Clinical Application of the GLOBE and United Kingdom-Primary Biliary Cholangitis Risk Scores in a Trial Cohort of Patients With Primary Biliary Cholangitis

Marco Carbone,[1,2*] Maren H. Harms,[3*] Willem J. Lammers,[3] Tonya Marmon,[4] Richard Pencek,[4] Leigh MacConell,[4] David Shapiro,[4] David E. Jones,[5] George F. Mells,[1**] and Bettina E. Hansen[3,6**]

The GLOBAL Primary Biliary Cholangitis (PBC) Study Group and United Kingdom-PBC (UK-PBC) Consortium have demonstrated that dichotomous response criteria are not as accurate as continuous equations at predicting mortality or liver transplantation in PBC. The aim of this analysis was to assess the clinical utility of the GLOBE and UK-PBC risk scores using data from POISE, a phase 3 trial investigating obeticholic acid (OCA) in patients with PBC. Data (N = 216) at baseline and month 12 were used to calculate the GLOBE and UK-PBC risk scores to assess the projected change in risk with OCA versus placebo. Additionally, the benefit of OCA was assessed in patients not meeting the POISE primary endpoint. Both the GLOBE and UK-PBC risk scores predicted a significant reduction in long-term risk of death and liver transplantation after OCA treatment ($P < 0.0001$). The differences in the relative risk reduction from baseline in the 10-year event risk after 1 year for OCA 10 mg versus placebo was 26% (GLOBE) and 37% (UK-PBC). The scores also predicted a significantly decreased risk in patients treated with OCA who did not meet POISE response criteria after 1 year of treatment compared to an increased risk with placebo ($P < 0.0001$). *Conclusion:* This analysis demonstrates the use of the GLOBE and UK-PBC risk scores to assess risk reduction of a cohort treated with OCA. While validation of this risk reduction in studies with clinical outcomes is needed, this study highlights the potential use of these scores in individualizing risk prediction in PBC both in clinical practice and therapeutic trials. (*Hepatology Communications* 2018;2:683-692)

In primary biliary cholangitis (PBC), progression of liver disease is highly variable.[1,2] In many cases, the disease is detected at an early stage and treatment with ursodeoxycholic acid (UDCA) improves biochemistry, impedes hepatic fibrosis, and can restore normal life expectancy.[3-5] However, in a substantial proportion of patients, the response to treatment with UDCA is inadequate. These patients experience progressive liver disease that may eventually lead to liver failure or hepatocellular carcinoma.[6] It is well established that the liver biochemistry on treatment with UDCA strongly predicts long-term outcomes in PBC.[7-11] The response to treatment with UDCA (so-called UDCA response) may therefore be defined in terms of the liver biochemistry measured at a specific time (usually 12 months) after starting

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LLN, lower limit of normal; ln, natural logarithm; LT, liver transplantation; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; UK-PBC Consortium, United Kingdom-PBC Consortium; ULN, upper limit of normal.

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**These authors contributed equally to this work.*
***These authors contributed equally to this work.*

treatment. Several definitions of the UDCA response have been proposed.[7-11] One of these definitions was the Toronto criteria, and a composite of Toronto along with other criteria were used to define treatment response criteria for POISE, a phase 3 trial of treatment with obeticholic acid (OCA) reported by Nevens et al.[12] By these criteria, response was defined as alkaline phosphatase (ALP) $<1.67 \times$ the upper limit of normal (ULN), $\geq$15% reduction in ALP, and total bilirubin $\leq$ULN.

For prognostication, definitions of UDCA response, such as the Toronto, Paris, Rotterdam, and Barcelona criteria, have two major limitations: first, they dichotomize UDCA response and thereby the long-term risk of death or liver transplantation (LT), whereas both are, in reality, a continuum; second, they do not account for the stage of disease. Two independent research groups, the Global PBC Study Group and the United Kingdom (UK)-PBC Consortium, developed and externally validated continuous prognostic models (the GLOBE score and UK-PBC risk score, respectively) that address these limitations.[13,14] These models include the liver biochemistry following treatment with UDCA as well as surrogate measurements of disease stage (e.g., serum albumin and platelet count). They estimate the risk of LT or death (overall death for the GLOBE score and liver-related death for the UK-PBC risk score) in patients with PBC at specific time points. Both scores outperformed previous response criteria[7-11,13,14] in terms of prognostic utility and could potentially help physicians identify patients at high risk of disease progression and in need of second-line therapy. They have also been validated in patients not treated with UDCA, strongly suggesting that such scoring systems reflect disease activity and stage expressed by the laboratory investigations, regardless of treatment. Recently published guidelines from the European Association for the Study of the Liver propose these criteria as tools to select patients for second-line therapies and possibly for a better design of clinical trials in PBC in the future.[15]

The aim of this study was to explore the utility of the GLOBE score and UK-PBC risk score in a trial data set comprising individual patient data from the phase 3 POISE trial of OCA. In addition, we use validated risk scores to evaluate the predicted risk reduction of OCA therapy in patients with PBC who inadequately respond to UDCA.

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ARTICLE INFORMATION:

From the [1]Academic Department of Medical Genetics, University of Cambridge, Cambridge, United Kingdom; [2]Division of Gastroenterology, University of Milan-Bicocca, Milan, Italy; [3]Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, the Netherlands; [4]Intercept Pharmaceutical, Inc., San Diego, CA; [5]Institute of Cellular Medicine, Newcastle University, Newcastle, United Kingdom; [6]Toronto Centre for Liver Disease, Toronto General Hospital, Toronto, ONT, Canada.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Bettina E. Hansen, M.Sc., Ph.D.
Toronto Centre for Liver Disease, Toronto General Hospital
200 Elizabeth Street
9th Floor Eaton Building, North Wing, Room 216 (9EB 216)
Toronto, ONT M5G 2C4, Canada
E-mail: bettina.hansen@utoronto.ca
Tel: +1-416-340-3111
Or

George Mells, M.B.B.S., Ph.D.
Academic Department of Medical Genetics
Box 238, Lv 6 Addenbrooke's Treatment Centre,
Addenbrooke's Hospital
University of Cambridge
Cambridge CB2 0QQ, United Kingdom
E-mail: gfm26@medschl.cam.ac.uk
Tel: +44 (0)1223 245151

Methods

STUDY POPULATION

The patient demographics and study design of the POISE trial were reported by Nevens and colleagues[12] (Table 1). Briefly, POISE was a phase 3, randomized, double-blind, placebo-controlled trial. PBC diagnosis was defined by American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines.[15,16] Patients were recruited across 13 countries. All patients were over 18 years old, met the study entry criteria of ALP $\geq$1.67 $\times$ ULN and/or total bilirubin >ULN but <2 $\times$ ULN, and had either been taking UDCA for at least 12 months or were unable to tolerate UDCA. A total of 216 patients were randomized and dosed (once daily) 1:1:1 to placebo, OCA 5-10 mg (patients were started on 5 mg of OCA and titrated up to 10 mg depending on tolerability/response to treatment),[12] or OCA 10 mg. The primary endpoint of the trial was defined as achieving a composite of ALP below 1.67 $\times$ ULN with at least a 15% reduction in ALP and total bilirubin at or below ULN after 12 months of OCA therapy (POISE trial criteria).

SCORES

GLOBE score

Derivation of the GLOBE score has been described in detail.[14] The derivation cohort consisted of 2,488 UDCA-treated patients. LT or all-cause mortality was considered as a composite clinical event. The final model, shown below, consisted of age at the beginning of UDCA therapy, total bilirubin after 12 months of treatment, ALP after 12 months of treatment, albumin after 12 months of treatment, and platelet count after 12 months of treatment. The final model is referred to as the GLOBE score that can be used to assess transplantation-free survival after 1 year of treatment. The score was validated in an independent cohort of 1,631 patients and was shown to accurately predict outcome (C statistic >0.80). Similar results were found when the score was validated in an untreated population, with a C statistic of 0.81. The GLOBE score has recently been validated externally.[17]

GLOBE score = 0.044378 $\times$ age at start of UDCA therapy + 0.93982 $\times$ ln(bilirubin $\times$ ULN at 1 year follow-up) + 0.335648 $\times$ ln(ALP $\times$ ULN at 1 year follow-up) − 2.266708 $\times$ albumin level $\times$ the lower limit of normal (LLN) at 1 year follow-up −0.002581 $\times$ platelet count per 10^9/L at 1 year follow-up +1.216865.

UK-PBC risk score

Derivation of the UK-PBC risk score has been described in detail.[13] The score was developed based on 1,916 UDCA-treated participants from the UK-PBC Research Cohort. The final model, shown below, consisted of the baseline albumin and platelet count as well as total bilirubin, transaminases, and ALP after 12 months of UDCA treatment. Linear predictors and baseline survivor functions were combined in equations to score the risk of an LT or liver-related death occurring within 5, 10, or 15 years. The risk score was validated in an independent cohort of 1,249 UDCA-treated participants from the UK-PBC Research Cohort. In the validation cohort, the 5-, 10-, and 15-year risk scores were highly accurate (C statistic >0.90). Similar results were found when the score was validated in an untreated population from the United Kingdom. The UK-PBC risk score has recently been validated externally.[17]

UK-PBC risk score = 1 – baseline survival function^ exp(0.0287854 $\times$ [ALP after 12 months of therapy $\times$ ULN – 1.722136304] – 0.0422873 $\times$ [{(ALT where this was available, otherwise AST, after 12 months of therapy $\times$ ULN/10)^–1} – 8.675729006] + 1.4199 $\times$ [ln{bilirubin after 12 months of therapy $\times$ ULN/10} + 2.709607778] – 1.960303 $\times$ [albumin at baseline $\times$ LLN – 1.17673001] – 0.4161954 $\times$ [platelet count at baseline $\times$ LLN –1.873564875]).

STATISTICAL ANALYSIS

Individual patient data at baseline and month 12 from the POISE trial were used to calculate both scores to compare the projected improvement in risk/survival after 1 year of OCA treatment versus placebo in patients enrolled in the POISE trial. The *P* value for comparing each OCA treatment to placebo is obtained using the rank analysis of covariance model with baseline value as a covariate. Individual baseline values were based on a mean of all available study evaluations prior to OCA treatment or placebo. In order to evaluate the change in risk using the GLOBE score, the participant's contemporaneous age was used in place of his or her age at the start of UDCA therapy. $P < 0.05$ was considered significant. All calculations represented were determined using SAS version 9.4.

TABLE 1. BASELINE DEMOGRAPHICS

	Placebo ± UDCA (n = 73)	OCA 5-10 mg ± UDCA (n = 70)	OCA 10 mg ± UDCA (n = 73)
Age, years	56 ± 10	56 ± 11	56 ± 11
Female, n (%)	68 (93)	65 (93)	63 (86)
Caucasian, n (%)	66 (90)	67 (96)	70 (96)
Weight, kg	70 ± 13	68 ± 13	71 ± 15
Body mass index, kg/m^2	26 ± 4	26 ± 5	26 ± 5
UDCA use, n (%)	68 (93)	65 (93)	67 (92)
Daily UDCA dose, mg/kg	15 ± 4	17 ± 5	16 ± 5
Duration PBC, years	8 ± 5	8 ± 6	9 ± 7

Data are mean ± SD where applicable.

Results

The demographic characteristics of the POISE trial cohort are reported in the original publication.[12] In summary, average (± SD) age was 56 ± 10 years, 91% of patients were female, and 94% Caucasian. The average age at time of PBC diagnosis was 47 ± 11 years, with 93% of patients receiving UDCA for >12 months prior to the beginning of the trial, with a mean daily dose of 16 ± 5 mg/kg. All three patient groups were generally well balanced, as shown in Table 1.

As reported by Nevens et al.,[12] there was a statistically significant reduction of the least squares mean values of ALP, ALT, and AST, both in the OCA 5-10-mg and the OCA 10-mg dose groups compared to the placebo group after 12 months of OCA treatment (Table 2). There was a statistically significant difference in mean total bilirubin level in both treatment groups compared to the placebo group after 12 months of treatment. No statistical differences were found in the albumin and platelet count between the three arms.

TABLE 2. LABORATORY MEASURES AT BASELINE AND 12 MONTHS

	Placebo ± UDCA (n = 73)	OCA 5-10 mg ± UDCA (n = 70)	OCA 10 mg ± UDCA (n = 73)
ALP (U/L)			
Baseline	327.5 (115.0)	325.9 (116.2)	316.34 (103.9)
12 months	321.3 (142.9)	219.5 (99.8)	192.3 (61.3)
Change from baseline	–14.4 (14.7)	–112.5 (14.4)†	–129.9 (14.6)†
AST (U/L)			
Baseline	48.8 (22.4)	52.3 (25.3)	50.5 (31.1)
12 months	51.6 (39.0)	39.5 (25.1)	36.4 (19.2)
Change from baseline	1.0 (4.2)	–13.0 (4.2)*	–15.0 (4.3)†
ALT (U/L)			
Baseline	56.0 (30.3)	61.6 (39.0)	56.3 (39.7)
12 months	52.8 (28.5)	39.0 (33.9)	32.1 (20.6)
Change from baseline	–5.0 (3.3)	–21.3 (3.3)†	–25.3 (3.4)†
Total bilirubin (μmol/L)			
Baseline	11.8 (7.2)	10.2 (5.5)	11.3 (6.6)
12 months	13.2 (8.7)	9.9 (4.8)	9.7 (4.7)
Change from baseline	2.0 (0.7)	–0.3 (0.7)*	–0.9 (0.7)†
Albumin (g/L)			
Baseline	42.8 (3.1)	43.0 (3.1)	43.7 (2.7)
12 months	41.8 (3.6)	42.7 (3.5)	43.1 (3.3)
Change from baseline	–1.2 (0.4)	–0.6 (0.4)	–0.9 (0.4)
Platelets (10^9/L)			
Baseline	223.6 (87.1)	224.8 (79.6)	232.9 (87.8)
12 months	222.5 (101.6)	225.4 (87.0)	228.5 (78.7)
Change from baseline	6.5 (8.4)	4.9 (8.2)	2.9 (8.5)
Patient age			
Baseline	55.5 (10.0)	55.8 (10.5)	56.2 (11.0)
12 months	56.3 (10.2)	56.6 (10.0)	56.2 (10.2)

Baseline and 12 months are mean (SD); change from baseline data are least squares mean (SE).
*$P < 0.01$, †$P < 0.0001$. The P value for comparing active treatments to placebo is obtained using an analysis of covariance model with the baseline value as a covariate and fixed effects for treatment and randomization strata factor.

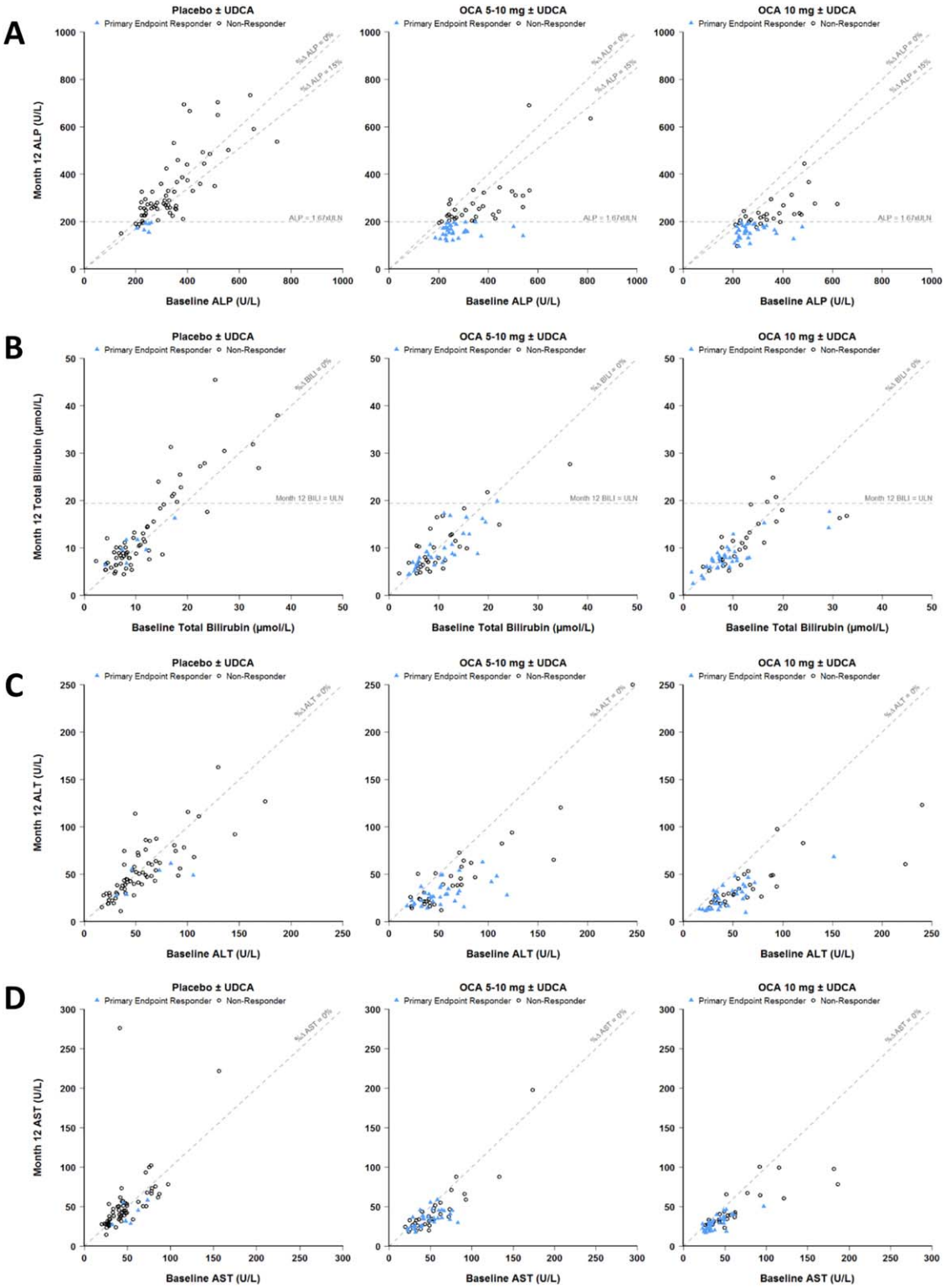

FIG. 1. Individual values in the biochemical components of the Globe and UK-PBC scores. (A) ALP (U/L). (B) Total bilirubin (μmol/L). (C) ALT (U/L). (D) AST (U/L). (E) Albumin (g/L). (F) Platelet count ($\times 10^9$/L). All patients were identified as having met the POISE primary response criteria or not. The diagonal line through each plot represents 0% change from baseline; in (A), a second diagonal line represents a 15% reduction.

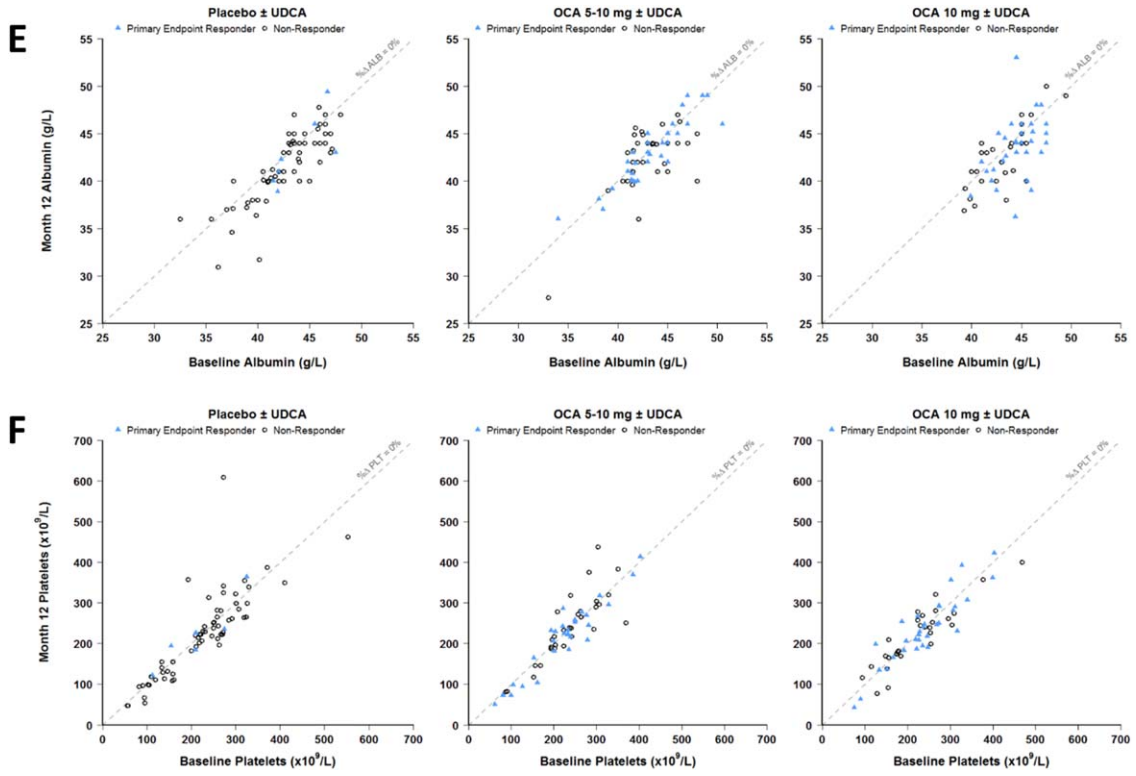

FIG. 1. Continued

Scatter plots showing changes in the laboratory measurements (included in the scores) after 12 months of treatment and their relationship with the primary composite endpoint (POISE criteria) used in the trial are shown in Fig. 1. Nearly all OCA-treated patients had a biochemical improvement in ALP, AST, and ALT, including those who did not meet the trial response criteria. No significant differences between

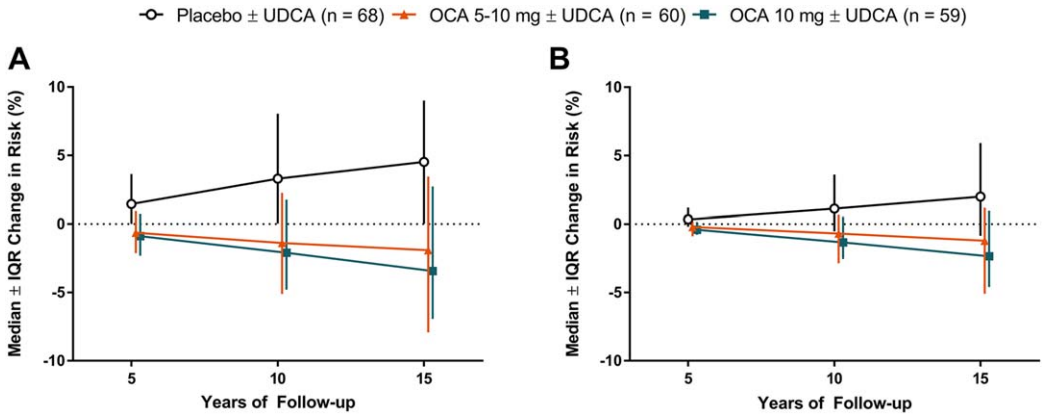

FIG. 2. Improvements in risk with the GLOBE score and UK-PBC risk score after 12 months of OCA treatment. Predicted median (Q1, Q3) change in risk from baseline with the (A) GLOBE score and (B) UK-PBC risk score. $P < 0.0001$ for all values in OCA treatment arms in both models. The P value for comparing active treatments to placebo is obtained using the rank analysis of covariance model with the baseline value as a covariate. Abbreviation: IQR, interquartile range.

TABLE 3. MEDIAN DIFFERENCE IN RISK BETWEEN PLACEBO AND OCA TREATMENT GROUPS AFTER 12 MONTHS OF TREATMENT

	Difference in Estimated Scores		Difference in Relative Risk Reduction From Baseline*	
	OCA 5-10 mg – Placebo (n = 60)	OCA 10 mg – Placebo (n = 59)	OCA 5-10 mg – Placebo (n = 60)	OCA 10 mg – Placebo (n = 59)
GLOBE score				
5 years	–2.34 (–3.49, –1.30)	–2.56 (–3.65, –1.57)	–26.94 (–38.03, –14.75)	–29.62 (–40.69, –18.82)
10 years	–5.15 (–7.43, –2.92)	–5.67 (–7.72, –3.53)	–23.51 (–33.49, –12.75)	–25.78 (–35.64, –16.60)
15 years	–6.83 (–9.94, –3.81)	–7.38 (–10.19, –4.74)	–20.20 (–28.97, –10.69)	–22.02 (–30.35, –13.85)
UK-PBC risk score				
5 years	–0.80 (–1.22, –0.40)	–0.87 (–1.26, –0.53)	–33.65 (–49.64, –17.39)	–39.05 (–54.44, –23.76)
10 years	–2.47 (–3.70, –1.26)	–2.69 (–3.85, –1.68)	–32.18 (–47.87, –16.74)	–37.24 (–52.48, –22.96)
15 years	–4.06 (–6.20, –2.14)	–4.58 (–6.52, –2.83)	–30.64 (–45.81, –15.83)	–35.59 (–49.94, –21.66)

$P < 0.0001$ for all values in OCA treatment arms in both models. The P value for comparing active treatments to placebo is obtained using the rank analysis of covariance model with the baseline value as a covariate. All values are medians (95% confidence interval).
*Relative differences are based on median differences in percentage change from baseline between placebo and OCA.

OCA and placebo were observed in change from baseline for albumin or platelet count.

Baseline and 12-month POISE data were used to calculate the GLOBE score and UK-PBC risk score. Complete biochemical data at 12 months were available for 68, 60, and 59 patients in the placebo, OCA 5-10-mg, and OCA 10-mg treatment groups, respectively. After 12 months of treatment with OCA ± UDCA, both scores showed reductions in median risk. Assessment of the change in 5-, 10-, and 15-year event risk associated with OCA is shown in Fig. 2. The comparisons between OCA and placebo arms on the reduction of event risk achieved statistical significance for both OCA dosages across all time points ($P < 0.0001$). Both models predicted improvements in long-term (liver-related and all-cause) risk of mortality or LT after OCA treatment. Furthermore, both models predicted increased risk over time in patients receiving placebo for 1 year, despite 93% of patients receiving concomitant UDCA, the current standard of care for PBC. While both scores showed improvements in projected risk reductions for the OCA treatment groups, the GLOBE score tended to indicate greater worsening in projected risk after 1 year of the placebo group compared with risk predicted by the UK-PBC risk score. Using the GLOBE score, the differences in relative risk reduction from baseline in LT or all-cause mortality after 5, 10, and 15 years between OCA 5-10 mg and placebo were 26.9%, 23.5%, and 20.2%, respectively (Table 3). Comparing the difference between OCA 10 mg and placebo, the relative risk reductions were 29.6%, 25.8%, and 22.0%, respectively. Applying the UK-PBC risk score, the differences in relative risk reductions from baseline between OCA 5-10 mg and placebo of LT or liver-related death after 5, 10, and 15 years were 33.7%, 32.2%, and 30.6%, respectively. The differences in relative risk reduction between OCA 10 mg and placebo were 39.1%, 37.2%, and 35.6%, respectively.

Previous studies have demonstrated that patients who are diagnosed with PBC at younger ages may be less likely to respond to UDCA therapy.[2] The change in risk following OCA treatment in both scores was assessed above and below the median age of diagnosis (48 years) in POISE (Supporting Fig. S1). Both subgroups showed a change in risk consistent with the total POISE cohort. Patients treated with OCA and diagnosed before the age of 48 years showed a significant reduction ($P < 0.01$) in risk across all estimated time points with the GLOBE score and UK-PBC risk score in contrast to an increase in risk in placebo-treated patients (Supporting Fig. S1A,B). Similarly, patients diagnosed after the age of 48 or older had significant reductions in projected risk with OCA treatment ($P < 0.01$) with both scores compared to an increase in risk with placebo (Supporting Fig. S1C,D).

Finally, we explored the change in risk for the subgroup of patients classified as inadequate responders to OCA therapy at 12 months. The median change in risk in patients not meeting the POISE primary endpoint after 12 months of OCA, which requires ALP below 1.67 × ULN with at least a 15% reduction in ALP and total bilirubin at or below ULN, is shown in Fig. 3. Patients who did not meet the POISE response criteria at month 12 had significant improvements in estimated risk at 5, 10, and 15 years with both scores compared to placebo ($P < 0.01$). We also evaluated the change in risk for patients classified as nonresponders by alternative response criteria, including Paris, Rotterdam, Toronto, and Barcelona. For

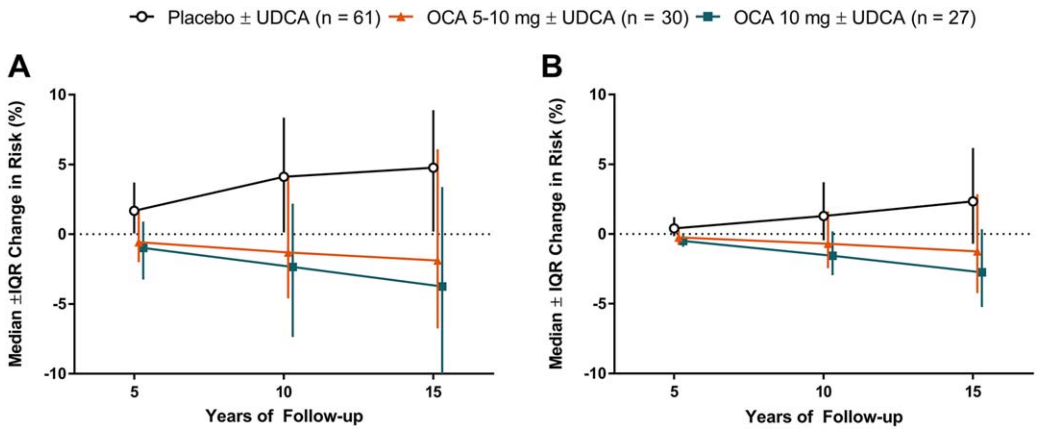

FIG. 3. Risk improvement in OCA nonresponders with the GLOBE score and UK-PBC risk score after 12 months of OCA therapy. Predicted median (Q1, Q3) change in risk from baseline with the (A) GLOBE score and (B) UK-PBC risk score. $P < 0.01$ for all values in OCA treatment arms in both models. The P value for comparing active treatments to placebo is obtained using the rank analysis of covariance model with the baseline value as a covariate. Abbreviation: IQR, interquartile range.

patients who had an inadequate response by these criteria, we report the median change in projected risk following 12 months of treatment as well as median baseline risk for context. Patients classified as nonresponders by these criteria showed significant improvements in estimated event risk at 5, 10, and 15 years with both scores after 1 year of OCA treatment compared to placebo in most cases (Supporting Table S1).

Discussion

In this analysis, we quantified the projected risk–benefit of OCA treatment in patients with PBC who inadequately responded or were intolerant to UDCA by applying liver biochemistry data from the phase 3 POISE trial to both the GLOBE score and UK-PBC risk score. Our findings promote the utility of such scoring systems in a clinical trial setting. Moreover, these results shed further light on the nature and scale of benefit from OCA treatment as demonstrated in the POISE trial by Nevens et al.[12]

Our analysis has two major conclusions. The first is that while the dichotomous POISE trial criteria accurately stratify patients into those at low or high risk of clinical outcomes, the GLOBE score and UK-PBC risk score enable the anticipated survival benefit for PBC patients treated with OCA to be quantified. This is an important step forward in assessing the effectiveness of OCA therapy and other potential new therapies for PBC.

The second conclusion is that the use of dichotomous response criteria in the POISE trial may underestimate therapeutic benefit. This finding is aligned with those presented in the studies in which the GLOBE score and UK-PBC risk score were developed and validated as well as with the results from a Chinese study validating this in a long-term follow-up cohort.[18] These studies all reported that the GLOBE score and UK-PBC risk score were superior in identifying patients with inadequate treatment response when compared to dichotomous response criteria in populations of patients with PBC that were treated with UDCA monotherapy.[13,14] Importantly, we found OCA treatment to be associated with a significant benefit of projected survival, even in patients not reaching the threshold for response by the original POISE criteria and other well-known dichotomous response criteria. This is a result of the inability of the trial criteria to take into account high baseline levels of ALP and/or total bilirubin and subsequent improvements in these markers, which were robust but did not meet the thresholds defined by the primary endpoint. For example, patients with highly elevated ALP levels at baseline (i.e., the highest risk group, in greatest need of improvement) were less likely to meet the dichotomous response criteria even when a substantial reduction of ALP and/or total bilirubin was seen. The therapeutic benefit overlooked by using the dichotomous trial criteria not only implies an underestimation of efficacy but could also impact future treatment options for the most severely affected patients,

especially given the current cost–utility analysis of OCA as measured by the incremental cost-effectiveness ratio threshold that may not be applicable to a rare disease.[19]

In this analysis, we observed differences in the projected risks between the GLOBE score and the UK-PBC risk score. These differences are most likely explained by the different endpoints used in the two scores; the GLOBE score takes into account LT and all-cause mortality while the UK-PBC risk score considers LT and liver-related death. Consequently, as the GLOBE score considers all causes of death, the baseline risk of an endpoint is higher using the GLOBE score. Likewise, the risk of all-cause mortality increases faster over time (with aging) than the risk of liver-related death and therefore shows a steeper trajectory of risk for the GLOBE score.

We acknowledge that the two scoring systems were developed to predict adverse outcome in patients taking UDCA. Neither score was validated in patients taking OCA. We believe the scores are applicable in the current context, however, because both were validated in cohorts of patients who had not received treatment with UDCA. Nevertheless, neither score can identify effects of OCA independent of those reflected by changes in liver biochemistry on treatment. In addition, we acknowledge the limitation that both scores depend on endpoints that are surrogates for clinical outcomes. Although these surrogate endpoints for outcome are likely to be accurate, other factors, such as toxicity or other adverse events, should not be overlooked when evaluating risks and benefits of new therapeutic agents. Therefore, the accuracy of predictions in the current analysis await confirmation by the ongoing phase 4 trial of OCA evaluating clinical outcomes in patients with PBC (COBALT; NCT02308111).[20] This analysis showed a median reduction in the 10-year event risk of 2.1% using the GLOBE score and 1.3% using the UK-PBC risk score after 12 months of treatment with OCA 10 mg compared to a median increase of 3.3% (GLOBE) and 1.1% (UK-PBC) after 12 months of placebo. This represents a difference in relative risk reduction from baseline between OCA 10 mg and placebo of 25.8% with the GLOBE score and 37.2% with the UK-PBC risk score. However, we emphasize that this is a selected trial cohort. In a real-life population with more advanced or aggressive disease, the impact of this new treatment might be different. Importantly, transient elastography is not included in either of the scores. Despite the prognostic value of transient elastography,[21-23] a great advantage of both presented risk scores in our study is that they are able to predict outcomes accurately based on readily available biochemical parameters and without the need for a dedicated instrument and skilled operator required for transient elastography.

In conclusion, we found that 1 year of OCA therapy was projected by both scores to reduce the risk of death and LT in this patient population, including patients not meeting the dichotomous POISE primary endpoint. We believe that the application of the GLOBE score and UK-PBC risk score in clinical practice would be an important step toward individualizing risk prediction in PBC and may eventually replace the use of other dichotomous therapy response criteria in clinical practice.

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Author names in bold designate shared co-first authorship.

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