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Published in:
Journal of Clinical Epidemiology

DOI:
10.1016/j.jclinepi.2021.11.036

Publication date:
2022

Journal of Clinical Epidemiology 000 (2022) 1–9

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Net clinical benefit of antiplatelet therapy was affected by patient preferences: A personalized benefit-risk assessment

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Accepted 24 November 2021; Available online 29 November 2021

Abstract

Objectives: To assess the effect of patient preferences on the net clinical benefit (NCB) of an antiplatelet therapy for the secondary prevention of cardiovascular complications.

Study Design and Setting: Risk equations were developed to estimate the individual predicted risk of key outcomes of antiplatelet treatment in patients with a prior myocardial infarction using the Clinical Practice Research Datalink linked to the Hospital Episode Statistics and UK Office of National Statistics databases. Patient preferences for outcomes of antiplatelet therapies were elicited in a separate discrete choice experiment survey. Trial hazard ratios, relative to placebo, were used to calculate the per-patient NCB using equal or preference weighting of outcomes.

Results: Risk equations were estimated using 31,941 adults in the Clinical Practice Research Datalink population, of which 22,125 were included in the benefit-risk assessment. The mean NCB was lower in the preference-weighted than in the equal-weighted analysis (0.040 vs. 0.057; $P < 0.0001$), but the direction of effect was unchanged by the weighting. In analyses stratified by the presence of bleeding risk factors, including preference weighting altered the ranking of subgroups by NCB.

Conclusion: Patient preference weighting may have a significant effect on NCB and should be included in personalized benefit-risk assessments.

Keywords: Benefit-risk analysis; Myocardial infarction; Net clinical benefit; Patient preferences; Antiplatelet; Secondary prevention

Introduction

Benefit-risk assessment uses a standard approach to compare the favorable outcomes (benefits) and unfavorable outcomes (risks) of emerging treatment options in the existing treatment landscape. The results of benefit-risk assessments may be used to inform regulatory, health technology assessment, and clinical decisions [1–3]. Historically, benefit-risk assessments have focused on the average patient [4,5], but such aggregate assessments may not always be useful for determining which treatment is suitable for an individual patient [6]. Personalized benefit-risk assessments that characterize the expected treatment effect on individual patients can be achieved by combining randomized controlled trial and real-world data [6,7]. The result is an estimated per-patient net clinical benefit (NCB) [8], which can be used to determine whether the treatment benefits outweigh the risks for the majority of patients or for important subgroups.

Consensus is growing among regulators and other decision-makers that patient preferences should be incorporated into benefit-risk decisions [9–12]. This is especially important when patients' weighting of benefit and risk outcomes may affect treatment decisions and when weighting may differ between clinically relevant subgroups [3,6,7,13,14]. For example, individual patients may put different weights on the benefits and risks of antiplatelet

Cathy Anne Pinto and Johanna Hyacinthe are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Thibaud Prawitz, Gin Nie Chua, and Tommi Tervonen are employees of Evidera, which was paid by Merck & Co., Inc. for work related to this study.

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https://doi.org/10.1016/j.jclinepi.2021.11.036

What is new?

Key findings

- This is the first study to report the feasibility of including patient preference data in a personalized, quantitative patient-centered benefit-risk assessment.
- Preference weighting of outcomes may affect the net clinical benefit (NCB) of the intervention in secondary prevention of atherothrombotic events. Even so, the direction of effect was unchanged irrespective of weighting in all analyses.

What this adds to what is known

- This study illustrated how patient preferences can be incorporated into a personalized NCB and to what extent these preferences can affect NCB estimates.

therapies [15–21], which include a reduced probability of thrombotic cardiovascular (CV) events but an increased risk of bleeding episodes [22–25].

Vorapaxar is an antiplatelet agent approved in the US for reducing thrombotic CV events in patients with prior myocardial infarction (MI) or peripheral artery disease [26]. In clinical trials, vorapaxar has demonstrated acceptable safety and been shown to reduce the risk of ischemic outcomes [27], but like other antiplatelet agents, it may increase the risk of bleeding [28]. Here, we report the results of a personalized, patient-centered benefit-risk assessment of vorapaxar in patients with prior MI in which real-world data on estimated baseline risks were combined with clinical trial data and outcome weighting from a bespoke patient preference study. The study aimed to illustrate how patient preferences can be incorporated into a personalized NCB and to what extent they can affect the estimates.

Methods

Study design

This was a retrospective, observational study conducted in the UK using data from the Clinical Practice Research Datalink (CPRD) [29] linked to secondary care Hospital Episodes Statistics [30] and official mortality data from the Office of National Statistics [31]. The CPRD contains longitudinal data from > 600 general practitioner practices in the UK, covering approximately 8% of the UK population. Because linkage to Hospital Episode Statistics is only available for a subset of CPRD practices in England, the source population was restricted to English clinics, representing approximately 57% of contributing CPRD practices in the UK.

The current analysis was based on clinical outcomes associated with the use of antiplatelet therapies in the secondary prevention of CV events post-MI. Six CV outcomes commonly used in benefit-risk assessment of antithrombotic treatments were selected: CV mortality, excluding fatal bleeds; nonfatal MI; nonfatal ischemic stroke (IS); nonfatal intracranial hemorrhage (ICH); severe nonfatal, non-ICH bleeds; and fatal bleeding [32,33]. Antithrombotic drugs are used for secondary prevention for their benefit of decreasing the patients' risks of CV mortality, nonfatal MI, and nonfatal IS, although they also increase the risk of bleeding outcomes.

Study population

The study included adults (aged > 18 years) from the CPRD who experienced an MI between January 1, 2006 and February 29, 2016, survived at least 14 days after their MI, and had at least 12 months computerized medical history available. To mirror the design of the vorapaxar randomized clinical trial for patients with stable disease [34], the index date was set to 14 days after a patient's first MI within the study period. Patients were excluded if they experienced a non-ICH bleed or had evidence of bleeding diathesis prior to their index date, any bleeding event within 30 days of their index date, or a stroke or transient ischemic attack prior to their index date. Patients were also excluded if they were not continuously registered with a general practitioner during the study period or had an estimated end of follow-up before or at their index date.

Analysis

Patient-level benefit-risk estimates were derived by combining real-world and clinical trial data in three steps: (1) baseline risks of expected ischemic and bleeding outcomes in the absence of therapy were estimated; (2) per-patient attributable benefits and risks associated with vorapaxar therapy were derived using hazard ratios observed in a randomized clinical trial setting; (3) attributable benefits and risks were weighted using either equal weighting or patient preference weighting and summed to derive the equal- and preference-weighted per-patient NCB.

Estimation of baseline risks

Risk equations were developed with CPRD data using Cox proportional hazards models to estimate individual predicted risks of the six CV outcomes associated with the use of antithrombotic drugs, considering the value of each predictor at baseline over 3 years of follow-up. Three-year risk estimates were used to match the time frame in the patient preference study [21]. Covariates included demographics, behavioral variables, selected CV medications, and laboratory variables. Clinical variables were derived using diagnostic codes prior to a patient's index date,

whereas behavioral and laboratory variables were considered within 1 year of the index date. Treatment status at baseline was defined as having a prescription for the relevant medication within 90 days of the index date. Spearman's rank correlation coefficient was calculated to assess the relationship between the predicted risks of composite ischemic and bleeding outcomes.

Per-patient NCB with equal and preference weighting

Attributable benefits and risks of treatment were computed by applying hazard ratios from the TRA-2P TIMI randomized clinical trial (NCT00526474) [34] for vorapaxar vs. placebo for each CV outcome of interest to the per-patient risk estimates derived using the risk equations (Table 1). The per-patient estimates of benefits and risks calculated using equal weighting were then summed to derive the per-patient equal-weighted NCB, and the per-patient estimates using preference weighting were summed to derive the per-patient preference-weighted NCB.

Preference weights were derived from a separate discrete choice experiment survey of 335 adults residing in England with acute or chronic MI [21]. The survey detected significant preference heterogeneity for patients aged $\geq$ 65 years, those with $\geq$ 1 bleeding risk factor, and those at high risk of developing future ischaemic events as indicated by a score $\geq$ 3 using the validated Thrombolysis In Myocardial Infarction (TIMI) risk prediction algorithm [35]. TIMI is based on nine risk factors: age $\geq$ 75 years, diabetes mellitus, hypertension, current smoking, peripheral artery disease, prior stroke, prior coronary artery bypass grafting, history of heart failure, and renal dysfunction [36].

Preference weights were estimated using a logit model for five outcomes in the patient preference study (CV death, nonfatal MI, nonfatal IS, nonfatal ICH, and nonfatal other severe bleeding) (Table 1). All deaths were considered equal, so fatal bleeding was assigned the same weight as CV death. To allow comparison with the equal-weighted NCB, the weights were then normalized so that they would sum to 6. The per-patient NCB was calculated as

$$\mathrm{NCB_i} = \sum_{j \in J} \left(r_j^i - 1 - \exp\left(-\delta_j\left(-\ln\left(1 - r_j^i\right)\right)\right) \cdot w_j^{g(i)} \right),$$

where J is the set of all six outcomes, δ_j is the hazard ratio of outcome j in the TRA-2P TIMI trial, r_j^i is the patient's predicted 3-year baseline risk of outcome j, and $w_j^{g(i)}$ is the weight of outcome j for preference study subgroup of this patient g(i). In the equal-weighted analysis, $w_j^{g(i)} = 1$ for all $j \in J$. When outcomes are weighted equally, NCB expresses the treatment's predicted effect on patient's 3-year risk of a composite outcome that consists of the six clinical events.

2.3.3. NCB analyses

The NCB analyses included patients with sufficient baseline data to be assigned to the preference classes detected in the patient preference study (age $\geq$ 65 years, $\geq$ 1 bleeding risk factor, and TIMI score $\geq$ 3). Bleeding risk factors that could be measured in the CPRD data included a body mass index $<$ 18.5 kg/m^2 and prior use of antiplatelet drugs. Subgroup analyses comparing equal- and preference-weighted NCB were performed in patients based on their age ($<$ 65 vs. $\geq$ 65 years), bleeding risk (0 vs. $\geq$ 1 bleeding risk factor), risk of future ischemic events (high [TIMI score $\geq$ 3] vs. low or medium risk [TIMI score $\leq$ 2]), and lowest and highest deciles of risks of each CV outcome.

Ethics

This study was approved by the Medicines and Healthcare Regulatory Authority Independent Scientific Approval Committee in January 2017 (protocol number 16_273). Patients provided electronic consent before taking part in the preference study, which was approved by the Bloomsbury Research Ethics Committee and Health Research Authority and was conducted in accordance with the General Data Protection Regulation.

3. Results

3.1. Study population

Risk equations were estimated using 31,941 individuals in the CPRD population, of which 22,125 were included in the benefit-risk assessment (Fig. 1). The 9,816 individuals excluded from the benefit-risk assessment population were missing data to determine whether they had bleeding risk factors.

The benefit-risk assessment population was predominantly male (64%) and White (93%), with a mean age of 70.8 (standard deviation, 13.3) years and a mean body mass index of 28.1 (standard deviation, 5.6) kg/m^2 (Table 2). Most were smokers (41%) or previous smokers (31%) and were taking lipid-lowering drugs (64%) or angiotensin converting enzyme inhibitors (60%). The two most common baseline (current or prior) CV conditions were hypertension (56%) and stable angina (36%).

Demographic and clinical characteristics were generally similar for the population used to generate the baseline risk estimates of CV outcomes (N = 31,941), the population used to generate personalized benefit-risk estimates (N = 22,125), the vorapaxar clinical trial population from which the treatment hazard ratios were derived (N = 16,897), and the population used to elicit patient preference information (N = 335) (Table 2). However, fewer patients in the risk equation population than in the benefit-risk assessment population had a history of CV complications (50% vs. 56%) and were on antithrombotic drugs (49% vs. 71%). Also, patients in the vorapaxar clinical trial and preference populations were younger, more

Table 1. Clinical trial hazard ratios, patient preference logit model, and derived preference weighting by subgroup

Outcome/variable[b]	RCT HR[c]	Patient preferences (logit model)	Normalized patient preference weights[a]							
			Age < 65 yr				Age ≥ 65 yr			
			No BRF		≥ 1 BRF		No BRF		≥ 1 BRF	
			Risk of ischemic events		Risk of ischemic events		Risk of ischemic events		Risk of ischemic events	
		Marginal utility (95% CI)[d]	Low-medium	High	Low-medium	High	Low-medium	High	Low-medium	High
CV death (excluding fatal bleed)	0.80	0.19[g] (0.15, 0.22)	1.26	0.94	1.12	0.69	1.20	0.89	1.06	0.64
Nonfatal MI	0.81	0.09[g] (0.06, 0.12)	0.63	0.74	0.35	0.43	0.87	1.02	0.65	0.79
Nonfatal IS	0.54	0.06[f] (0.02, 0.11)	0.42	0.50	0.51	0.63	0.41	0.48	0.48	0.59
Nonfatal ICH	1.22	0.20[g] (0.17, 0.23)	1.38	1.63	1.65	2.03	1.31	1.55	1.56	1.89
Nonfatal other severe bleeding	1.07	0.16[g] (0.13, 0.18)	1.05	1.25	1.26	1.55	1.00	1.18	1.19	1.45
Fatal bleeding	0.99		1.26	0.94	1.12	0.69	1.20	0.89	1.06	0.64
Interaction terms of the logit model										
Nonfatal MI * Age ≥ 65 yr	-	0.04[f] (0.01, 0.07)								
Nonfatal MI * ≥ 1 BRF	-	-0.05[f] (-0.08, -0.02)								
CV death * ≥ 1 BRF	-	-0.05[e] (-0.09, -0.01)								
CV death * TIMI ≥ 3	-	-0.07[f] (-0.12, -0.02)								

Abbreviations: BRF, bleeding risk factor; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ICH, intracerebral hemorrhage; IS, ischemic stroke; RCT, randomized clinical trial.
Patient preference logit model fit: Log-likelihood = −2,283, McFadden's Adjusted $R^2 = 0.295$.

[a] Subgroup sizes are provided in Supplemental Table 1.

[b] Spearman's rho = 0.89 ($P < 0.001$) for the correlation between ischemic outcomes (nonfatal MI and nonfatal IS) and bleeding outcomes (nonfatal ICH, nonfatal other severe bleeding, and fatal bleeding) in the benefit-risk assessment population.

[c] From Scirica et al. [34].

[d] From Pinto et al. [21].

[e] $P < 0.05$.

[f] $P < 0.01$.

[g] $P < 0.001$.

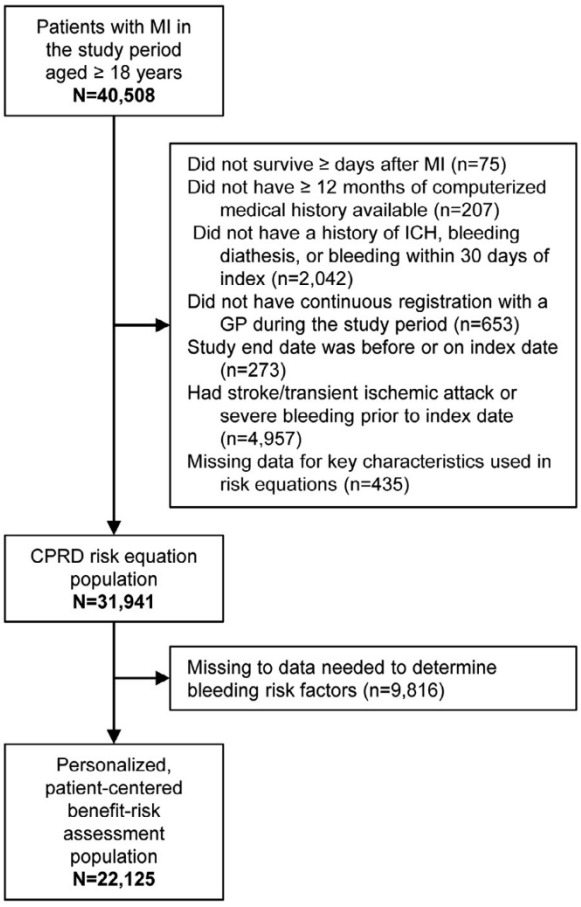

Fig. 1. Study population selection.
Abbreviations: CPRD, Clinical Practice Research Datalink; GP, general practitioner; ICH, intracranial hemorrhage; MI, myocardial infarction.

frequently male, and less often current smokers than the patients in the benefit-risk assessment and risk equation populations. Finally, patients in the preference population were more likely to be on antithrombotic drugs (97%) than patients in the vorapaxar clinical trial (78%), benefit-risk assessment (71%), and risk equation populations (49%).

3.2. NCB

The overall mean NCB was 0.057 using equal weighting of outcomes, indicating a mean expected reduction of 5.7% in the composite risk of CV events in patients treated for 3 years with vorapaxar. The overall mean NCB was significantly lower in the preference-weighted analysis than in the equal-weighted analysis (0.040 vs. 0.057; $P < 0.0001$) (Fig. 2) but the direction of effect of the NCB was unchanged in all outcome subgroups, irrespective of the weighting used. Also, irrespective of weighting, the highest NCB values were in the same subgroups of patients, including those with the highest risk of CV death (0.124 [95% CI, 0.123–0.125] using equal weighting and 0.086 [95% CI, 0.085–0.087] using preference weighting), nonfatal MI (0.113 [95% CI, 0.112–0.114] using equal weighting and 0.079 [95% CI, 0.078–0.080] using preference weighting), and nonfatal IS (0.112 [95% CI, 0.111–0.112] using equal weighting and 0.077 [95% CI, 0.076–0.078] using preference weighting). Predicted densities of NCB were similarly shaped between equal and preference weightings, although the distribution of preference-weighted outcomes was shifted closer to 0 (Fig. 3).

Because of the observed heterogeneity in the patient preference study [21], subgroup analyses were conducted to compare equal- and preference-weighted NCB based on age, bleeding risk, and risk of future ischemic events. The direction of effect of the NCB was unchanged by weighting in all subgroups, although the NCB was always lower with preference weighting than equal weighting of outcomes (Fig. 2). In all subgroups stratified by age, however, preference weighting had a differential effect: the equal-weighted NCB was higher for patients with $\geq$ 1 bleeding risk factor than for those with no bleeding risk factors, whereas the preference-weighted NCB was higher for patients with no bleeding risk factors than for those with $\geq$ 1 bleeding risk factor. For example, in patients aged $\geq$ 65 years and with a high risk of future ischemic events, the equal-weighted NCB was higher for those with $\geq$ 1 bleeding risk factor (0.088 [95% CI, 0.087–0.089]) than for those with no bleeding risk factors (0.080 [95% CI, 0.079–0.081]), whereas the preference-weighted NCB was lower for those with $\geq$ 1 bleeding risk factor (0.059 [95% CI 0.059–0.059]) than for those with no bleeding risk factors (0.069 [95% CI 0.068–0.070]).

Discussion

This is the first study to report the feasibility of including patient preference data in a personalized, patient-centered benefit-risk assessment. The study demonstrated that including preference weighting can affect the overall NCB and the NCB for subgroups.

In analyses with equal weighting of CV outcomes, patients with a high predicted risk of experiencing bleeding events had higher NCB. This could have been due to the correlation between the predicted risks of ischemic and bleeding endpoints, which, in turn, may be because the current standard of care for ischemic events also affects the bleeding risk [23]. Introducing patient preferences significantly altered the NCB, which suggests that benefit-risk assessments should consider both clinicians' value judgements (ie, equal weighting of benefits and risks with irreversible harm) and patients' preferences.

Previous studies have demonstrated the feasibility of combining data from electronic health records with clinical trial effects in the estimation of NCB of dual antiplatelet in patients with a prior MI [6,7] and hormone therapy in postmenopausal women [37]. Using population-based linked electronic health records, Pasea et al. provided personalized estimates of risks associated with major CV and bleeding events in patients with prior MI [7]. A poten-

Table 2. Demographics and baseline characteristics of the risk equation, benefit-risk, vorapaxar clinical trial, and patient preference populations

	Risk equation population[a]	Benefit-risk assessment population	Vorapaxar clinical trial population[b]	Patient preference population[c]
Characteristic	N = 31,941	N = 22,125	N = 16,897	N = 335
Age at index (y), mean (SD)	69.8 (13.8)	70.8 (13.3)	58.6 (10.5)	64.2 (9.6)
Gender or sex, n (%)				
Male	20,417 (64)	14,162 (64)	13,498 (80)	274 (82)
Female	11,524 (36)	7,963 (36)	3,399 (20)	60 (18)
Race, n (%)				
White	29,746 (93)	20,597 (93)	14,896 (88)	NA
Asian	980 (3)	762 (3)	661 (4)	NA
Black	185 (1)	138 (1)	349 (2)	NA
Other	368 (1)	242 (1)	982 (6)	NA
Unknown	662 (2)	386 (2)	9 (< 1)	NA
Body mass index				
Mean (SD)	28.1 (5.6)	28.1 (5.6)	28.55 (4.9)	28.4 (14.5)
Missing, n (%)	17,118 (54)	7,302 (33)	37 (< 1)	16 (5)
Smoking status, n (%)				
Current smoker	13,338 (42)	9,023 (41)	3,328 (20)	20 (6)
Former smoker	9,115 (29)	6,808 (31)	8,687 (51)	195 (58)
Never smoker	9,488 (30)	6,294 (28)	4,882 (29)	120 (36)
Medical history, n (%)				
Diabetes	7,275 (23)	6,386 (29)	3,623 (21)	71 (21)
Atrial fibrillation	6,307 (20)	4,981 (23)	657 (4)	49 (15)
Hypertension	15,820 (50)	12,356 (56)	10,387 (61)	148 (44)
Peripheral vascular disease	4,269 (13)	3,502 (16)	847 (5)	11 (3)
Angina	11,648 (37)	9,635 (44)	NA	64 (19)
Unstable angina	5,716 (18)	4,601 (21)	4,258 (25)	NA
Stable angina	9,035 (28)	7,864 (36)	2,480 (15)	NA
Heart failure	8,115 (25)	6,211 (28)	1,415 (8)	40 (12)
Chronic kidney disease	5,553 (17)	4,583 (21)	670 (4)	9 (3)
Treatment, n (%)				
Antithrombotic drugs	15,621 (49)	15,621 (71)	13,235 (78)	324 (97)
Clopidrogel	5,980 (19)	5,980 (27)	13,110 (78)	53 (16)
Lipid-lowering drugs	15,390 (48)	14,081 (64)	16,117 (95)	257 (77)
ACE inhibitors	15,248 (48)	13,333 (60)	15,805 (60)	NA
Beta blockers	11,695 (37)	10,660 (48)	14,403 (85)	NA

Abbreviations: ACE, angiotensin converting enzyme; NA, not available.
[a] Pinto et al. [6].
[b] TRA-2P-TIMI randomized clinical trial (NCT00526474) [34].
[c] Pinto et al. [21].

tially positive NCB of prolonged dual antiplatelet therapy was observed in the majority of patients (94%) with CV complications and a risk of major bleeding events. These findings also illustrated that how events are weighted can substantially affect the proportion of patients estimated to have a positive NCB. Nonetheless, personalized treatment decisions based on individual patient preferences were not accounted for in the study but are warranted to inform clinical decision-making. In a similar study using CPRD data, van Staa et al. evaluated the benefit-risk profile of hormone therapy among postmenopausal women [37]. As in the current study, they demonstrated considerable heterogeneity in the potential benefit-risk profile, with younger patients tending to have more favorable benefit-risk profile than older patients. Another study by van Staa et al. used this approach to evaluate the benefit-risk profile of selective Cox-2 inhibitors [38]. They demonstrated that individuals with CV comorbidities were less likely to have a beneficial benefit-risk profile than those without CV comorbidities. More recently, we demonstrated that personalized benefit-

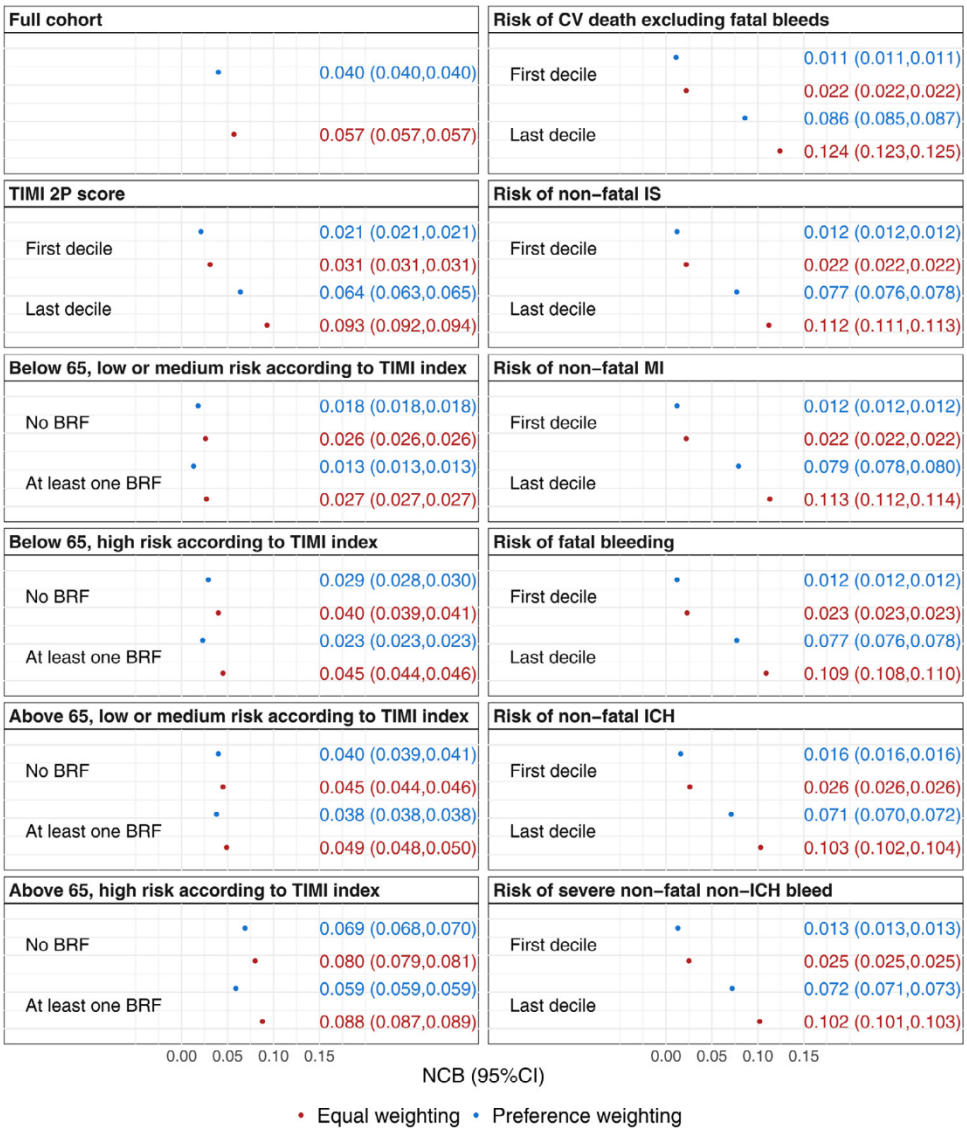

Fig. 2. Net clinical benefit (NCB) using equal and patient preference weighting of outcomes, stratified by baseline risk of cardiovascular events (right) and patient characteristics associated with preference heterogeneity (bottom-left).
Abbreviations: BRF, bleeding risk factor; CV, cardiovascular; ICH, intracranial hemorrhage; IS, ischemic stroke; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction.

risk assessments are feasible, clinically valuable, and can be used to better predict the benefit-risk balance within a population ahead of broad clinical use [6]. The current study adds to the previous research by illustrating how the benefit-risk balance can vary when events are weighted differently. The preference-weighted NCB was lower than the equal-weighted NCB across subgroups because patients consistently put more weight on treatment risks than benefits.

A potential limitation of this study is that the treatment effect estimates were from a clinical trial, whereas the risk equations were constructed for the CPRD population and the patient preference data were from a separate discrete choice experiment. Participants in the preference and clinical trial populations were younger, more likely to be male, and less likely to be smokers than patients in the risk equation and benefit-risk assessment populations. This could affect the generalizability of specific findings, although this should not affect the conclusions about the feasibility of using multiple data sources for personalized, patient-centered benefit-risk assessments.

Conclusions

This study showed that patient preferences for clinical outcomes and heterogeneity in these preferences may significantly affect the NCB of a treatment and should therefore be taken into account in personalized benefit-risk assessments. The study also showed that personalized patient-centered benefit-risk assessment can provide insight

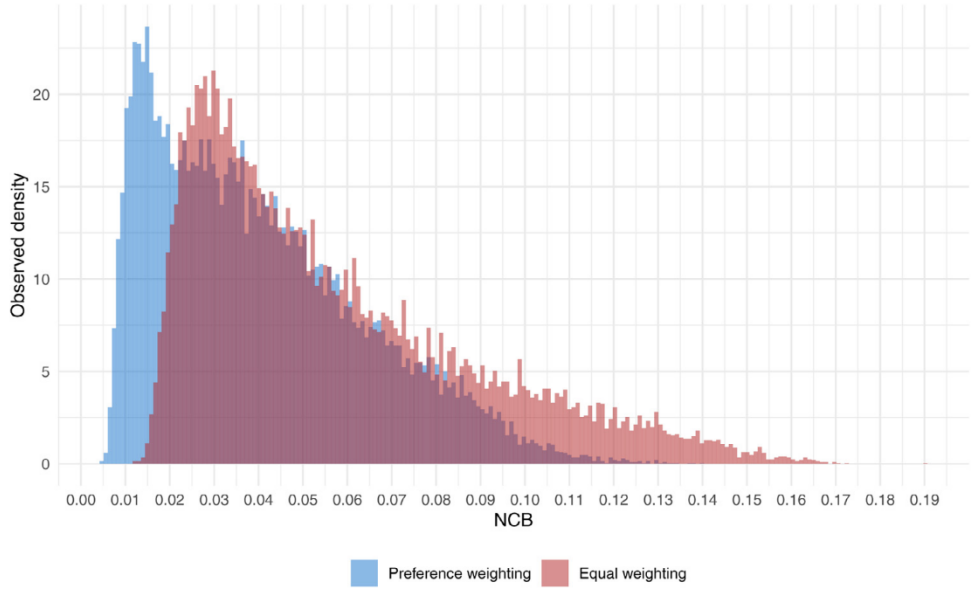

Fig. 3. Net Clinical Benefit (NCB) with equal and patient preference weighting of outcomes.

into how to individualize care based on patient characteristics, which may translate into a more favorable NCB.

Authors' contributions

Tommi Tervonen: Conceptualization, Methodology, Supervision, Writing – Review & Editing. Thibaud Prawitz: Software, Formal analysis, Writing – Review & Editing. Gin Nie Chua: Methodology, Software, Formal analysis, Writing – Review & Editing, Project administration. Johanna Hyacinthe: Project administration, Writing – Review & Editing. Cathy Anne Pinto: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Funding acquisition.

Funding

This study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Acknowledgments

Medical writing was provided by Phillip S. Leventhal and Rangan Gupta (Evidera) and paid for by Merck Sharpe & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD). The authors would like to thank personnel at NHS sites (University Hospitals Plymouth, Chesterfield Royal Hospital, Kent Community Health and Imperial College Hospitals NHS Trusts) for supporting patient recruitment for the preference study, and Tarek Hammad (formerly MSD) and Andrew Tershakovec (formerly MSD) for support during study design.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.11.036.

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