Physicians' stated trade-off preferences for chronic hepatitis B treatment outcomes in Germany, France, Spain, Turkey, and Italy

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Objective To quantify physicians' preferences among possible outcomes associated with chronic hepatitis B treatments and to determine which outcomes are most important to physicians in making treatment decisions.

Methods Physicians in five countries who treat chronic hepatitis B patients completed a web-enabled, choice-format, conjoint-analysis survey. The survey presented physicians with four treatment-choice questions for three different patient types. Each treatment-choice question included a pair of hypothetical medication profiles. Medication outcomes included how long the medication has been studied (weight of evidence); the probability that a patient's viral load remains undetectable for 5 years, with a possible histological improvement or reversal of disease progression (long-term efficacy); the 5-year treatment-related risk of fracture; the 5-year treatment-related risk of renal dysfunction; and patient cost. Treatment-choice questions were derived from a predetermined experimental design with known statistical properties. For each country, the random-parameters logit was used to estimate preference weights for all outcome levels and the mean relative importance of each outcome.

Results Long-term efficacy and risk of renal dysfunction were the most important outcomes for the 788 physicians completing the survey, whereas weight of evidence was the least important. However, physicians perceived significant differences in weight of evidence timeframes. Physicians in Germany and France ranked efficacy above side-effect risk, whereas physicians in Spain, Italy, and Turkey ranked side-effect risk above efficacy in importance.

Conclusion Physician preferences among treatment profiles indicate systematic differences in the relative importance of treatment outcomes. Physicians require higher efficacy for treatments with higher side-effect risk but somewhat less efficacy for treatments with longer evidence. *Eur J Gastroenterol Hepatol* 24:419–426 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction

The goal of chronic hepatitis B (CHB) treatment is to prevent progression to cirrhosis, hepatic decompensation, and hepatocellular carcinoma [1]. This goal is best accomplished by complete suppression of hepatitis B virus (HBV) replication. Thus, European Clinical Guidelines recommend the use of the most potent treatments with optimal resistance profiles as first-line monotherapies for the treatment of CHB [1]. However, long-term safety should also be considered, given that most patients treated for hepatitis B will require years, if not lifelong treatment, to obtain lasting clinical benefits. Several CHB treatment options exist for individual patients, making optimal treatment choices sometimes difficult [1]. Postmarketing studies, addressing the long-term safety profile of available nucleoside and nucleotide analogs for CHB, are currently underway, including assessment of nephrotoxicity, myopathy, mitochondrial toxicity, and bone mineral density [2].

Ideally, researchers derive physicians' willingness to accept tradeoffs between efficacy and safety from observed prescribing decisions. However, regulatory and other institutional constraints severely limit the range of prescribing options, thus providing little data on such tradeoffs. Stated-preference methods offer a means of obtaining preference weights from preferences elicited under experimentally controlled conditions [3–11]. To our knowledge, ours is the first study to quantify physicians' preference weights for CHB treatment outcomes. Our study is also the first to measure the relative importance to physicians of the weight of efficacy and safety evidence in any therapeutic area. Weight of evidence is a major concern for licensing new drugs and for reimbursement decisions, but there are no existing data on the relative importance of weight of evidence in physicians' treatment decisions.

Materials and methods
Survey instrument

Choice-format conjoint-analysis studies or discrete-choice experiments have been used increasingly to quantify preferences for outcomes of health, health care, and health care policy [3,4]. Choice-format conjoint analysis is a systematic method of eliciting tradeoffs to quantify the relative importance respondents assign to various treatment attributes or outcomes. It is based on the premise that medical interventions are composed of a set of attributes or outcomes and that the attractiveness of a particular intervention to an individual is a function of these attributes [5–13].

The attributes in our study were chosen to meet two criteria: (a) attributes were clinically relevant and (b) attributes incorporated physicians' assessments of patient concerns. Likewise, the range of levels of each attribute met three criteria: (a) the range of attribute levels spanned the clinically relevant range of outcomes seen in clinical trials or clinical practice, (b) differences in levels encompassed the range of improvements in efficacy outcomes or the range of increases in side-effect or risk outcomes that were seen in clinical trials or clinical practice, and (c) the range of attribute levels encompassed the range over which respondents were willing to accept tradeoffs among attributes. Using input from clinical experts, review of product inserts, and face-to-face interviews with 10 physicians who treat CHB patients in Spain, we identified five treatment attributes to describe the CHB treatment alternatives in this study (Table 1): how long the medication has been studied (weight of evidence); the probability that the patient's viral load remains undetectable for 5 years, with possible histological improvement or reversal of disease progres-sion (long-term efficacy); the 5-year treatment-related risk of a fracture; the 5-year treatment-related risk of renal dysfunction where a fracture has not yet been detected; and personal cost to the patient each month. Personal cost to the patient was included to make this survey completely comparable with a patient survey with the same attributes and levels. Personal cost to the patient was included in the patient survey because a goal of that survey was to estimate the monetary equivalent value of improvements in CHB treatment outcomes to patients (not what they are willing to pay and not for the purpose of setting prices).
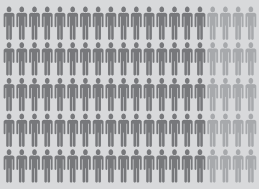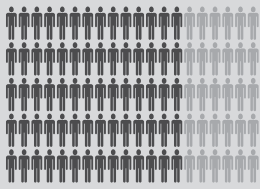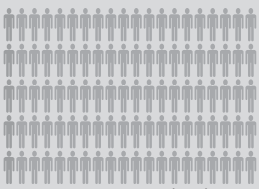
Physicians answered 12 treatment-choice questions (Fig. 1) from among pairs of constructed medication profiles: four treatment-choice questions for each of three hypothetical patients. Each medication profile was defined by varying levels of the five treatment attributes. Physicians were asked to select the hypothetical medication they would prescribe if only the two medications were available. The three hypothetical patients were developed to encompass the range of possible CHB patients for whom physicians would prescribe initial treatment, using European clinical treatment guidelines (Table A1). The patient profiles were also constructed to determine whether patient character-istics (such as age or sex) or disease characteristics (such as HBV early-antigen status, baseline HBV DNA levels, or fibrosis) affect treatment decisions. All patient profiles specified that the patient had CHB, alanine aminotransfer-ase at two times the upper limits of normal, and no significant comorbidities. Introductory text indicated that each patient was treatment naïve.

To create the treatment profiles for the choice questions, we utilized the D-efficient main-effects criteria using SAS

Table 1 Attributes and levels for the choice questions

Attribute	Atribute description	Abbreviated attribute label	Levels
How long the medication has been studied (weight of evidence)	Different hepatitis B medications have been studied in clinical trials or postmarketing studies for different amounts of time	How long the medication has been studied	6 years 3 years 1 year
Probability that the patient's viral load remains undetectable for 5 years, with possible histological improvement or reversal of disease progression	No additional description was provided	Probability of viral load being undetectable	95 out of 100 (95%) 80 out of 100 (80%) 70 out of 100 (70%)
5-year treatment-related risk of a fracture	The probability that a patient taking the medication will have a fracture some time during the first 5 years of treatment. The fracture results from a decrease in bone mineral density caused by renal insufficiency, where the patient's kidneys are not reabsorbing phosphates correctly Medications with a higher risk of renal insufficiency may require more frequent monitoring of the patient's kidney function	5-year treatment-related risk of a fracture	None 1 out of 100 (1%) 5 out of 100 (5%) 10 out of 100 (10%)
5-year treatment-related risk of renal insufficiency, where a fracture has not been detected yet	The probability that a patient taking the medication will have renal insufficiency, where lower bone mineral density has yet to be confirmed during the first 5 years of treatment	5-year treatment-related risk of renal insufficiency	None 1 out of 100 (1%) 5 out of 100 (5%) 10 out of 100 (10%)
Personal cost to the patient each month	No additional description was provided	Cost	€0 €10 €25 €75 or €150

Fig. 1

Medication features	Medication A	Medication B
How long the medication has been studied	1 year (doctors are <u>not sure</u> about the chance of benefits or side-effects)	6 years (doctors <u>know exactly</u> the chance of benefits and side-effects)
Probability that the patient's viral load remains undetectable for 5 years with possible histological improvement or reversal of disease progression	80 out of 100 (80%)	70 out of 100 (70%)
5-year treatment-related risk of a fracture	No chance	1 out of 100 (1%)
5-year treatment-related risk of renal insufficiency where a fracture has not been detected yet	5 out of 100 (5%)	1 out of 100 (1%)
Personal cost to the patient each month	75€	10€
Which medication would you choose if these were the only medications available?	Medication A ○	Medication B ○

Example choice question. Patient 1: a 55-year-old woman with chronic hepatitis B. She is HBeAg(−), with HBV DNA at 2500 IU/ml and ALT at 2 × ULN. A liver biopsy showed severe active necroinflammations. The patient's health is otherwise good (no significant comorbidities). ALT, alanine aminotransferase; HBeAg(−), hepatitis B virus early-antigen negative; HBV, hepatitis B virus; ULN, upper limit of normal.

version 9.2 (SAS Institute Inc., Cary, North Carolina, USA), resulting in 36 choice pairs [14–18]. The final experimental design consisted of three survey versions, each containing 12 treatment-choice questions. Each physician was randomly assigned to one of the three versions. The survey instrument also collected information on physician sex, years in practice, average number of CHB patients treated each month, average number of CHB patients each month who are prescribed CHB antiviral treatments, practice type, and practice setting [10]. The survey was approved by Research Triangle Institute International's Office of Research Protection and Ethics.

Survey sample

All physicians were required to be board certified (or board eligible) and currently treating CHB patients. Harris Interactive (HI), an international survey-research company that specializes in survey research using both telephone and online surveys, recruited physician-respondents in five countries: Germany, Spain, France, Italy, and Turkey. Physicians in Germany, Spain, France, and Italy were recruited from HI's online physician panel. Physicians in Turkey were recruited through clinics. HI administered the web-enabled survey to all respondents in May 2010.

Statistical analysis

For each country, we used multivariate, random-parameters logit to estimate the choice model. Random-parameters logit avoids potential estimation bias from unobserved decision-weight heterogeneity in discrete-choice models by estimating a distribution of preference weights across physician-respondents for each choice parameter [19,20]. In addition, because each physician-respondent provided responses to more than one choice question, the model controlled for within-respondent correlation.

The random-parameters choice model estimated the effect of each attribute on the probability of choosing a medication alternative. In this model, the dependent variable is the physician choice and the explanatory variables include the levels of the factors included in Table 1. We used effects coding (where the parameter for the omitted category was the negative sum of the included categories) [21,22], instead of dummy coding, for probability viral load is undetectable, for the 5-year treatment-related risk of renal dysfunction, and for the 5-year treatment-related risk of a fracture. In addition, the none and 1% levels for the 5-year treatment-related risk of a fracture were combined as 0.5% because physicians indicated no difference in preferences between these two adjacent levels. How long the medication has been studied and cost were modeled as linear variables on the basis of the results of specification tests. The parameter estimates from random-parameters logit models can be interpreted as mean preference weights, indicating the relative strength of preference for each attribute level [23]. For each country, the parameter estimate with the highest value (the best level) was assigned a preference weight of 10 and the parameter estimate with the lowest value (the worst level) was assigned a preference weight of 0. All other attribute levels were scaled relative to the best and worst levels [10].

Figure 2 presents the scaled preference weights, by country, for the efficacy and evidence attributes (probability viral load is undetectable and how long the medication has been studied). Because we found no statistically significant differences among the three patient profiles evaluated by the physicians, Fig. 2 shows the pooled estimates across the three patient types. Outcomes that are more preferred have higher preference weights than outcomes that are less preferred. As expected, estimated preference weights for all attributes were consistent with the natural ordering of the categories. That is, better clinical outcomes were preferred to worse clinical outcomes. The vertical bars around each mean parameter estimate indicate the 95% confidence interval (CI) for that estimate. If the CIs do not overlap for adjacent levels in a particular attribute, the mean estimates are statistically different from each other at the 5% level of significance. Thus, the adjacent levels for all attributes for each country, except for the 0–1% levels for the 5-year treatment-related risk of renal dysfunction, were all statistically different from each other ($P < 0.05$).

Fig. 2
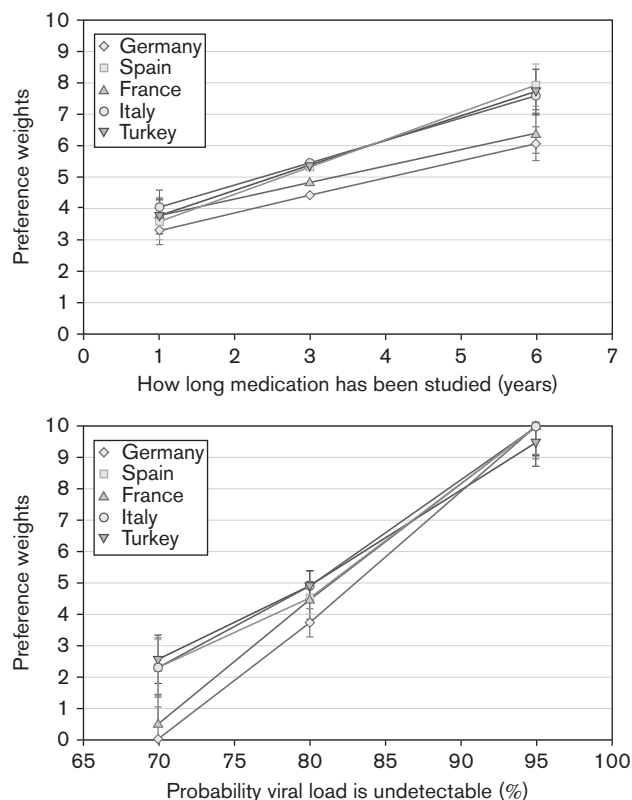
Preference weights for how long the medication has been studied and probability viral load is undetectable. The vertical bars surrounding each mean importance estimate denote the 95% confidence interval about the point estimate.

The distance between the parameter estimates for the best and worst levels of an attribute can be interpreted as the overall relative importance of the attribute over the specific ranges presented in the survey. The overall relative importance weight for each attribute was estimated for each country. For example, the importance of the long-term efficacy attribute was estimated as the importance of increasing long-term efficacy from 70 to 95%. The same approach was used to estimate the relative importance for each attribute.

In addition, we also estimated the minimum acceptable benefit (MAB) for various improvements in treatment attributes and outcomes, to demonstrate how the preference data can be useful in making clinical decisions. A discussion of the definition of MAB is included in the subsection on MAB results.

Results
Study sample
The final study sample of physicians who were eligible and agreed to participate was 788 (Germany = 158; Spain = 158; France = 155; Italy = 158; and Turkey = 159). The

majority of all respondents were men (76%) and had practiced medicine for over 10 years (85%). Less than half of all physicians treated more than 10 CHB patients (46%) per month in their practices. Almost a third of the physicians administered antiviral medications to more than 10 patients (31%) per month in their practices. The distribution around type of practice varied by country. The most common practice types were public (44%) and university hospitals (31%). Of the physicians in the final study sample (all five countries), 13% were hepatologists, 19% were gastroenterologists, 14% were infectious disease specialists, 15% were internists, 11% were primary care physicians, 25% were nephrologists, and 3% were classified as 'other'.

Preference weights

The preference weights for how long the medication has been studied are very similar for Spain, Italy, and Turkey, and thus the slopes are almost the same. In contrast, the slopes for Germany and France are flatter, indicating that the weight of evidence attribute was less important to physicians in these two countries than to physicians in the other three countries. The preference weights for Spain, Italy, and Turkey were very similar for probability viral load being undetectable, and the slopes were almost the same. In contrast, German and French physicians ranked lower efficacy levels as less important than did physicians in the other three countries.

Figure 3 presents the scaled preference weights for each country for the two risk attributes (5-year treatment-related risk of a fracture and 5-year treatment-related risk of renal dysfunction). The preference weights for all five countries were very similar for the 5-year treatment-related risk of a fracture. In this case, the slopes for all five countries were similar, although German physicians were generally somewhat less concerned about fracture risk relative to other treatment attributes. Again, Spanish, Italian, and Turkish physicians had very similar preferences for the 5-year treatment-related risk of renal dysfunction. However, French physicians were less concerned, and German physicians were much less concerned about lower risks of renal dysfunction.

The vertical distance between adjacent preference weights indicates the relative importance of moving from one level of an attribute to an adjacent level of that attribute. For example, the following were the approximate relative importance levels of an improvement from 80 to 95% on probability viral load that is undetectable:

(1) 6.3 (= 10.0–3.7) for Germany,
(2) 5.5 (= 10.0–4.5) for Spain,
(3) 5.6 (= 10.0–4.4) for France,
(4) 5.2 (= 10.0–4.8) for Italy,
(5) 4.6 (= 9.5–4.9) for Turkey.

Similarly, the following were the relative importance levels of an improvement from 5 to 1% on the 5-year treatment-related risk of renal dysfunction:

Fig. 3
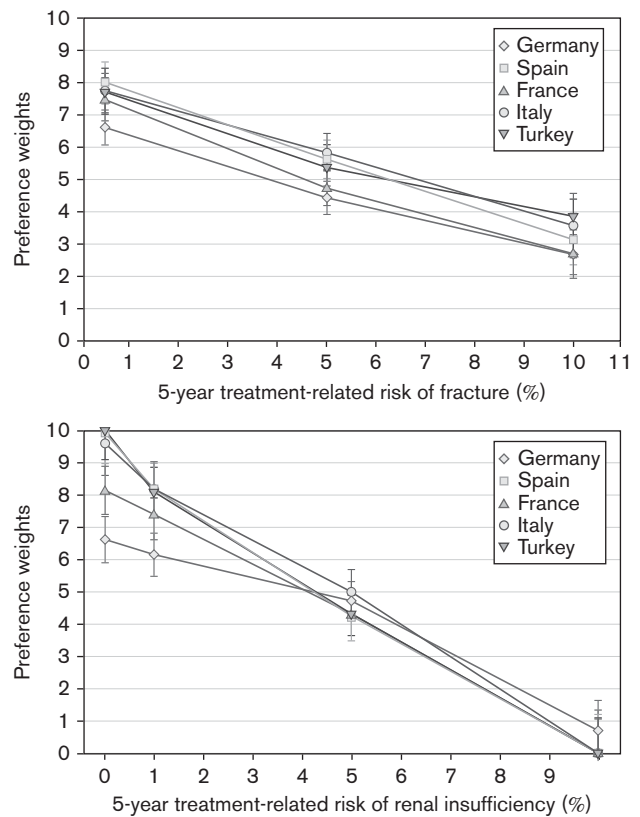
Preference weights for the 5-year treatment-related risk of fracture and renal dysfunction (insufficiency). The vertical bars surrounding each mean importance estimate denote the 95% confidence interval about the point estimate.

(1) 1.4 (= 6.2–4.7) for Germany,
(2) 3.9 (= 8.2–4.2) for Spain,
(3) 3.1 (= 7.4–4.3) for France,
(4) 1.6 (= 8.2–5.0) for Italy,
(5) 3.8 (= 8.1–4.3) for Turkey.

Therefore, the importance of an improvement from 80 to 95% on probability viral load is undetectable relative to an improvement from 5 to 1% on the 5-year treatment-related risk of renal dysfunction as follows:

(1) 4.5 (= 6.3÷1.4) for Germany,
(2) 1.4 (= 5.5÷3.9) for Spain,
(3) 1.8 (= 5.6÷3.1) for France,
(4) 1.6 (= 5.2÷3.3) for Italy,
(5) 1.2 (= 5.6÷3.8) for Turkey.

Thus, for German physicians, the relative importance of an improvement in the efficacy attribute versus the renal dysfunction risk was approximately 2.5–3 times higher compared with physicians from other countries. In general, we found strong similarities among Spanish,

Italian, and Turkish physicians, whereas German and French physician preferences often differed from the preferences of physicians in the other three countries.
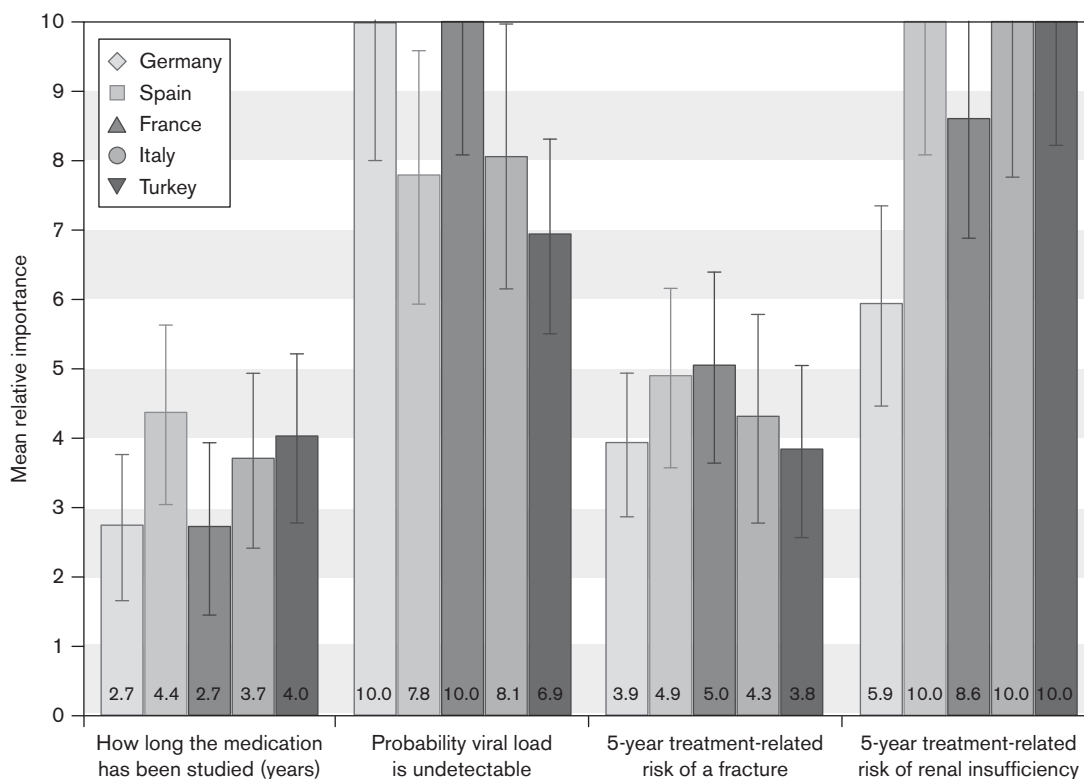
Relative importance

Figure 4 presents the mean relative importance weights (and 95% CIs) for the four clinical attributes for all five countries. The absolute scale of the relative importance weights is arbitrary. Only relative differences among attribute levels are meaningful. Given the range of levels of each attribute in the study, probability viral load being undetectable was the most important attribute for Germany and France, followed by the 5-year treatment-related risk of renal dysfunction, the 5-year treatment-related risk of a fracture, and how long the medication has been studied. The most important attribute for Spain and Italy was the 5-year treatment-related risk of renal dysfunction, followed by probability viral load is undetectable, the 5-year treatment-related risk of a fracture, and how long the medication has been studied. The pattern was almost the same for Turkey (i.e. the most important attribute is the 5-year treatment-related risk of renal dysfunction, followed by probability viral load is undetectable), except that how long the medication has been studied was slightly more important than the

5-year treatment-related risk of a fracture. Although the mean relative importance differed among all attributes, these differences were not always statistically significant. For example, for Germany, the attribute probability viral load being undetectable was statistically significantly more important than the other three attributes ($P < 0.05$). In addition, for Germany, the attribute the 5-year treatment-related risk of renal dysfunction was 2.2 times as important as the attribute how long the medication has been studied ($P < 0.05$).

Minimum acceptable benefits

Table 2 presents the MAB estimates for the five countries for a 0.5% and a 1% increase in the 5-year treatment-related risk of renal dysfunction. In this study, MAB is the smallest increase in a given benefit, such as an increase in the probability viral load is undetectable, a decrease in fracture risk, or an increase in years of evidence, which would be required in order to compensate for a clinically plausible increase in the 5-year treatment-related risk of renal dysfunction. Safety of long-term exposure with newer oral antiviral agents in HBV-infected patients is a main concern for regulators. More specifically, regulatory authorities typically demand risk-management plans to regularly assess and update the

Fig. 4

Relative attribute importance. Relative importance defined over the specific range of levels shown in the trade-off questions. The vertical bars surrounding each mean importance estimate denote the 95% confidence interval about the point estimate.

potential benefit of a new antiviral treatment against the potential important safety risks, such as renal or bone toxicity. Our MAB estimates offered some indication of what physicians would require as the minimum increase in long-term efficacy, decrease in the 5-year treatment-related risk of a fracture, or additional years of evidence that would compensate for a potential additional long-term risk of renal dysfunction. For a 1% increase in the 5-year treatment-related risk of renal dysfunction, Turkish physicians required the largest increase in long-term viral suppression, at 6.2% (2.4–10.5%); German physicians required the smallest increase, at 1.3% (0.0–3.7%). These MAB estimates indicated that if, for example, a new drug had a 1% increase in the 5-year treatment-related risk of renal dysfunction but only a 4% increase in long-term efficacy, only German and French physicians would find the new treatment acceptable. Turkish physicians also required the largest increase in years of evidence, at 2.3 years (1.0–3.9 years); German physicians required the smallest increase, at 1.0 year (0.0–2.8 years). These MAB estimates indicated that if, for example, a new antiviral treatment had a 1% increase in the 5-year treatment-related risk of renal dysfunction but only one additional year of evidence compared with an existing antiviral treatment, only German physicians find the new treatment acceptable.

Discussion

This study of physician preferences for CHB treatment outcomes yielded several important results. First, the pattern of choices observed in the choice questions indicated that although long-term efficacy (i.e. probability that the patient's viral load remains undetectable for 5 years, with possible histological improvement or reversal of disease progression) is important to physicians, the 5-year treatment-related risk of renal dysfunction, where a fracture has not yet been detected, also influences physicians' treatment choices. The finding that the 5-year treatment-related risk of renal dysfunction also affects physicians' treatment choices indicates that physicians are considering not only the long-term clinical benefits for CHB treatments but also their long-term safety, as these treatments are required to be taken for several years. Comparison of the findings of our study with physician preference studies in other disease areas was hampered by

the lack of published evidence on this topic. Nevertheless, another physician preference study found that gastroenterologists' risk tolerance for Crohn's disease treatments varied, depending on patient type. For example, gastroenterologists were less tolerant of serious adverse-event risks for middle-aged patients for an improvement from moderate symptoms to remission [8].

Second, this study found that patient characteristics such as age and sex or disease characteristics such as HBV early-antigen status, baseline HBV DNA levels, or fibrosis did not influence physician treatment choices. This result was surprising, as other preference studies have found that patient characteristics influence physician treatment choices [10]. A possible explanation for this finding is that in fields like oncology or diabetes, there are many available treatments for patients, whereas in CHB, there are a smaller number of available treatments. Thus, patient characteristics are less influential on physician treatment choices.

Third, for each country, the weight of evidence attribute was the least important relative to the ranges of other attribute levels shown in the survey. However, physicians perceived significant differences in weight of evidence timeframes. These results imply that weight of evidence mattered to physicians and that the shorter the time a medication had been studied meant more uncertainty in long-term outcomes. More uncertainty is acceptable if treatment benefits are larger or treatment risks are smaller.

Fourth, the paper demonstrates how preference data can be useful in helping regulators compare treatment benefits and risks. If a new treatment has a difference in long-term efficacy that is greater than the MAB, then the physicians' stated preferences indicated the new treatment is better than an existing drug, even with the increase in treatment risk. Alternatively, if a new antiviral treatment poses a potential incremental safety risk, then the physicians' stated preferences indicated that the new treatment is acceptable if additional years of evidence are available to reduce uncertainty in long-term outcomes.

All of these results are best interpreted with an awareness of several issues and qualifications. First, although choice-format conjoint-analysis methods are increasingly used to

Table 2 Minimum acceptable increase in benefits

Improvement	Mean MAB (95% CI)				
	Germany	Spain	France	Italy	Turkey
0.5% increase in the 5-year treatment-related risk of renal dysfunction					
Increase in probability viral load is undetectable	0.6% (0.0–1.9%)	2.5% (0.8–4.4%)	1.1% (0.0–2.6%)	2.1% (0.3–4.1%)	3.1% (1.2–5.2%)
Decrease in the 5-year treatment-related risk of a fracture	1.1% (0.5–2.2%)	2.3% (1.0–4.0%)	1.2% (0.5–2.2%)	2.3% (0.8–5.0%)	2.4% (1.2–4.0%)
Additional years of evidence	0.5 (0.0–1.4)	1.0 (0.0–1.8)	0.8 (0–2.0)	1.0 (0.0–2.0)	1.2 (0.0–2.0)
1.0% increase in the 5-year treatment-related risk of renal dysfunction					
Increase in probability viral load is undetectable	1.3% (0.0–3.7%)	4.9% (1.4–8.8%)	2.1% (0.0–5.3%)	4.2% (0.8–8.1%)	6.2% (2.4–10.5%)
Decrease in the 5-year treatment-related risk of a fracture	1.6% (0.5–4.0%)	4.0% (1.5–6.9%)	1.8% (0.5–3.9%)	4.0% (1.0–7.4%)	4.4% (1.9–8.1%)
Additional years of evidence	1.0 (0.0–2.8)	2.1 (0.6–3.7)	1.6 (0–4.1)	2.0 (0.3–3.9)	2.3 (1.0–3.9)

CI, confidence interval; MAB, minimum acceptable benefit.

support regulatory decisions, to identify optimal treatment guidelines, and to promote patient-centered medicine, they have limitations. The most important limitation is that respondents evaluate hypothetical treatments. These tradeoffs are intended to simulate possible clinical decisions but obviously do not have the clinical consequences of actual decisions. Thus, differences can arise between stated and actual choices. In this study, an attempt was made to minimize such potential differences by offering alternatives that mimic real-world tradeoffs as closely as possible. Nevertheless, there are many factors that can influence actual treatment decisions, which are not accounted for in our study. Further, this study is based on relatively small physician samples from each country. If these samples are insufficiently representative, our comparisons among countries could be affected.

In summary, we found strong similarities among Spanish, Italian, and Turkish physicians; German and French physician preferences often differed from the preferences of physicians in the other three countries. Physicians' preferences indicate that they require higher efficacy (probability viral load is undetectable) for treatments with higher side-effect risks (renal dysfunction and fracture) but require somewhat less efficacy for treatments that had been studied for a longer time.

Acknowledgements

Conflicts of interest
There are no conflicts of interest.

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