



Comparing Patient Preferences for Antithrombotic Treatment During the Acute and Chronic Phases of Myocardial Infarction: A Discrete-Choice Experiment

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Abstract

Background Antithrombotic drugs are used as preventive treatment in patients with a prior myocardial infarction (MI) in both the acute and chronic phases of the disease. To support patient-centered benefit–risk assessment, it is important to understand the influence of disease stage on patient preferences.

Objective The aim of this study was to examine patient preferences for antithrombotic treatments and whether they differ by MI disease phase.

Methods A discrete-choice experiment was used to elicit preferences of adults in the acute (≤ 365 days before enrolment) or chronic phase (> 365 days before enrolment) of MI for key ischemic events (risk of cardiovascular [CV] death, non-fatal MI, and non-fatal ischemic stroke) and bleeding events (risk of non-fatal intracranial hemorrhage and non-fatal other severe bleeding). Preference data were analyzed using the multinomial logit model. Trade-offs between attributes were calculated as the maximum acceptable increase in the risk of CV death for a decrease in the risk of the other outcomes. To assess the potential effect of sociodemographic and clinical characteristics on patient preferences, subgroups were introduced as interaction terms in logit models.

Results The evaluable population included 155 patients with MI in the acute phase of disease and 180 in the chronic phase. The overall population was 82% male, mean age was 64.2 ± 9.6 years, and 93% had not experienced bleeding events or key ischemic events other than MI. Patients valued reduction in the risk of non-fatal intracranial hemorrhage more than CV death ($p < 0.01$) and CV death more than non-fatal ischemic events ($p < 0.01$). Preferences were similar in the acute and chronic populations ($p = 0.17$). However, older patients valued reduction in risk of MI more than younger patients ($p = 0.04$), and patients with bleeding risk factors valued reduction in the risk of CV death ($p = 0.01$) and MI ($p = 0.01$) less than patients without bleeding risk factors. Also, patients who were at high risk of future ischemic events valued reduction of the risk of CV death less than those at low risk ($p = 0.01$).

Conclusion Patient preferences for antithrombotic treatments were unaffected by disease stage but varied by bleeding risk and other factors. This heterogeneity in preferences is an important consideration because it can affect the benefit–risk balance and the acceptability of antithrombotic treatments to patients.

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Key Points

Patient preferences for antithrombotic treatment attributes were similar between the acute and chronic phases of myocardial infarction.

Patients with myocardial infarction are willing to accept significant increases in the mortality risk to avoid increases in non-fatal bleeding events.

1 Introduction

Antithrombotic treatments reduce the risk of cardiovascular (CV) events, including stroke and myocardial infarction (MI) [1, 2], but also increase the risk of bleeding episodes [3]. Historically, benefit–risk decision making for antithrombotic treatments has been based on expert opinion and has not included patient perspectives on the importance of key outcomes [4–6]. However, the growing consensus among regulators and other key stakeholders is that patient preferences should be incorporated into benefit–risk decisions [5, 7–9], especially when preferences of patients may differ from those of clinicians or other healthcare providers [10, 11]. This patient-centered approach is becoming an important part of decision making by regulatory authorities [12, 13], and data collected on patient preferences can form the basis for shared decision making between patients and their healthcare professionals [14].

Antithrombotic drugs are used as preventive treatment in patients with a prior MI in both the acute and chronic phases of disease [15]. To support patient-centered benefit–risk assessment, it is important to understand the influence of disease stage on patient preferences. Although patients generally underestimate their risk of recurring cardiac events, especially after an intervention such as coronary artery bypass surgery [16–20], we hypothesized that disease chronicity may affect a patient's tolerance for an increased probability of adverse events. The relative importance of benefit and risk attributes of antithrombotic therapies in various CV diseases, including MI, has been explored [11, 21–26] but the influence of disease phase has not.

This study examined whether patient preferences for antithrombotic treatments differ by MI disease phase. The findings from this study should help inform drug development decisions as antithrombotic drugs are investigated and approved for initial administration at different stages of the disease process. The findings from this study should also support efforts of the IMI-PREFER consortia [27], a collaborative research project of the Innovative Medicines Initiative, which is developing recommendations to industry, regulatory authorities, and health technology assessment bodies in the European Union on how and when to include patient preferences for benefits and risks of medicinal products.

2 Methods

2.1 Study Design

An online discrete-choice experiment (DCE) survey was conducted between February 2019 and May 2020 to elicit

preferences for antithrombotic treatment attributes from patients with MI during the acute and chronic phases of disease. The study followed best practice guidelines on preference-based methods from the International Society for Pharmacoeconomics and Outcomes Research [28, 29].

Adults (≥ 18 years of age) living in England with a previous hospitalization for MI were recruited. Patients in the acute phase of MI (≤ 365 days before enrolment) were recruited by clinicians and research staff from five participating National Health Service organizations across England. Patients in the chronic phase of MI (> 365 days before enrolment) were recruited from online patient databases. Patients were excluded if they could not read and understand English, had an acute psychopathology, or had a potential cognitive, visual, or hearing impairment that, in the opinion of the investigator, could interfere with their ability to complete the survey. Study participants were remunerated for completing the study.

Potential attributes and levels to be included in the DCE were identified through a systematic literature review of Embase and MEDLINE [11, 21–26, 30, 31], consultation with clinicians, and based on events with irreversible harm traditionally selected by regulators and other stakeholders for making benefit–risk decisions about antithrombotic drugs. Accordingly, the key benefit and risk attributes included CV death, non-fatal MI, non-fatal ischemic stroke (IS), non-fatal intracranial hemorrhage (ICH), and non-fatal other severe bleeding (as defined by Global Use of Strategies to Open Occluded Arteries [GUSTO] [32]). Given the relatively low annual risk of severe bleeding events associated with the use of antithrombotic drugs, 3-year risk levels were applied to ensure sufficient variation in attribute levels. The 3-year risk levels were based on the range of estimated differences in extrapolated risks observed in the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P)-TIMI 50 trial of an antiplatelet medication [33].

Semi-structured pilot interviews were conducted in two rounds of five patients each to test the attributes and levels, confirm comprehension of the wording used in the DCE, and refine the DCE survey, attributes, and levels. Next, a quantitative pilot survey was conducted with 40 patients in the chronic phase of MI. The main survey was planned to include approximately 200 patients in the acute phase of MI and 200 in the chronic phase of MI. Attributes and levels included in the final DCE are summarized in Table 1. The risks of bleeding events (i.e., non-fatal ICH and non-fatal GUSTO) were presented as an increase in risk associated with the use of antithrombotic drugs, whereas the risks of CV death, non-fatal MI, and non-fatal stroke were presented as a reduction in risk (i.e., a treatment benefit). This was done to help patients distinguish between treatment benefits and risks and based on feedback obtained during the

Table 1 Treatment attributes and levels included in the discrete-choice experiment

Attribute	Description provided to participants	Levels
CV death	Cardiovascular death. The risk of dying from cardiovascular disease (e.g., heart attack, stroke, or severe bleeding)	Risk reduced to 1 patient out of 100 (1%) Risk reduced to 5 patients out of 100 (5%) Risk reduced to 10 patients out of 100 (10%) Risk reduced to 16 patients out of 100 (16%)
Non-fatal MI	Heart attack (non-fatal). The risk that you develop a new heart attack You will not die of the heart attack but it may lead to temporary or permanent disability such as reduced mobility, decreased stamina, and fatigue	Risk reduced to 8 patients out of 100 (8%) Risk reduced to 11 patients out of 100 (11%) Risk reduced to 14 patients out of 100 (14%) Risk reduced to 18 patients out of 100 (18%)
Non-fatal IS	Stroke (non-fatal). The chance that you experience a stroke. A stroke can happen if something keeps the blood from flowing as it should in the brain, causing damage to that part of the brain. You will not die of the stroke but it may lead to temporary or permanent disability, such as paralysis, reduced mobility, and problems with thinking, memory and speech	Risk reduced to 0 patients out of 100 (0%) Risk reduced to 2 patients out of 100 (2%)
Non-fatal ICH	Bleeding within the skull (non-fatal). The risk that you experience a bleed within the skull. Bleeding within the skull is a serious medical emergency because the buildup of blood within the skull can lead to increases in skull pressure, which can cause brain and nerve damage. You won't die of the bleeding within the skull but it may lead to temporary or permanent disability, including functional disability and difficulties with memory and speech	No increase in risk: 0 out of 100 patients (0%) Risk increases to 3 patients out of 100 (3%)
Non-fatal other severe bleeding ^a	Other form of severe bleeding (non-fatal). The chance of experiencing another form of severe bleeding (e.g., bleeding in the throat, stomach, intestines, or anus) that requires a blood transfusion	No increase in risk: 0 out of 100 patients (0%) Risk increases to 3 patients out of 100 (3%)

CV cardiovascular, ICH intracranial hemorrhage, IS ischemic stroke, MI myocardial infarction

^aAs defined by Global Use of Strategies to Open Occluded Coronary Arteries[32]

pilot interviews. In addition to completing the DCE survey, patients completed a questionnaire assessing their health literacy [34] and numeracy [35] skills.

2.2 Discrete-Choice Experiment Design


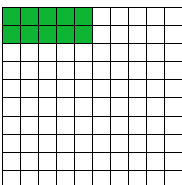
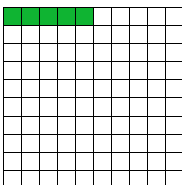
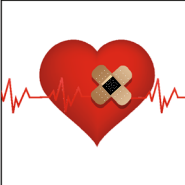
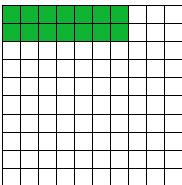
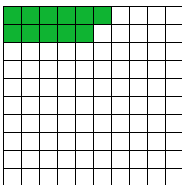

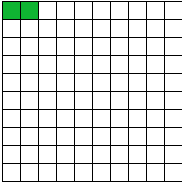
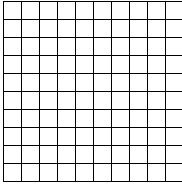
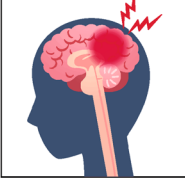
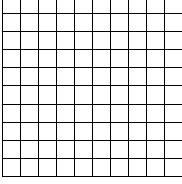
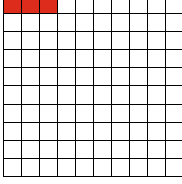
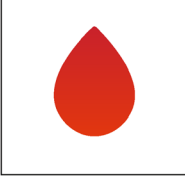
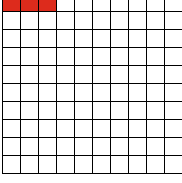
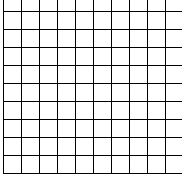
The DCE was designed with the d_p -optimal method using Ngene software version 1.1.2 (ChoiceMetrics, Sydney, Australia). Results from the quantitative pilot were used as priors to update the DCE design for the main survey. Each choice task in the DCE presented patients with two hypothetical scenarios representing trade-offs on the probability of occurrence of clinical events. An example choice task is shown in Fig. 1. Patients first completed a practice choice task, after which they completed 14 experimental choice tasks, a repeat of the first choice task placed at a random location between the 7th and the 12th choice tasks, and a fixed-choice task placed at a random location between the 2nd and 15th choice task. The repeated choice task was intended to test preference stability. The fixed-choice task had one option described by the most favorable level of one or more attributes and the other by the least favorable level of the same attributes, and it was intended as a dominance test, wherein patients are expected to choose the better alternative. Attributes were grouped into benefits (favorable outcomes) and risks (unfavorable outcomes) to minimize error variance,

and the order of the groups and the order of the attributes within the groups were randomized between patients to minimize attribute ordering effects [36].

2.3 Statistical Analysis

Statistical analysis was conducted using Stata version 15.1 (StataCorp LLC, College Station, TX, USA). The DCE preference data for all attributes were analyzed using a multinomial logit (MNL) model within the framework of random utility maximization [37, 38]. Although presented as discrete levels in the experiment, the attributes were coded as continuous variables in the model with a linear specification. An MNL model with dummy coding for all attributes was also estimated and used to test the linearity assumptions. The linear-coded MNL model was used to derive a meaningful marginal rate of substitution as the maximum acceptable increase in the risk of CV death for a decrease in the risk of the other outcomes. In addition, a heteroscedastic MNL model was estimated to assess the presence of scale heterogeneity between acute and chronic samples that could affect validity of pooling data from the two samples. The presence of serial correlation of choices within each patient was tested by estimating an MNL model with individual-specific error component.

You have been diagnosed with a heart attack (myocardial infarction). Your doctor asked you to decide between two treatment options, Treatment A and Treatment B. Each treatment is associated with 3-year probabilities of different things happening to you. Which treatment would you choose?

Event	Treatment A	Treatment B
Cardiovascular death 	Risk reduced to 10 patients out of 100 (10%) 	Risk reduced to 5 patients out of 100 (5%) 
Heart-attack (Non-fatal) 	Risk reduced to 14 patients out of 100 (14%) 	Risk reduced to 11 patients out of 100 (11%) 
Stroke (Non-fatal) 	Risk reduced to 2 patients out of 100 (2%) 	Risk reduced to no patients out of 100 (0%) 
Bleeding within the skull (Non-fatal) 	No increase in risk: 0 patients out of 100 (0%) 	Risk increases to 3 out of 100 patients (3%) 
Other severe bleeding (Non-fatal) 	Risk increases to 3 out of 100 patients (3%) 	No increase in risk: 0 patients out of 100 (0%) 

Which treatment would you choose? Treatment A Treatment B

Fig. 1 Example choice task

To assess a potential effect of sociodemographic and clinical characteristics on preference heterogeneity, the following subgroups were introduced as an interaction term with the treatment attributes in the MNL model: disease stage (acute vs chronic), bleeding risk factors (0 vs ≥ 1), past MIs (> 1 vs 1), family member or close friend with health outcomes of interest (yes vs no), age (< 65 vs ≥ 65 years), gender (male vs female), and risk of future ischemic events (low vs medium vs high). Bleeding risk factors included low body weight, prior use of antithrombotic drugs, and prior CV disease. Risk of future ischemic events was scored using a validated TIMI (thrombolysis in myocardial infarction) risk prediction algorithm [39]. The TIMI risk score is calculated based on the following nine risk factors: age ≥ 75 years, diabetes mellitus, hypertension, current smoking, peripheral artery disease, prior stroke, prior coronary artery bypass grafting, history of heart failure, and renal dysfunction. The presence of each risk factor is given a score of 1. Patients are categorized as low (risk score = 0–1), medium (risk score = 2), and high (risk score ≥ 3) risk. Details of the MNL model specifications are provided in Online Resource 1 (see electronic supplementary material [ESM]).

2.4 Ethics

Patients had to provide electronic consent before taking part in the study. The study was approved by the Bloomsbury Research Ethics Committee and Health Research Authority (reference no. 17/LO/2076) and was conducted in accordance with the General Data Protection Regulation.

3 Results

3.1 Sample Characteristics

Of 1042 patients with MI screened (206 in the acute phase, 836 in the chronic phase), 335 (155 in the acute phase, 180 in the chronic phase) completed the survey (Fig. 2). Patients were predominantly male (82%), the mean age was 64.2 ± 9.6 years, and 39% had a college degree or higher (Table 2). Most patients (93%) had not experienced comorbidities related to the treatment attributes (IS, ICH, or other bleeding events). The most common CV comorbidities were placement of a coronary stent (50%), hypertension (44%), high cholesterol (43%), and diabetes (21%). Most patients had a history of smoking (58%), although few (6%) were current smokers. The most common currently or previously used medications for MI or stroke were antithrombotic drugs, followed by cholesterol-lowering drugs. Most patients had adequate health literacy (77%) and numeracy (89%).

Patients in the acute phase of MI were younger than those in the chronic phase (mean 61.2 vs 66.8 years; $p < 0.001$).

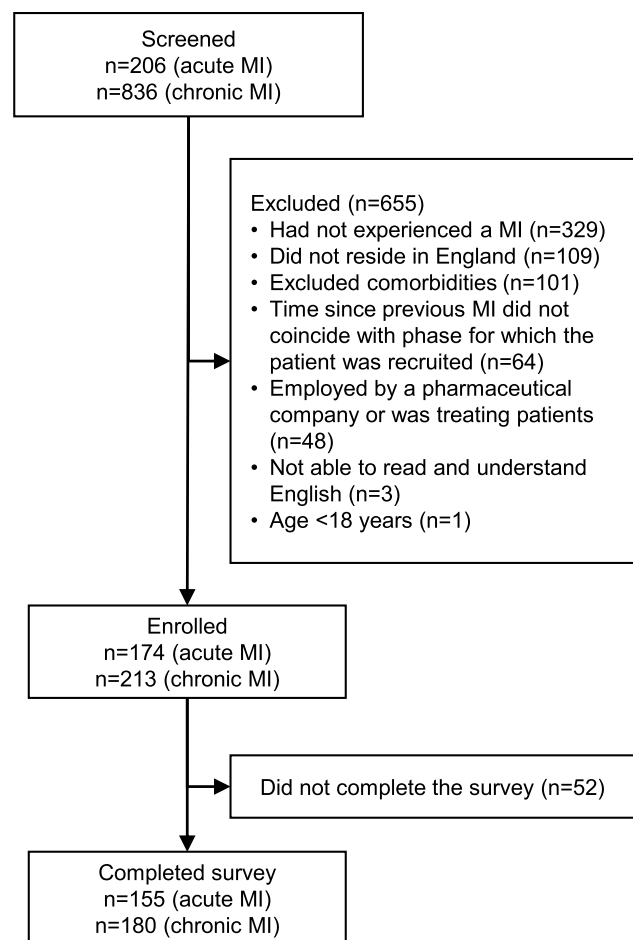


Fig. 2 Participant disposition in the main survey. The acute phase of MI disease was defined as last MI ≤ 365 days before enrolment, and the chronic phase of MI disease was defined as last MI > 365 days before enrolment. *MI* myocardial infarction

Patients in the acute phase were also less likely than patients in the chronic phase to have high cholesterol (52% vs 32%; $p < 0.001$), less likely to have had a coronary artery bypass graft (21% vs 8%; $p = 0.002$), but more likely to have had placement of a coronary stent (40% vs 62%; $p < 0.001$). Furthermore, patients in the acute phase less often previously used antithrombotic drugs (46%) than those in the chronic phase (79%), although antithrombotic drugs were used as current treatment by most patients in both the acute (99%) and chronic phases (95%).

3.2 Validity Assessments

Of the 335 patients included, 313 (93%) passed the dominance test and 276 (82%) demonstrated consistency in answering repeated choice questions (Online Resource 2, see ESM). All but one participant were considering all the alternatives presented (i.e., did not choose either all option A or all option B) when making decisions across

Table 2 Patient demographics and baseline characteristics in the main survey

Characteristic	Overall sample (<i>N</i> = 335)	Acute phase of MI ^a (<i>N</i> = 155)	Chronic phase of MI ^b (<i>N</i> = 180)	<i>p</i> value ^c
Gender, <i>n</i> (%)				
Female	60 (18)	31 (20)	29 (16)	0.355
Male	274 (82)	123 (79)	151 (84)	
Other	1 (< 1)	1 (< 1)	0 (0)	
Age, mean (SD)	64.2 (9.6)	61.2 (9.5)	66.8 (8.9)	<0.001
Education level, <i>n</i> (%)				
Elementary/primary school	4 (1)	2 (1)	2 (1)	0.080
Secondary/high school	104 (31)	43 (28)	61 (34)	
Some college	81 (24)	43 (28)	38 (21)	
College degree	92 (28)	39 (25)	53 (29)	
Postgraduate degree	37 (11)	15 (10)	22 (12)	
Others	17 (5)	13 (8)	4 (2)	
Prior ischemic or bleeding event, <i>n</i> (%)				
Stroke	21 (6)	7 (5)	14 (8)	0.219
Intracranial hemorrhage	9 (3)	3 (2)	6 (3)	0.430
Other severe bleeding	10 (3)	4 (3)	6 (3)	0.686
None of the above	311 (93)	147 (95)	164 (91)	0.187
> 1 MI in the past, <i>n</i> (%)				
No	274 (82)	134 (86)	140 (78)	0.040
Yes	61 (18)	21 (14)	40 (22)	
Other CV comorbidities, <i>n</i> (%)				
Heart failure	40 (12)	12 (8)	28 (16)	0.028
Diabetes mellitus	71 (21)	28 (18)	43 (24)	0.193
Arrhythmia	49 (15)	16 (10)	33 (18)	0.039
High cholesterol	143 (43)	50 (32)	93 (52)	<0.001
Hypertension	148 (44)	60 (39)	88 (49)	0.061
Peripheral artery disease	11 (3)	2 (1)	9 (5)	0.057
Placement of a coronary stent	168 (50)	96 (62)	72 (40)	<0.001
Coronary artery bypass graft	50 (15)	13 (8)	37 (21)	0.002
None of the above	40 (12)	19 (12)	21 (12)	0.868
Smoking status, <i>n</i> (%)				
Current smoker	20 (6)	7 (5)	13 (7)	0.326
Previous smoker	195 (58)	87 (56)	108 (60)	
Never smoked	120 (36)	61 (39)	59 (33)	
Other	10 (3)	8 (5)	2 (1)	
Current medication for MI or stroke, <i>n</i> (%)				
Cholesterol-lowering drugs	257 (77)	116 (75)	141 (78)	0.450
Antithrombotics	324 (97)	154 (99)	170 (94)	0.012
Others	180 (54)	93 (60)	87 (48)	0.033
None of the above	4 (1)	1 (1)	3 (2)	0.391
Risk of future ischemic events (TIMI risk score), <i>n</i> (%)				
Low (score = 0–1)	219 (65)	120 (77)	99 (55)	<0.001
Medium (score = 2)	79 (24)	25 (16)	54 (30)	
High (score ≥3)	37 (11)	10 (7)	27 (15)	
Health Literacy^d, <i>n</i> (%)				
Inadequate	71 (21)	31 (20)	40 (22)	0.841
Marginal	5 (2)	2 (1)	3 (2)	
Adequate	259 (77)	122 (79)	137 (76)	
Numeracy^e, <i>n</i> (%)				
Inadequate	11 (3)	3 (2)	8 (4)	0.229

Table 2 (continued)

Characteristic	Overall sample (<i>N</i> = 335)	Acute phase of MI ^a (<i>N</i> = 155)	Chronic phase of MI ^b (<i>N</i> = 180)	<i>p</i> value ^c
Marginal	25 (8)	9 (6)	16 (9)	
Adequate	299 (89)	143 (92)	156 (87)	

CV cardiovascular, MI myocardial infarction, SD standard deviation, TIMI thrombolysis in myocardial infarction

^aLast MI ≤ 365 days before enrolment

^bLast MI > 365 days before enrolment

^cChi-square test (categorical data) and independent *t* test (continuous data) were employed to test for differences in sociodemographic and clinical characteristics between patients with MI during the acute and chronic phases of disease

^dSubjective health literacy was assessed by a set of brief screening questions (SBSQ) developed by Chew and colleagues [34]. Participants responded to the three SBSQs with a five-point Likert scale, indicating the frequency in which they experience each item. Responses were scored between 1 (always) and 5 (never). Each participant's scored responses were averaged for a composite score ranging from 1 to 5. 'Adequate' subjective literacy scores were defined as ≥ 4 on Chew's SBSQs whereas an average score of 3 indicates marginal literacy and < 3 indicates inadequate literacy.

^eThe numeracy assessment was examined by a subset of items from the Numeracy Scale [47]. Patients were given one point for each correctly answered question (maximum numeracy score = 5). 'Adequate' numeracy was defined as a score of ≥ 4, whereas an average score of 3 indicates marginal numeracy skill and < 3 indicates inadequate numeracy skill

the choice questions, and only 21% made decisions based solely on a single attribute. Most patients (79%) took at least 20 minutes to complete the survey.

3.3 Model Selection

Significant correlations of choices within patients and scale heterogeneity were not observed between acute and chronic MI patients (Online Resource 3, see ESM). The latter finding indicated that data from these two populations could be pooled. Because the dummy-coded MNL model showed preferences for attributes with four levels to be highly linear ($R^2 = 0.85\text{--}0.99$; Online Resource 4, see ESM), a linear-coded MNL model was used for analysis of attribute preferences.

3.4 Preferences for Attributes

All attributes were significantly valued by patients (Fig. 3). Patients most valued a 1% reduction in the risk of non-fatal ICH (coefficient = 0.20 [95% CI 0.17–0.23]), followed by a 1% reduction in the risk of non-fatal other severe bleeding (coefficient = 0.15 [95% CI 0.13–0.18]), a 1% reduction in the risk of CV death (coefficient = 0.14 [95% CI 0.12–0.16]), a 1% reduction in the risk of non-fatal MI (coefficient = 0.08 [95% CI 0.07–0.1]), and a 1% reduction in the risk of non-fatal IS (coefficient = 0.06 [95% CI 0.02–0.11]).

3.5 Willingness to Make Trade-Offs Between Attributes

Willingness to make trade-offs between attributes was estimated as the maximum acceptable risk of CV death. On average, patients were willing to accept an increase in the risk of CV death of 1.39% (95% CI 1.14–1.64) to reduce the risk of non-fatal ICH by 1%, 1.06% (95% CI 0.85–1.26) to reduce the risk of non-fatal other severe bleeding by 1%, 0.57% (95% CI 0.48–0.66) to reduce the risk of non-fatal MI by 1%, and 0.41% (95% CI 0.10–0.73) to reduce the risk of non-fatal IS by 1% (Table 3).

3.6 Differences in Preferences Between Participant Subgroups

Patients aged ≥ 65 years were more likely than those aged < 65 years to choose a treatment that reduces the risk of MI (odds ratio [OR] 1.03, 95% CI 1.00–1.06). On the other hand, patients with one or more bleeding risk factors were less likely than those without any bleeding risk factors to choose a treatment that reduces the risk of CV death by 1% (OR 0.94, 95% CI 0.90–0.98) and to choose a treatment that reduces the risk of MI by 1% (OR 0.95, 95% CI 0.92–0.99) (Fig. 4). Also, patients who were at high risk of developing a future ischemic event (TIMI risk score of ≥ 3) were less likely than those who were at low risk (TIMI risk score ≤ 1) to choose a treatment that reduces the risk of CV death by 1% (OR 0.93, 95% CI 0.88–0.98). No significant difference in preferences were observed according to gender

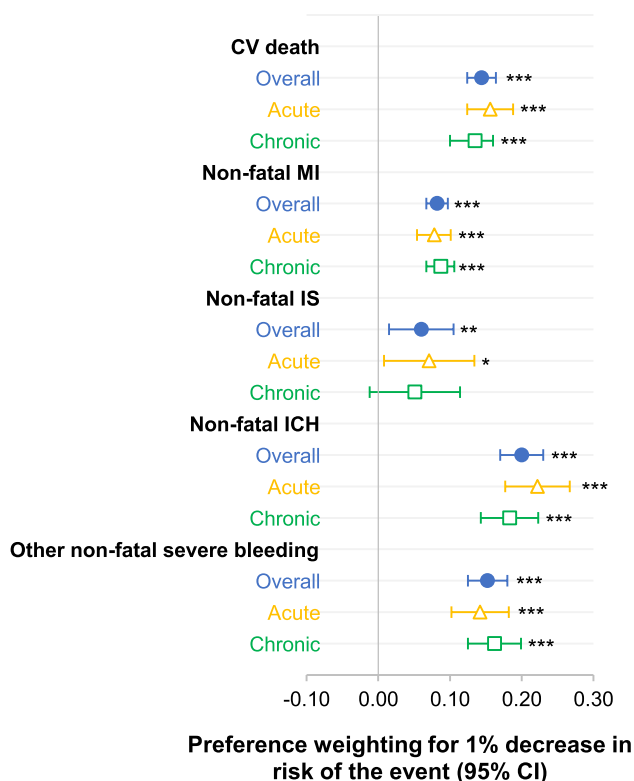


Fig. 3 Preferences for attributes of antithrombotics overall and by MI disease phase. Preferences for changes in the attributes are expressed as preference weights. *Markers* indicate maximum likelihood estimates and the *bars* indicate 95% CI. The preference weights were obtained from separate MNL model results for the overall, acute, and chronic MI patients. The acute phase of MI disease was defined as last MI ≤ 365 days before enrolment, and the chronic phase of MI disease was defined as last MI > 365 days before enrolment. *CI* confidence interval, *CV* cardiovascular, *ICH* intracranial hemorrhage, *IS* ischemic stroke, *MI* myocardial infarction; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

($p = 0.32$), family history of MI ($p = 0.12$), having experienced more than one MI in the past ($p = 0.35$), or disease stage ($p = 0.17$) (Online Resource 5, see ESM).

Table 3 Maximum acceptable risk of cardiovascular death for a 1% increase in the risk of other attributes

Attribute	Overall ($N = 335$) MAR (95% CI)	Acute phase of MI disease ^a ($N = 155$) MAR (95% CI)	Chronic phase of MI disease ^b ($N = 180$) MAR (95% CI)	p value ^c
Non-fatal MI	0.57 (0.48–0.66)	0.50 (0.39–0.61)	0.64 (0.50–0.78)	0.11
Non-fatal IS	0.41 (0.10–0.73)	0.46 (0.04–0.87)	0.38 (–0.09 to 0.84)	0.81
Non-fatal ICH	1.39 (1.14–1.64)	1.42 (1.05–1.79)	1.35 (1.01–1.69)	0.79
Non-fatal other severe bleeding	1.06 (0.85–1.26)	0.91 (0.64–1.17)	1.20 (0.88–1.52)	0.17

CI confidence interval, *ICH* intracranial hemorrhage, *IS* ischemic stroke, *MAR* maximum acceptable risk, *MI* myocardial infarction

^aLast MI ≤ 365 days before enrolment

^bLast MI > 365 days before enrolment

^cMAR between acute and chronic phase of MI disease was compared using a Z test

4 Discussion

The results demonstrated that preferences for antithrombotic treatment attributes did not vary between patients with a prior MI during the acute and chronic phases of disease. The most valued attribute was reducing the risk of non-fatal ICH, followed by reducing the risk of non-fatal other severe bleeding, CV death, non-fatal MI, and non-fatal IS. The study also showed that patients with MI were willing to accept a significant increase in CV mortality risk in exchange for a reduced risk of non-fatal bleeding and ischemic events.

Preference for a reduced risk of bleeding over a reduced risk of IS and further CV complications was also reported in patients treated for atrial fibrillation [40–42]. Similar to the current study, these studies presented the risk of bleeding as an increase in treatment risk associated with the use of antithrombotic drugs, and the risk of stroke as a reduction in risk as a result of antithrombotic treatment. Framing the risks in this way, however, could have resulted in the patients avoiding risks in favor of gaining benefits, a common phenomenon known as ‘loss aversion’ [43].

Patient preferences for alternative approaches to antithrombotic prophylaxis can vary substantially depending on disease context [21, 24]. Factors influencing preference heterogeneity between studies include prior experience with the treatments, type of health outcomes and treatment benefits considered, and the methods used for preference elicitation. In the current study, patients aged ≥ 65 years valued reduction in the risk of nonfatal MI more than those aged < 65 years, and those without any bleeding risk factors valued reduction in the risk of CV death and nonfatal MI more than those who had at least one bleeding risk factor, whereas patients who were at high risk of developing a future ischemic event valued the risk of CV death less than those who were at low risk. Although previous MI or stroke can influence perceptions

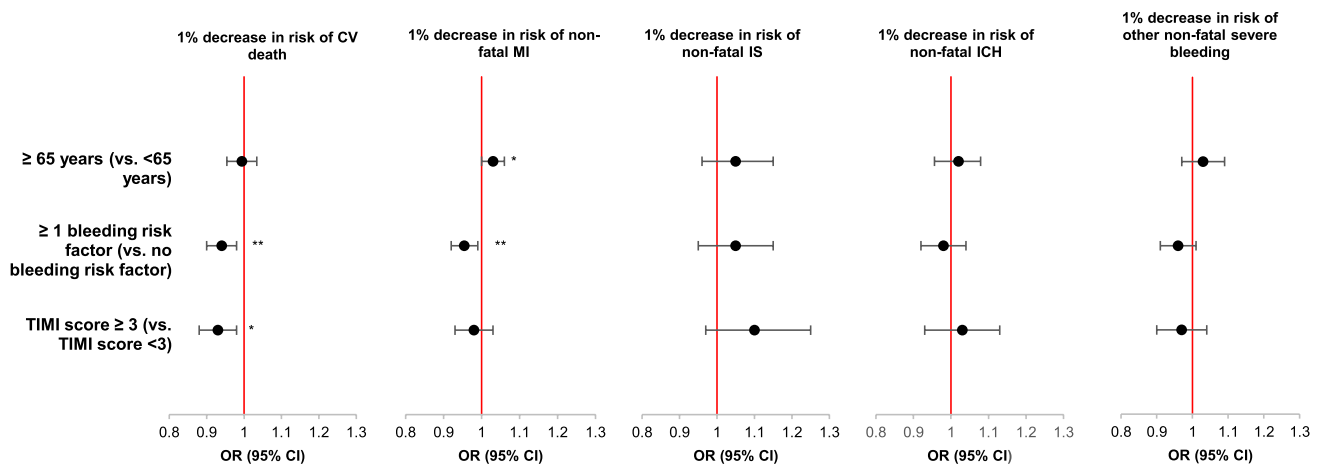


Fig. 4 Subgroup analysis by age, bleeding risk factors, and risk of ischemic events. *CI* confidence interval, *CV* cardiovascular, *ICH* intracranial hemorrhage, *IS* ischemic stroke, *MI* myocardial infar-

tion, *OR* odds ratio, *TIMI* thrombolysis in myocardial infarction; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

about antithrombotic therapies [11, 12], prior CV events other than MI, having experienced more than one previous MI, and having family or close friends with CV disease did not affect preferences in the current study. Importantly, the study also found that preferences were similar between patients in the acute and chronic phases of MI, suggesting that the amount of time since the last MI did not influence patient preferences. Had differences in patient preferences been found between patients with acute and chronic MI disease, they could alter the benefit–risk profile for a given drug and influence decisions about prioritization of assets and product development. Heterogeneity of preferences for a particular drug can also indicate subgroups of patients for whom a drug has an acceptable benefit–risk profile even when it is unfavorable for the full population [44]. Such information can also help support regulatory decision making.

A potential limitation of this study is that it adopted a between-sample rather than a within-sample approach to compare preferences between patients with MI in the acute and chronic phases of disease. Because the results were obtained from two independent groups of patients, it could not account for the variation in individual-specific effects or assess whether preferences of each individual change over time. Although a within-sample approach may have been more statistically rigorous, it would have required substantially more resources to measure preferences longitudinally and would have been subject to losses to follow-up and missing data.

A related limitation was that this study compared two different samples recruited from two different sources (i.e., NHS sites and online patient databases). Chronic-phase patients were identified from online patient databases because early feasibility assessment suggested that they are

difficult to recruit from the cardiology specialist clinics at the NHS site as they are more likely to attend follow-ups in a primary care setting once their conditions have stabilized. Although an effort was made to recruit acute- and chronic-phase patients with similar characteristics, there were some differences. Notably, patients in the chronic phase of disease were older and had more co-morbidities (e.g., heart failure and hypercholesterolemia) than those in the acute phase. Analysis controlling for the effect of disease stage, however, confirmed the robustness of the findings from the subgroup analysis. This suggests that the differences in sociodemographic and clinical characteristics between disease phases did not affect overall preferences for the attributes of antithrombotic drugs in this study.

Another potential limitation is that although the study was designed to assess patient preferences for both acute and chronic MI, it was not specifically powered to detect differences between groups. Although no obvious differences in preferences were detected between acute and chronic MI, it is possible that some small differences could have been detected with a larger sample. However, the current results indicate that the effect size would likely be too small to affect benefit–risk assessment.

In this study, a separate qualitative research was not conducted to identify and formulate the attributes and levels included in the DCE [45]. The initial list of treatment attributes included CV effects with irreversible clinical harm (MI, IS, ICH, severe bleeding), which have been traditionally used by regulators and other key stakeholders for benefit–risk decision making. However, to ensure that the attribute definitions and their levels were relevant and comprehensible, they were discussed in qualitative pilot interviews, and the survey instrument was updated based on review of the feedback. As part of this, patients

were asked for their opinion about possible additional attributes that may be included. Therefore, although the attributes and levels were not selected from separate qualitative research, the qualitative pilot testing helped ensure that all attributes included in this study were relevant and meaningful for patients.

A final potential limitation of this study was that no reference was made to baseline risks of developing the CV or bleeding events when framing the DCE choice question. This could have influenced the way patients interpreted the treatment benefits and risks and therefore had some effect on their preferences. Including baseline risk in an opt-out alternative in the DCE choice tasks may help standardize interpretation of risks in future studies.

5 Conclusion

This study provided information that should help inform regulatory decisions about antithrombotic drugs. Our findings suggest that phase of MI is not an important consideration for patient-centered benefit–risk assessments of antithrombotic drugs, although age, bleeding risk factors, and risk of future ischemic events are. The study also indicated that patients with MI are willing to accept increases in the mortality risk in exchange for avoiding increases in non-fatal bleeding events. This suggests that patients are averse to the risk of bleeding events and, as such, when assessing the benefits and risks of antithrombotic drugs, a treatment will need to achieve a greater reduction in risk of further ischemic events to have a positive benefit–risk balance. The results of this study can also support decisions about drug development, such as whether to seek to seek approval for an antithrombotic drug for both phases of MI disease. Finally, although undertaken primarily as an industry-sponsored preference study, the current results will be used to support development of guidelines by the PREFER project [46] on how and when to include patient perspectives on benefits and risks of medicinal products.

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Declarations

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Conflict of interest Cathy Anne Pinto and Johanna Hyacinthe are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Gin Nie Chua, Ella Brookes, and Tommi Tervonen are employees of Evidera, which was paid by Merck & Co for work related to this study. John F.P. Bridges received consulting fees by Evidera and has previously received grant, travel, and consultation fees from Merck & Co.

Ethics approval The study was approved by the Bloomsbury Research Ethics Committee and Health Research Authority and was conducted in accordance with the General Data Protection Regulation.

Consent to participate Patients had to provide electronic consent before taking part in the study.

Consent for publication Not applicable.

Availability of data and material The datasets generated during and/or analyzed during the current study are not publicly available as no consent was sought from participants to allow sharing of data with third parties.

Code availability Not applicable.

Author contributions CAP contributed to conception, design, interpretation of results, and revision of the manuscript. GNC contributed to the implementation of the work and analysis, interpretation of data for the work, and drafting and revision of the manuscript. JFPB contributed to design, interpretation of results, and revision of the manuscript. EB contributed to the implementation of the work and revision of the manuscript. JH contributed to the implementation of the work and revision of the manuscript. TT contributed to the conception, design, and implementation of the work and analysis, interpretation of data for the work, and drafting and revision of the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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