
Master degree	55 (16)	46 (13)			43 (15)	41 (14)		
Doctorate	11 (3)	10 (3)			9 (3)	10 (4)		
No. of dependent children, *n* (%)			0.69	0.09			0.76	0.03
None	228 (65)	217 (63)			184 (65)	180 (63)		
One	56 (16)	54 (16)			45 (16)	41 (14)		
Two	48 (14)	43 (13)			38 (13)	40 (14)		
Three or more	20 (6)	27 (8)			17 (6)	23 (8)		
Self-reported current health status, *n* (%)			<0.01	0.98			<0.01	0.83
Excellent	32 (9)	7 (2)			22 (8)	7 (2)		
Very good	118 (33)	43 (13)			99 (35)	38 (13)		
Good	117 (33)	64 (19)			90 (32)	55 (19)		
With some health problems	67 (19)	170 (50)			57 (20)	140 (49)		
Having serious health problems	17 (5)	57 (17)			15 (5)	44 (16)		
Have you seen anyone among your close family or friends who has been hospitalized for heart attack of stroke, or has died as a result of these conditions? *n* (%)			<0.01	0.46			<0.01	0.37
Multiple	101 (29)	155 (45)			88 (31)	133 (47)		
One	98 (28)	106 (31)			79 (28)	87 (31)		
None	153 (43)	80 (23)			117 (41)	64 (22)		
Have you previously had any of the following health problems? *n* (%)								
Heart attack	11 (3)	118 (35)	<0.01	0.87	9 (3)	91 (32)	<0.01	0.83
Stroke	8 (2)	70 (21)	<0.01	0.60	7 (2)	59 (21)	<0.01	0.62
Coronary artery disease	8 (2)	74 (22)	<0.01	0.63	6 (2)	62 (22)	<0.01	0.63
Angina	11 (3)	78 (23)	<0.01	0.61	9 (3)	65 (23)	<0.01	0.6
Acute coronary syndromes	1 (0)	16 (5)	<0.01	0.29	1 (0)	14 (5)	<0.01	0.29
Arrhythmia	20 (6)	117 (34)	<0.01	0.77	18 (6)	104 (37)	<0.01	0.74
Atrial fibrillation	12 (3)	78 (23)	<0.01	0.60	11 (4)	63 (22)	<0.01	0.55
Heart failure	9 (2)	66 (19)	<0.01	0.56	8 (3)	53 (19)	<0.01	0.51

Table 1 (continued)

Variable	Before matching				After matching			
	General population $N=352$	Patients $N=341$	p value for difference	Standardized difference	General population $N=284$	Patients $N=284$	p value for difference	Standardized difference
Peripheral artery disease	11 (3)	47 (14)	<0.01	0.39	10 (4)	40 (14)	<0.01	0.35
Pulmonary embolism	11 (3)	25 (7)	<0.01	0.19	8 (3)	23 (8)	<0.01	0.21
Congenital heart disease	5 (1)	39 (11)	<0.01	0.42	2 (1)	36 (13)	<0.01	0.5
Inflammatory heart disease	3 (1)	23 (7)	<0.01	0.31	3 (1)	19 (7)	<0.01	0.31
Metabolic syndrome	31 (9)	71 (21)	<0.01	0.34	27 (10)	63 (22)	<0.01	0.33
Are you currently using any of the following medications? *n* (%)			<0.01					
Aspirin	141 (40)	243 (71)	<0.01	0.66	122 (43)	198 (70)	<0.01	0.56
Clopidogrel	9 (3)	66 (19)	<0.01	0.56	7 (2)	52 (18)	<0.01	0.56
Prasugrel	2 (1)	10 (3)	<0.01	0.18	2 (1)	8 (3)	<0.01	0.16
Ticagrelor	2 (1)	15 (4)	<0.01	0.25	1 (0)	14 (5)	<0.01	0.26
Warfarin	10 (3)	41 (12)	<0.01	0.36	9 (3)	34 (12)	<0.01	0.32
Dabigatran	6 (2)	24 (7)	<0.01	0.26	5 (2)	21 (7)	<0.01	0.24
Rivaroxaban	2 (1)	14 (4)	<0.01	0.24	2 (1)	14 (5)	<0.01	0.21
Apixaban	2 (1)	2 (1)	0.97	0	1 (0)	1 (0)	1.00	0
Have you ever used any of the following medications? *n* (%)								
Aspirin	213 (60)	262 (77)	<0.01	0.36	177 (62)	214 (75)	<0.01	0.29
Clopidogrel	12 (3)	95 (28)	<0.01	0.71	10 (3)	75 (26)	<0.01	0.68
Prasugrel	1 (0)	19 (6)	<0.01	0.32	1 (0)	19 (7)	<0.01	0.31
Ticagrelor	4 (1)	20 (6)	<0.01	0.26	2 (1)	19 (7)	<0.01	0.29
Warfarin	16 (5)	74 (22)	<0.01	0.53	14 (5)	63 (22)	<0.01	0.51
Dabigatran	5 (1)	21 (6)	<0.01	0.25	4 (1)	18 (6)	<0.01	0.22
Rivaroxaban	3 (1)	20 (6)	<0.01	0.28	3 (1)	18 (6)	<0.01	0.27
Apixaban	2 (1)	7 (2)	0.08	0.13	1 (0)	6 (2)	<0.01	0.14

SD standard deviation

minor bleeding, major bleeding, and fatal bleeding, for a treated patient with AF. The seventh attribute was the need to have regular blood tests for international normalized ratio monitoring. These attributes were selected to reflect major outcomes of clinical trials of anticoagulants and, in our discussions with several practicing physicians in our division, were identified as being central to making treatment decisions. We also sought to minimize the potential overlap among these attributes [13]. The ranges selected for the attribute levels were based on the observed event probabilities in the major warfarin and novel oral anticoagulant randomized clinical trials [1–3, 14]. To promote understanding of outcome probabilities, we converted annual outcome rates to 5-year rates, assuming a constant hazard rate over time [15]. Participants were able to access definitions of these attributes and a graphical representation of these rates in real-time in pop-up windows at any time while completing the questionnaire.

We used these seven attributes and combinations of different values for each attribute to generate hypothetical treatment options. The final DCE questionnaires comprised 14 choice questions. Each choice question contained three hypothetical treatment options randomly labeled "new drug", "old drug", and a fixed "no drug" option. The random labeling was used to explore whether respondents had a bias towards choosing new or old medications, independent of their attributes. We included the "no drug" option to avoid forcing respondents to choose the "new drug" or "old drug" option [16]. 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 choice questions.

The observed patterns of participants' stated choices in the 14 choice questions were used to estimate their underlying preference weights for different treatment attributes. Two of the 14 choice questions included a treatment option that was clearly better than other options in all aspects (i.e., a 'dominant' treatment option). We assessed the rationality of responses by determining whether a respondent selected the dominant treatment option in these two choice questions.

The design of the web-based questionnaire and data collection was performed using the Choice Based Conjoint Application of Sawtooth (Sawtooth Software Inc., SSI web version 8.2.4, Provo, Utah, USA). We created a fractional factorial design and verified the design to be balanced and nearly orthogonal [13]. By varying the seed for a random number generator, we generated and compared numerous designs and then selected the final design with a larger D efficiency given a fixed sample size [16, 17]. The sample size was calculated by simulating responses using Sawtooth, assuming that 20% of respondents would pick the "no drug" option and the rest were indifferent to the remaining two alternatives. We estimated that a sample size of 250 respondents were needed to achieve the standard errors of <0.035 for all attribute levels.

2.4 Statistical Design and Analysis

According to the underlying model for DCEs [18], given a set of options, the log odds ratio of choosing one option is proportional to a linear function of attributes of each option. We coded the choice data for all attributes as continuous variables and we defined two dummy variables for old drug and no drug. We used conditional logistic models, with choice as the dependent variable and the attributes of treatment options as independent variables, to estimate how the attributes influence respondents' choices. The estimated coefficients in this regression, or relative preference weights, reflect the average impact of an attribute on the likelihood of choice. We also calculated ratios of each coefficient relative to the coefficient of death from bleeding to obtain maximum acceptable risks (MARs) [19, 20], which indicate the average magnitude of risk that participants are willing to accept in one of the attributes in exchange for achieving a 1% decrease in the risk of fatal bleeding.

The same DCE questionnaire was used for all participants; we fitted a conditional logistic regression using PROC MDC, SAS 9.2 to each of the choice data (SAS Institute, Cary, NC, USA) and compared the estimated MARs in the sample of patients with CVD with those in the sample of the general population. We used propensity score matching to improve the comparability of baseline characteristics between the two samples. For this purpose, we estimated the propensity of being a patient with CVD in the pooled data using age, sex, education, and number of dependent children. We then used 1:1 matching to select general population members and patients with CVD who were similar, based on their predicted propensity score.

3 Results

A total of 352 members of the general population and 341 patients completed all 14 choice scenarios of the DCE questionnaire. A significant number of patients were current or past users of anticoagulant or antiplatelet medications (Table 1). Of 6892 and 11,943 initial invitations that were sent to the panels of patients with CVD and general population members, 688 (10%) and 609 (5%) considered the invitation and clicked on the link, respectively, and were directed to the website where they could see the purpose of the survey. Of these, 101 (15%) patients and 143 (24%) members of the general population declined participation. In addition, 132 individuals (19%) in the patient panel were disqualified because they did not identify themselves as having any of the 13 categories of CVD. Of those who started the survey, 114 patients (16%) and 114 members of the general population (19%) did not complete all 14 choice questions.

Patients with CVD in our sample, on average, were approximately 5 years older than our sample of general population members (51 vs. 46 years old; $p<0.01$) and a larger proportion of patients were male (63% vs. 50%; $p<0.01$) before matching (Table 1). These differences were successfully removed after propensity score matching and age, sex, education, and the number of dependent children were similar among the remaining 284 matched pairs. As expected, self-reported health problems, history of MI, history of stroke, and medication use remained significantly larger in patients with CVD.

Among the 352 respondents from the general population, seven (2%) chose the new drug, four (1%) chose the old drug, and 30 (8%) chose no drug in all 14 choice questions. Among the 341 patients, 15 (4%) chose the new drug, three (1%) chose the old drug, and ten (3%) chose no drug in all 14 choice questions, regardless of the probabilities presented. In the remaining respondents, 115 (33%) of the general population members and 123 (36%) of patients failed to choose the dominant treatment option in at least one of two fixed-choice scenarios, but they were included the final analysis [21].

Estimated preference weights for the different attributes in the matched sample of general population members ($n=284$) and patients ($n=284$) who completed all 14 choice questions in the DCE questionnaire are presented in Table 2. The estimated preference weights are log odds ratios of choice probabilities. For example, everything else being equal, the odds of choosing a treatment option associated with a 1% higher risk of a non-fatal MI was 0.95 [exp (-0.052)] in the sample of the general population and 0.91

[exp (−0.088)] in the sample of patients with CVD. The general population preference weight for a 1% increase in the risk of a non-fatal MI (−0.052; $p<0.001$) was smaller than its weight in patients (−0.088; $p<0.001$), where the negative sign indicates the disutility of MI as a health state. In contrast, the general population preference weight for cardiovascular death (−0.78; $p<0.001$) was larger than its weight in patients with CVD (−0.55; $p<0.001$). Similarly, the general population preference for minor bleeding (−0.015; $p<0.001$) were larger than the preference in patients (−0.011; $p<0.001$). General population members' and patients with CVD preference weights for non-fatal stroke, major bleeding, and fatal bleeding were all statistically significant and similar across the two samples.

Preference weights for having one additional, international normalized ratio monitoring test in a year was 0.002 ($p=0.024$) for the general population, while the corresponding preference weight for patients with CVD was not significant (−0.001, $p=0.232$). The preference weight for choosing "no drug" compared to "old drug" or "new drug" was not significant for general population members. In contrast, this preference weight was −0.358 ($p<0.001$) for patients (p-value for difference <0.001). Similarly, the preference weight for choosing "old drug" compared to "new drug", assuming everything else being equal, was not significant for general population members. In contrast, this preference weight was −0.220 ($p<0.001$) for patients, suggesting that they preferred the new drug regardless of its actual attributes.

Maximum acceptable risks and their confidence intervals for the general population and patients (propensity-matched samples) are reported in Table 3 and Fig. 1. A 1% increase in the risk of fatal bleeding was used as the reference for the calculation of MARs. General population members were willing to accept a 3.5% increase in the risk of a non-fatal stroke, a 4.2% increase in the risk of a non-fatal MI, a 2.8% increase in the risk of cardiovascular death, a 14.1% increase in the risk of minor bleeding, and a 6.5% increase in the risk of major bleeding to avoid a 1% increase in the risk of fatal bleeding. Patients in contrast were willing to accept a 2.0% increase in the risk of a non-fatal MI, a 3.2% increase in the risk of cardiovascular death, and a 16.7% increase in the risk of minor bleeding to avoid a 1% increase in the risk of fatal bleeding. The estimated confidence intervals of MARs for a non-fatal MI and non-fatal stroke for the general population did not include the point estimates for patients with CVD (and vice versa). Figure 2 also presents the estimated MARs in the full samples of patients ($n=341$)

Table 3 Estimated maximum acceptable risk (MAR) in propensity-matched samples, assuming a 1% increase in the risk of fatal bleeding as the reference

	MAR[a] (95% CI)[b]	
	General population	Patients with CVD
Stroke	3.5 (2.5–4.5)	2.6 (1.3–2.7)
Myocardial infarction	4.2 (2.3–6.1)	2.0 (1.8–3.4)
Cardiovascular death	2.8 (2.2–3.5)	3.2 (2.3–4.1)
Minor bleeding	14.1 (10.7–17.6)	16.7 (11.6–21.7)
Major bleeding	6.5 (4.7–8.3)	5.7 (4.0–7.4)
Fatal bleeding	1.0	1.0

CI confidence interval, *CVD* cardiovascular disease

[a]For example, patients were willing to accept a 2.6% reduction in the risk of stroke in exchange for a 1% increase in the risk of death from bleeding. In other words, patients, on average, were indifferent between a 2.6% decrease in the risk of stroke and a 1% increase in the risk of fatal bleeding. MAR was calculated as the ratio of estimated coefficients in Table 2 to the fatal bleeding (reference attribute)

[b]The 95% CI for MAR has been estimated using delta method (1): $\mathrm{Var}(\mathrm{MAR}_k) = \left[\left(\frac{1}{\hat{\beta}_k}\right)^2 \mathrm{var}(\hat{\beta}_r) + \left(\frac{\hat{\beta}_r}{\hat{\beta}_k^2}\right)^2 \mathrm{var}(\hat{\beta}_k) + 2\left(-\frac{1}{\hat{\beta}_k}\right)\left(\frac{\hat{\beta}_r}{\hat{\beta}_k^2}\right) \mathrm{cov}(\hat{\beta}_k, \hat{\beta}_r)\right]$

Table 2 Estimated relative preference weights in propensity-matched samples of patients and the general population

	General population ($n=284$)			Patients with CVD ($n=284$)		
	Mean weight	SE	p value	Mean weight	SE	p value
Stroke	−0.062	0.006	<0.001	−0.068	0.006	<0.001
Myocardial infarction	−0.052	0.011	<0.001	−0.088	0.011	<0.001
Cardiovascular death	−0.078	0.005	<0.001	−0.055	0.005	<0.001
Minor bleeding	−0.015	0.001	<0.001	−0.011	0.001	<0.001
Major bleeding	−0.033	0.003	<0.001	−0.031	0.003	<0.001
Fatal bleeding	−0.218	0.022	<0.001	−0.177	0.021	<0.001
Need for monitoring	0.002	0.001	0.024	−0.001	0.001	0.232
No drug	0.087	0.087	0.319	−0.358	0.088	<0.001
Old drug	−0.014	0.041	0.720	−0.220	0.039	<0.001

CVD cardiovascular disease, *SE* standard error

McFadden's likelihood ratio index = 0.1611; Log likelihood (LL) = −7328; Log likelihood null (LL0) = −8736; Log likelihood ratio (2 × (LL − LL0)) = 2815

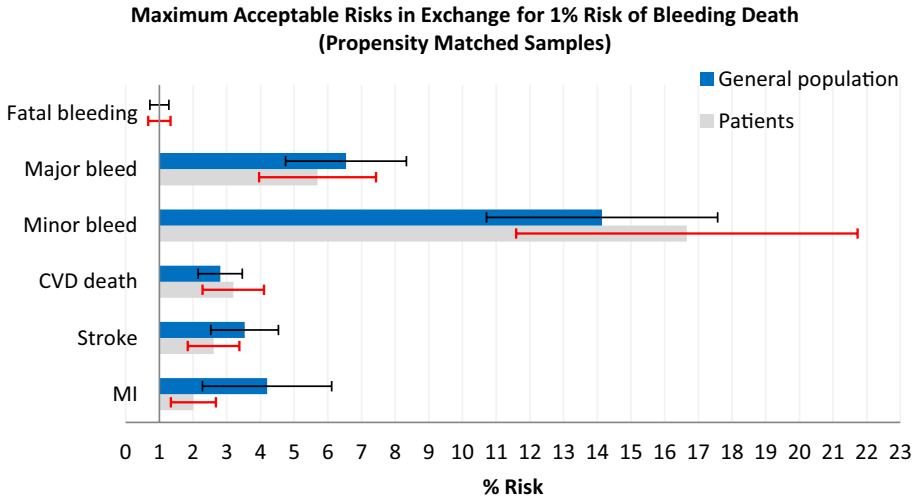

Fig. 1 Maximum acceptable risk of different outcomes in exchange for a 1% risk of death from bleeding (propensity-matched samples)

and the general population ($n = 352$). The estimated MARs in the full samples were comparable to the estimates in the propensity-matched samples with slightly tighter confidence intervals.

4 Discussion

Using a DCE, we elicited and compared preferences for different benefits and risks of anticoagulant therapy in a sample of patients with CVD and a sample from the general population. Members of the general population in our sample valued a 1% increase in the risk of fatal bleeding as being the same as a 4.2% increase in the risk of a non-fatal MI, a 2.8% increase in the risk of cardiovascular death, and a 14.1% increase in the risk of minor bleeding. In contrast, patients with CVD valued a 1% increase in the risk of fatal bleeding as being the same as a 2.0% increase in the risk of a non-fatal MI, a 3.2% increase in the risk of cardiovascular death, and a 16.7% increase in the risk of minor bleeding.

General population members perceived fatal cardiovascular events as being worse than non-fatal cardiovascular events. In contrast, patients with CVD weighted non-fatal cardiovascular events as being worse than fatal cardiovascular events. This finding suggests that, on average, patients perceive the debilitating consequences of serious cardiovascular events and the impact of such events on their quality of life to be worse than death. This observation is consistent with findings from other studies that have elicited patient preferences using other methods [22, 23]. Our results highlight the importance of choosing preferences of relevant populations depending on the decisions that need to be made. For example, for benefit-risk decisions, considering preferences of patients seems to be the most relevant perspective, as they are the main risk takers. However, in regulatory decisions, the choice of perspective is more debatable. Patients have vested interest

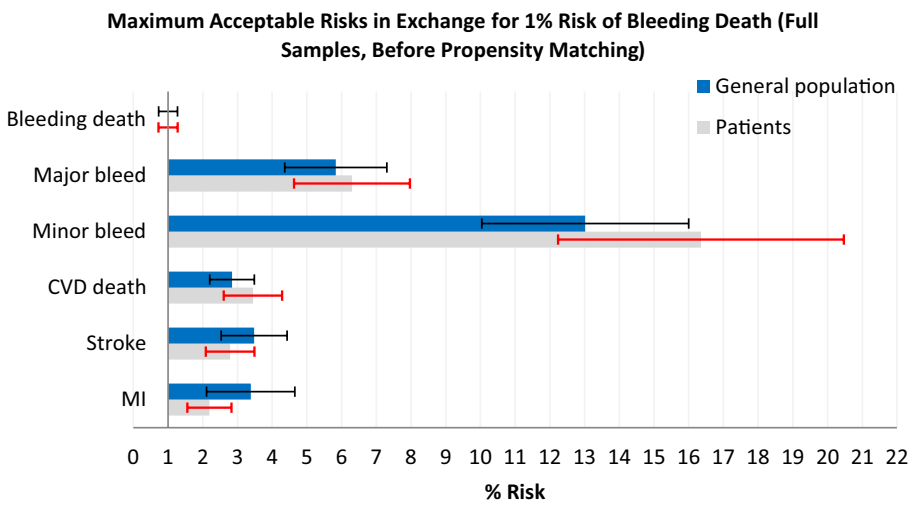

Fig. 2 Maximum acceptable risk of different outcomes in exchange for a 1% risk of death from bleeding in the full samples (unmatched samples)

in the trade-offs that are involved. For example, in our study, patients were reluctant to choose a drug labeled as an "old drug" regardless of the actual benefit-risk profiles of presented choices. Members of the general population, however, were indifferent to drug labels. This suggests that members of the general population who are behind the 'veil of ignorance' might provide more impartial preferences when we are concerned with the equity and social justice aspects of our decisions [24].

Although patients' and physicians' preferences related to the benefits and risks of anticoagulant therapy have been compared before [8, 22, 25–28], to the best of our knowledge this is the first study that has compared preferences of patients with those of the general population for anticoagulant medications. Considering our findings in the context of preferences of physicians and trialists [22] suggests similarities between physician preferences and those of the general population. For example, as compared with patients, both physicians [8, 22] and general population members are more risk averse with respect to non-fatal bleeding events. Similarly, both physicians [22] and general population members perceive the risk of non-fatal thrombotic events to be less important than the risk of fatal thrombotic events, an observation that is in contrast with patient preferences. It is conceivable that society's preferences and norms partially influence physicians', payors', and decision makers' prior beliefs about relative weights of benefits and risks. Whether this effect is significant and to what extent it can affect treatment decisions, medication coverage decisions, or drug approval or withdrawal decisions needs to be explored in the future.

In addition to the important finding that patients and general population members differ with respect to their preferences for the outcomes of anticoagulants, other interesting observations emerged from our study. We found that both patients and general population members perceived fatal bleeding as being approximately three times worse than cardiovascular death, a finding that is in contrast to the common perception of death as a single uniform health state [29]. The odds of opting for "no drug" or a treatment labeled "old drug" were 28% and 14% lower, respectively, than the odds of opting for a "new drug," independent of the actual risks and benefits of the treatment options. Members of the general population did not appear to be affected by these labels. The effect of labeling on treatment choices has also been shown in other studies. For example, labeling the treatment options as a 'coronary stent' and 'coronary bypass surgery' had a significant effect on patient choice beyond actual risks and benefits, reflecting that the different treatment labels imply intrinsic value beyond those captured by the assigned attributes [30].

Our study has several limitations. Our samples may not completely represent the entire universe of patients with cardiovascular conditions and the general population in USA, as they were selected from online panels. The demographic characteristics of our sample and corresponding national statistics are reassuring, but any generalization of our findings should be made with caution. In addition, the most common indication for anticoagulants is AF; nevertheless, patients in our study were sampled from those with general CVD to achieve a sufficient sample size. When we compared the preferences of 78 patients with AF in our sample with the preferences of the rest of the patients with CVD, patients with AF had a larger negative preference for death from bleeding. Preferences of patients with AF were similar to patients without AF for other benefits and risks. Stated preferences elicited in the choice experiments may differ from patients' actual treatment choices [31]. We assumed that the main reported outcomes of clinical trials reflect the most important aspects of anticoagulant therapy [6] and did not consider some other attributes in our analysis, such as the availability of reversal agents or potential interactions with food [32]. Although the patient's perspective is perhaps most relevant to support prescription decisions in a shared decision-making process, the choice of the appropriate perspective is less obvious in making coverage and approval decisions, especially when fairness and social justice aspects are considered. Quantifying preferences from different perspectives and integrating them in quantitative benefit-risk analysis can support net benefit assessments that are more transparent and acceptable for all stakeholders. Finally, while our finding of differences between patient and population preferences is interesting, we focused on the specific scenario of the benefits and risks of anticoagulant treatments. Further studies are warranted to determine whether differences also prevail in other treatment settings.

Despite these limitations, our findings have important clinical and policy implications. We found that patient preferences for the outcomes of anticoagulants differ from those of the general population, which appear to resemble those of prescribers. Patient preferences should be explicitly considered in treatment decisions. Net benefit estimations may vary if patient rather than general population preferences are used.

5 Conclusions

We found that the general population and patients with CVD had slightly different preferences for treatment outcomes. These differences can potentially influence estimated benefits, risks, and patient-centered treatment decisions depending on the perspective chosen.

Data Availability Data and SAS codes used in this study are available through contacting the corresponding author

and upon ensuring institutional review board requirements are met.

Author Contributions MN participated in the conception, design, data collection, analysis, interpretation of findings, drafting of the manuscript, and approval of the final version. SSS participated in the study conception, design, interpretation of findings, and the revision and approval of the final version. NKC participated in the study conception, design, interpretation of findings, and revision and approval of the final version. JA participated in the study conception, design, interpretation of findings, and the revision and approval of the final version. JJG participated in the study conception, design, analysis, interpretation of findings, and the revision and approval of the final version.

Compliance with Ethical Standards

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Conflict of interest Sebastian Schneeweiss is the principal investigator of the Harvard-Brigham Drug Safety and Risk Management Research Center funded by the US Food and Drug Administration (FDA). His work is partially funded by grants/contracts from Patient Centered Outcome Research Institute; the FDA; and the National Heart, Lung, and Blood Institute. Sebastian Schneeweiss is also a consultant to WHISCON, LLC and to Aetion, Inc., a software manufacturer of which he also owns shares. He is the principal investigator of investigator-initiated grants to Brigham and Women's Hospital from Novartis, and Boehringer Ingelheim unrelated to the topic of this study. Mehdi Najafzadeh is the principal investigator of an investigator-initiated unrestricted grant from Novartis Pharmaceuticals Corporation and Baxalta to Brigham and Women's Hospital unrelated to the topic of this study. Joshua J. Gagne is the principal investigator of an investigator-initiated unrestricted grant from Novartis Pharmaceuticals Corporation to Brigham and Women's Hospital. He is a consultant to Aetion, Inc., a software company. Niteesh K. Choudhry, Jerry Avorn, and Joshua J. Gagne have no conflicts of interest directly relevant to the content of this article.

Appendix

See Tables 4 and 5 and Figs. 3 and 4.

Table 4 Attributes and levels used for the discrete choice experiment questionnaire design

Attribute	Levels
Risk of heart attack The proportion of patients who will have a heart attack (but remain alive) over the next 5 years. These numbers are in addition to those that experience a heart attack or stroke and die. The damage to the heart may be a temporary problem that resolves after weeks. However, in half of the cases, a heart attack causes permanent problems such as shortness of breath, fatigue, and swelling in the ankles and feet	0%, 2%, 4%, 6%
Risk of non-fatal stroke The proportion of patients who will have a stroke (but remain alive) over the next 5 years. These numbers are in addition to those that experience a heart attack or stroke and die. The damage to the brain may be a temporary problem that resolves after weeks. However, in half of the cases, stroke will result in brain damage with the patient living with long-term disability. Those disabilities can be physical (e.g., losing control on one side of the body or one side of the face or one arm) or mental (difficulty in talking, thinking, or remembering)	0%, 4%, 7%, 10%
Risk of death from heart attack or stroke The proportion of patients who will die as a result of a heart attack or stroke over the next 5 years. These numbers are in addition to those that have a heart attack or stroke but do not die	0%, 5%, 10%, 15%
Risk of minor bleeding The proportion of patients who will have minor bleeding as a treatment side effect over the next 5 years (e.g., nose bleeds or bleeding gums that can be easily and safely resolved and are not life threatening)	0%, 30%, 45%, 60%
Risk of major bleeding The proportion of patients who will have major bleeding (but remain alive) as a treatment side effect over the next 5 years. Bleeding in the stomach, intestines, or brain are examples of major bleeding. Major bleeding can cause significant health problems requiring hospitalization, medication, or a blood transfusion	0%, 10%, 15%, 20%
Risk of death from bleeding The proportion of patients who will die as a result of a treatment side effect (bleeding) over the next 5 years. These numbers are in addition to those that experience minor or major bleeding but do not die	0%, 1%, 2%, 3%
Need for monitoring Whether the drug requires monthly visits to the doctor who will perform a blood test to ensure that the drug dose is at an appropriate concentration. Changes in dosing can result; not having this routine monitoring can mean that the drug is not working or is working too well; both can lead to bad events	Every 6 months, every 3 months, every month, no monitoring

Table 5 Relative preference weights estimated in the full samples (before propensity matching)

Parameter	Estimate	SE	*t*	Pr > |*t*|
Patients with CVD (*N* = 341)				
MI	−0.0888	0.0097	−9.15	< 0.0001
Stroke	−0.0698	0.0056	−12.4	< 0.0001
CVD death	−0.0565	0.0042	−13.38	< 0.0001
Minor bleed	−0.0119	0.0010	−12.39	< 0.0001
Major bleed	−0.0309	0.0028	−10.93	< 0.0001
Bleeding death	−0.1946	0.0194	−10.05	< 0.0001
INR monitoring	−0.0010	0.0008	−1.25	0.2098
No drug	−0.3283	0.0807	−4.07	< 0.0001
Old drug	−0.1463	0.0354	−4.13	< 0.0001
General population (*N* = 352)				
MI	−0.0597	0.0099	−6.06	< 0.0001
Stroke	−0.0580	0.0057	−10.11	< 0.0001
CVD death	−0.0710	0.0043	−16.44	< 0.0001
Minor bleed	−0.0155	0.0010	−15.74	< 0.0001
Major bleed	−0.0346	0.0029	−12.02	< 0.0001
Bleeding death	−0.2018	0.0198	−10.17	< 0.0001
INR monitoring	0.0027	0.0008	3.4	0.0007
No drug	0.1138	0.0774	1.47	0.1412
Old drug	−0.0209	0.0365	−0.57	0.5663

CVD cardiovascular death, *INR* international normalized ratio, *MI* myocardial infarction, *SE* standard error

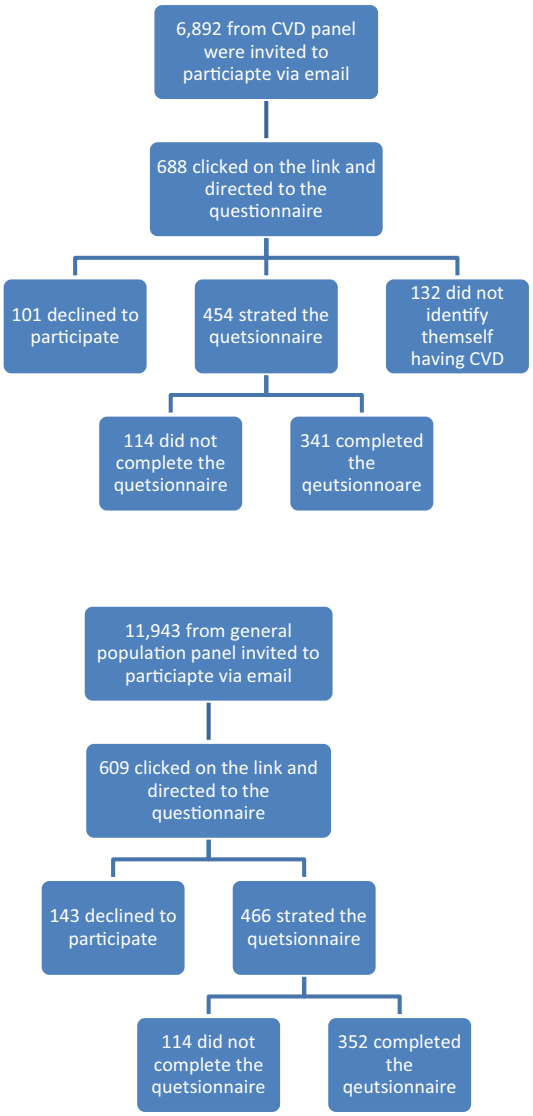
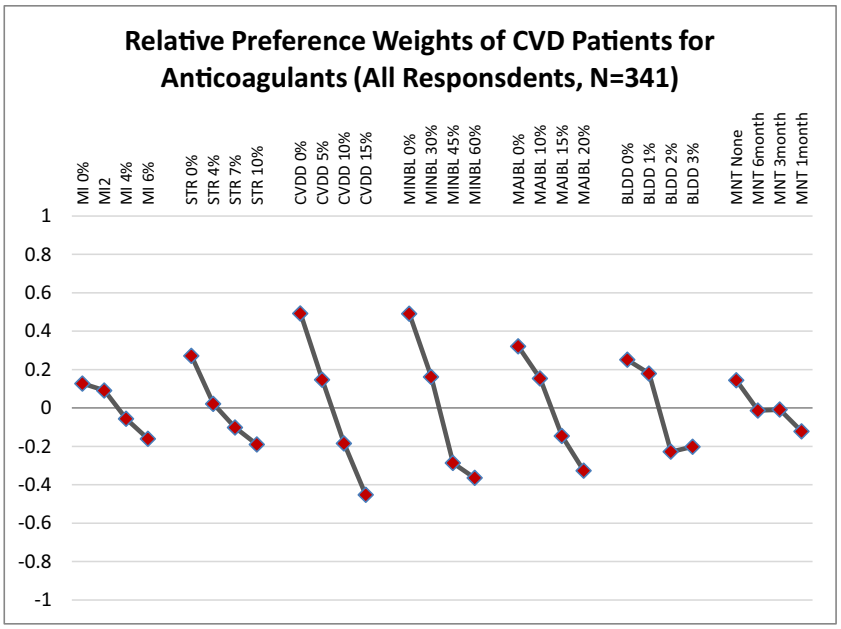


Fig. 3 Study participants. *CVD* cardiovascular disease



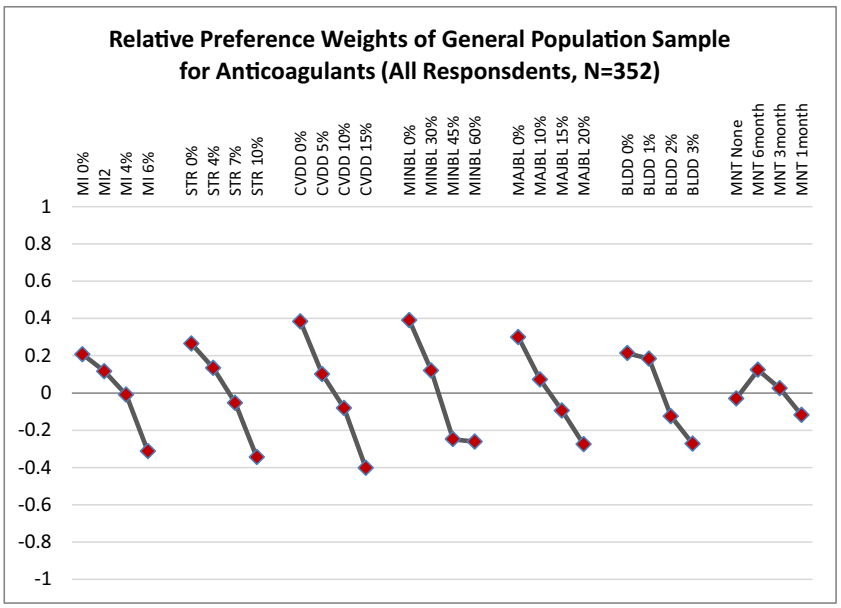


Fig. 4 Estimated relative preference weights using effect-coded variables. *CVD* cardiovascular disease

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