IMPACT OF RACE/ETHNICITY ON EFFICACY AND SAFETY OF TWO STARTER INSULIN REGIMENS IN PATIENTS WITH TYPE 2 DIABETES: A POSTHOC ANALYSIS OF THE DURABLE TRIAL

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Objective: To explore the impact of race/ethnicity on efficacy and safety of twice-daily insulin lispro mix 75/25 (LM75/25; 75% lispro protamine suspension, 25% insulin lispro) and once daily insulin glargine (GL).

Design, Setting, Patients: More than 2,000 Patients with type 2 diabetes enrolled in the 24-week initiation phase of the DURABLE Trial.

Main Outcome Measures: Efficacy and safety variables at endpoint, including hemoglobin A1c (HbA1c), self-monitored plasma glucose (SMPG), and hypoglycemia, in each racial/ethnic group were compared to Caucasians within treatment groups.

Results: Asian patients had less (LM75/25: −1.46%, $P<.01$; GL: −1.25%, $P<.01$) and Hispanic patients had greater (LM75/25: −2.17%) HbA1c reduction from baseline vs Caucasian patients (LM75/25: −1.84%; GL: −1.78%). Fewer Asian (LM75/25: 20%, $P<.001$; GL: 22%, $P<.001$) and Hispanic patients (LM75/25: 40%, $P<.01$) reached HbA1c target (<7%) vs Caucasian patients (LM75/25: 53%; GL: 44%). Fasting plasma glucose was similar among groups, postprandial glucose (PPG) with GL was lower for African patients post-breakfast and post-dinner and higher for Asian patients post-lunch. Only PPG with LM75/25 was lower for Hispanic patients post-breakfast. Weight gain was lower in Asian patients (LM75/25). Insulin dose was higher for Asian (LM75/25 and GL) and lower for African patients (GL). Hypoglycemia rate was lower for Asian (LM75/25 and GL) and Hispanic patients (LM75/25).

Conclusions: There were significant efficacy and safety differences among racial/ethnic groups in the DURABLE trial. These differences may be important in designing insulin based treatment plans. (*Ethn Dis*. 2013;23[4]:393–400)

Key Words: Type 2 Diabetes, Race, Ethnicity, Insulin

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INTRODUCTION

Type 2 diabetes mellitus (T2D), a major chronic disease, affecting more than 300 million people worldwide and projected to increase to more than 550 million worldwide by 2030,[1] disproportionately affects racial and ethnic minority groups. Data from the 2003–2006 cohort of the National Health and Nutrition Examination Survey demonstrated that prevalence was more than 2 times higher in non-Hispanic Blacks and Mexican Americans vs non-Hispanic Whites for diagnosed, undiagnosed, and total diabetes in the United States.[2] A posthoc analysis of pooled data from 11 multinational clinical trials of patients with T2D revealed significantly different metabolic responses between racial/ethnic groups, dependent in part on insulin type and regimen intensity.[3]

Variation in the safety and efficacy of insulin regimens by race/ethnicity is an underexplored area. Most insulin clinical trials to date have been conducted in populations where the majority of patients are Caucasian resulting in a paucity of information regarding clinically meaningful differences in efficacy and safety outcomes between individuals of different self-identified race/ethnicity with T2D.

The Assessing the Durability of Basal Versus Lispro Mix 75/25 Insulin Efficacy (DURABLE) trial enrolled a large, diverse cohort of patients, and the primary objective was to compare the efficacy, safety, and durability of 2 starter insulin regimens in patients with T2D.[4] This study, which enrolled patients from 11 countries, provides a unique opportunity to assess the patterns of baseline characteristics and efficacy and safety outcomes according to race/ethnicity in an insulin clinical trial in patients with T2D.

The objective of our study was to explore potential differences in clinically important outcomes of insulin therapy according to race/ethnicity. Thus we explored the baseline characteristics of patients and the efficacy and safety of twice-daily insulin lispro mix 75/25 (LM75/25; 75% lispro protamine suspension, 25% insulin lispro) and once daily insulin glargine (GL) in patients

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with T2D enrolled in the 24-week initiation phase of the DURABLE trial.

METHODS

Study Design

This study was a posthoc analysis of data from the DURABLE trial initiation phase. A detailed description of the DURABLE study design has been previously published.[4,5] Briefly, the DURABLE trial was a randomized, open-label, parallel, 30-month trial conducted in 11 countries (Argentina, Australia, Brazil, Canada, Greece, Hungary, India, Romania, Spain, The Netherlands, and the United States). The trial enrolled insulin-naïve patients with T2D aged ≥30 to <80 years, with hemoglobin A1c (HbA1c) > 7.0%, on at least 2 oral antihyperglycemic medications (OAMs): ≥1500 mg/day metformin (MET); at least one-half maximal daily dose sulphonylurea (SU), or thiazolidinedione (TZD [≥30 mg/day pioglitazone or ≥4 mg/day rosiglitazone]). In the 24-week initiation phase,[4] patients were randomized 1:1 to a twice-daily LM75/25 or GL once daily, both in combination with prestudy OAMs. The minimum starting dose was 10 units twice daily for LM75/25 and 10 units once daily for GL. Insulin dose adjustments were made to achieve a target HbA1c goal of ≤6.5%, utilizing regimen specific, insulin dose titration algorithms.[4,6,7] After the 24-week initiation phase, patients with HbA1c ≤7.0% were followed for up to an additional 24 months (maintenance phase)[8] to evaluate how long the HbA1c goal could be maintained (the HbA1c goal was either HbA1c ≤7.0% or HbA1c >7.0%, but increased <.4% from last HbA1c ≤7.0%). Hypoglycemia was recorded any time a patient experienced symptoms of hypoglycemia or had a self-monitored plasma glucose (SMPG) ≤70mg/dL (3.9 mmol/L), and an event was deemed severe if the patient required assistance. Hemoglobin A1c was measured at a central laboratory, and SMPG measurements were performed using Roche Active or Roche Aviva meters.

Patient Characteristics

At study entry, patients self-reported racial/ethnic origin based on the following categories: Caucasian (European, Mediterranean, Middle Eastern); Black (African descent); Hispanic (Mexican American, Mexico, Central and South America); Western Asian (Pakistani, Indian Subcontinent); East/Southeast Asian (Myanmarese, Chinese, Japanese, Korean, Mongolian, Vietnamese) and other (mixed-racial parentage, American Indian, Inuit). East and West Asian groups were combined as Asian for racial/ethnic analyses. The self-reported racial/ethnic origin does not indicate current residence in the country of origin. Baseline characteristics were recorded for all participants on day one of study; these included: age, sex, body weight (kg), BMI, diabetes duration (years), HbA1c (%), fasting blood glucose (FBG, mg/dl), and concomitant OAMs.

Statistical Methods

The descriptive information for baseline characteristics is presented as percentages and mean ± SD, for endpoint values as least squares (LS) mean ± SE. Means were compared between Caucasian and other racial/ethnic groups using analysis of variance. For continuous variables, the Dunnett's test was used for pairwise comparisons of each racial/ethnic group to the Caucasian group adjusting for multiple comparison. Categorical variables were compared with the Fisher exact test. Change in HbA1c from baseline to endpoint, endpoint insulin dose, weight change, 7 point SMPG profile, and hypoglycemia rates were compared using analysis of covariance. Treatment, baseline value (if applicable), and stratification variables (country, TZD use, and SU use) were included in the model. All the analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Patient Characteristics

A comparison of baseline characteristics by racial/ethnic groups within each treatment arm is given in Table 1. All groups were younger than Caucasians except for Black patients in the LM75/25 arm. Asians had lower weight and body mass index (BMI) in both treatment arms, higher HbA1c (LM75/25), shorter duration of T2D, more females and lower fasting blood glucose (GL). Compared with Caucasians, Hispanic patients had lower weight, a greater percentage of females in both treatment arms, lower BMI (LM75/25). Compared with Caucasians, Black patients had a greater percentage of females (LM75/25).

A greater percentage of Black patients used a combination of 3 OAMs, whereas a smaller percentage used a combination of 2 OAMs compared with Caucasians (GL). In both treatment arms, the SU/MET combination was used by a smaller percentage of Black patients compared with Caucasians. The TZD/MET combination was used by a greater percentage of Black patients compared with Caucasians (GL), whereas, in both treatment arms, the TZD/MET combination was used by significantly fewer Asians compared with Caucasians. The SU/TZD combination was used by a greater percentage of Black patients compared with Caucasians (LM75/25).

Changes in Body Weight, BMI and Insulin Dose During the Trial

Weight gain was lower in Asians compared with Caucasians (LM75/25: 2.6 ± .3 kg vs 3.6 ± .2 kg; $P<.05$) (Table 2). Weight gain was similar across other racial/ethnic groups within

Table 1. Baseline characteristics of the DURABLE trial population by race/ethnicity and by treatment arm

	GL					LM75/25				
	C	B	A	H	O	C	B	A	H	O
Characteristic	(*n*=668)	(*n*=70)	(*n*=163)	(*n*=116)	(*n*=29)	(*n*=651)	(*n*=62)	(*n*=157)	(*n*=136)	(*n*=39)
Age, years	58 ± 10	53 ± 10[c]	53 ± 9[c]	54 ± 10[c]	53 ± 9[a]	59 ± 9	56 ± 11	53 ± 9[c]	53 ± 10[c]	55 ± 9[a]
Sex, n(%)										
Female	288(43)	33(47)	90(55)[b]	68(59)[b]	15(52)	280(43)	37(60)[a]	81(52)	75(55)[a]	20(51)
Male	380(57)	37(53)	73(45)[b]	48(41)[b]	14(48)	371(57)	25(40)[a]	76(48)	61(45)[a]	19(49)
Weight, kg	93 ± 20	95 ± 21	69 ± 15[c]	85 ± 17[c]	85 ± 20	94 ± 20	94 ± 20	70 ± 14[c]	84 ± 20[c]	88 ± 21
BMI, kg/m^2	33 ± 6	33 ± 6	27 ± 5[c]	32 ± 6	31 ± 6	33 ± 6	33 ± 6	27 ± 5[c]	31 ± 6[a]	32 ± 6
Diabetes duration, years	10 ± 6	8 ± 7	8 ± 6[b]	10 ± 6	8 ± 5	10 ± 6	9 ± 8	9 ± 6	10 ± 6	13 ± 8[a]
HbA1c, %	9.0 ± .1	9.0 ± .2	9.1 ± .1	9.2 ± .1	9.6 ± .2[a]	8.9 ± .1	9.1 ± .17	9.3 ± .1[b]	9.6 ± .1[b]	9.8 ± .2[b]
FBG, mg/dL	200 ± 2	184 ± 7	186 ± 4[a]	195 ± 5	216 ± 11	193 ± 2	183 ± 7	193 ± 4	196 ± 5	204 ± 9
Concomitant OAMs, n(%)										
Patients with 3 drugs	138(21)	22(31)[a]	37(23)	23(20)	5(17)	146(22)	20(32)	30(19)	32(24)	5(13)
Patients with 2 drugs	522(78)	48(69)[a]	125(77)	93(80)	24(83)	499(77)	42(68)	127(81)	104(77)	34(87)
SU/MET	420(63)	31(44)[b]	116(71)	77(66)	21(72)	417(64)	27(44)[b]	113(72)	83(61)	34(87)[b]
TZD/MET	53(8)	12(17)[a]	0(0)[c]	10(9)	3(10)	53(8)	7(11)	4(3)[a]	17(13)	0(0)
SU/TZD	49(7)	5(7)	9(6)	6(5)	0(0)	29(5)	8(13)[a]	10(6)	4(3)	0(0)

Data are presented as percentages or absolute mean ± SD.

B, Black (African-descent); A, Asian; BMI, body mass index; C, Caucasian; FBG, fasting blood glucose; GL, once-daily insulin glargine; H, Hispanic; LM75/25, twice-daily insulin lispro mix 75/25 (LM75/25; 75% lispro protamine suspension, 25% insulin lispro); MET, metformin; O, other; OAM, oral antihyperglycemic medication; SU, sulphonylurea; TZD, thiazolidinedione.

For continuous variables, *P*s are from pairwise comparisons of each racial/ethnic group to the Caucasian group using Dunnett's test; for categorical variables, *P*s are from pairwise comparisons of each racial/ethnic group to the Caucasian group using Fisher exact test.

[a] $P<.05$.

[b] $P<.01$.

[c] $P<.001$.

each treatment arm. There was no change in BMI during the trial in any group.

Daily insulin dose of GL was lower among Asian and Black patients, but the GL insulin dose (U/kg) was higher for Asian and lower for Black patients compared with Caucasians (Table 2). Daily insulin dose of LM75/25 was similar across race/ethnicities, but the LM75/25 insulin dose (U/kg) was higher among Asians versus Caucasians. Change in HbA1c by insulin dose was lower among Asians compared with Caucasians in both treatment arms.

Glycemic Control and Hypoglycemia during the Trial

Endpoint fasting plasma glucose (FPG) levels were similar across groups in both arms (Table 3). However, differences in post-meal glycemic excursion were observed when the ethnicities were compared with Caucasians. Black

Table 2. Body weight and insulin dose at endpoint

	GL					LM75/25				
Characteristic	C	B	A	H	O	C	B	A	H	O
Weight change from baseline, kg	2.5 ± .2	2.3 ± .5	2.0 ± .3	2.5 ± .4	5.4 ± .7[b]	3.6 ± .2	3.7 ± .5	2.6 ± .3[a]	4.5 ± .4	4.4 ± .6
Daily insulin dose, U	37.6 ± .8	29.7 ± 2.7[a]	32.4 ± 1.7[a]	36.9 ± 2.0	40.9 ± 4.1	43.2 ± .9	37.1 ± 2.8	45.1 ± 1.8	41.2 ± 1.9	40.7 ± 3.5
Insulin dose, U/kg	.39 ± .01	.31 ± .03[a]	.47 ± .02[b]	.43 ± .02	.45 ± .04	.44 ± .01	.40 ± .03	.63 ± .02[b]	.48 ± .02	.45 ± .04
HbA1c change/ insulin dose	−6.1 ± .3	−6.3 ± .9	−4.5 ± .6[a]	−5.2 ± .6	−7.2 ± 1.3	−5.1 ± .2	−5.1 ± .9	−3.3 ± .5[b]	−5.1 ± .6	−6.4 ± 1.0

Data are presented as absolute LS mean ± SE (LS mean) at endpoint.

B, Black(African-descent); A, Asian; C, Caucasian; GL, once-daily insulin glargine; H, Hispanic; LM75/25, twice-daily insulin lispro mix 75/25 (LM75/25; 75% lispro protamine suspension, 25% insulin lispro); O, other.

For continuous variables, *P*s are from pairwise comparisons of each racial/ethnic group to the Caucasian group using Dunnett's test.

[a] $P<.05$.

[b] $P<.01$.

Although both regimens resulted in HbA1c reductions, some important treatment differences were observed across races/ethnicities.

patients had lower glycemic excursion after the AM and PM meals while Asians demonstrated greater noontime post-meal excursion (GL), and Hispanic patients demonstrated lower post AM meal excursion (LM75/25). Compared to Caucasians, Asians had higher HbA1c (LM 75/25) and more Asian females had lower fasting glucose levels (LM 75/25). Hispanic patients had higher HbA1c (LM75/25) compared to Caucasians.

In both treatment arms, Asians had less HbA1c reduction from baseline (LM75/25: −1.46 ± .11%; GL: −1.25 ± .10%, $P<.01$ vs Caucasian) at endpoint (Fig. 1). HbA1c reduction was greater for Hispanic patients (LM75/25: −2.17 ± .12; $P<.05$ vs Caucasian) (Fig. 1). In both treatment arms, fewer Asians vs Caucasians reached HbA1c target (LM75/25: 20% vs 53%, $P<.001$; GL: 22% vs 44%, $P<.001$); whereas in the LM75/25 arm only, fewer Hispanic patients vs Caucasians reached HbA1c target (40% vs 53%, $P<.01$) (Fig. 2). There was no difference in HbA1c reduction between Blacks and Caucasians.

Compared with Caucasians, the hypoglycemia rate was lower for Asians in both arms, and lower for Hispanic patients in the LM75/25 arm (Table 4). In both treatment arms, compared with Caucasians, the overall incidence of hypoglycemia was lower in Black, Asian, and Hispanic patients compared with Caucasians. Nocturnal hypoglycemia incidence was lower for Asians in both treatment arms. Severe hypoglycemia incidence was rare and similar across groups within each treatment arm.

DISCUSSION

Our analysis examined variation in efficacy and safety of two starter insulin regimens, LM 75/25 and GL in a large, ethnically diverse cohort of patients with T2D. Although both regimens resulted in HbA1c reductions, some important treatment differences were observed across races/ethnicities.

At baseline, all groups but Blacks were younger than Caucasians. The difference in age likely reflects a younger presentation of diabetes. Lower weight and BMI in Asians are expected based on previously published demographics;[9] however, it is interesting that this group had a higher HbA1c despite a lower fasting glucose, and a shorter duration of T2D. This finding is indirectly supported by the literature. It has been noted that at the same BMI, Asians have more than double the risk of developing T2D than Whites; Hispanics and Blacks also had a higher risk of diabetes than Whites, but to a lesser degree.[10] It is possible that the lower fasting blood glucose and shorter duration of diabetes influenced clinicians to take a more conservative stance in dosing insulin due to concerns of inducing hypoglycemia. Compared with Caucasians, all ethnicities had a greater percentage of females in both treatment arms. Studies suggest that females are more likely than males to seek medical attention.[11]

Patterns of use in OAMs demonstrate a greater percentage of Black patients using combination of 3 OAMs, whereas a smaller percentage used a combination of 2 OAMs compared with Caucasians. Use of 3 OAMs may reflect a need for more rigorous treatment to achieve blood glucose control. Differences in the combinations of OAMs (SU/MET or TZD/MET) seen between Caucasians and other ethnicities may simply reflect practitioner preference.

Weight gain with insulin treatment is a concern for patients with T2D. This concern has been confirmed by several, large, prospective studies, such as the UKPDS. In the UKPDS, most patients gained weight over the study period, but patients who were assigned to insulin

Table 3. Plasma glucose profiles at endpoint

Characteristic	GL					LM75/25				
	C	B	A	H	O	C	B	A	H	O
FPG, mg/dL	120 ± 1	124 ± 5	124 ± 3	123 ± 3	124 ± 7	134 ± 1	122 ± 5	139 ± 3	129 ± 3	130 ± 6
AM 2-hr excursion, mg/dL	52 ± 2	32 ± 6[b]	58 ± 4	42 ± 4	52 ± 9	35 ± 2	28 ± 7	40 ± 4	21 ± 4[a]	35 ± 8
Noon 2-hr excursion, mg/dL	30 ± 2	31 ± 6	40 ± 3[a]	37 ± 4	34 ± 9	39 ± 2	24 ± 6	43 ± 4	28 ± 4	32 ± 7
PM 2-hr excursion, mg/dL	36 ± 2	18 ± 6[a]	34 ± 3	30 ± 4	35 ± 8	20 ± 2	8 ± 6	26 ± 4	11 ± 4	18 ± 7

Data are presented absolute LS mean ± SE (LS mean) at endpoint.

B, Black (African descent); A, Asian; C, Caucasian; FPG, fasting plasma glucose; GL, once-daily insulin glargine; H, Hispanic; LM75/25, twice-daily insulin lispro mix 75/25 (LM75/25; 75% lispro protamine suspension, 25% insulin lispro); O, other.

For continuous variables, *P*s are from pairwise comparisons of each racial/ethnic group to the Caucasian group using Dunnett's test.

[a] $P<.05$.

[b] $P<.01$.

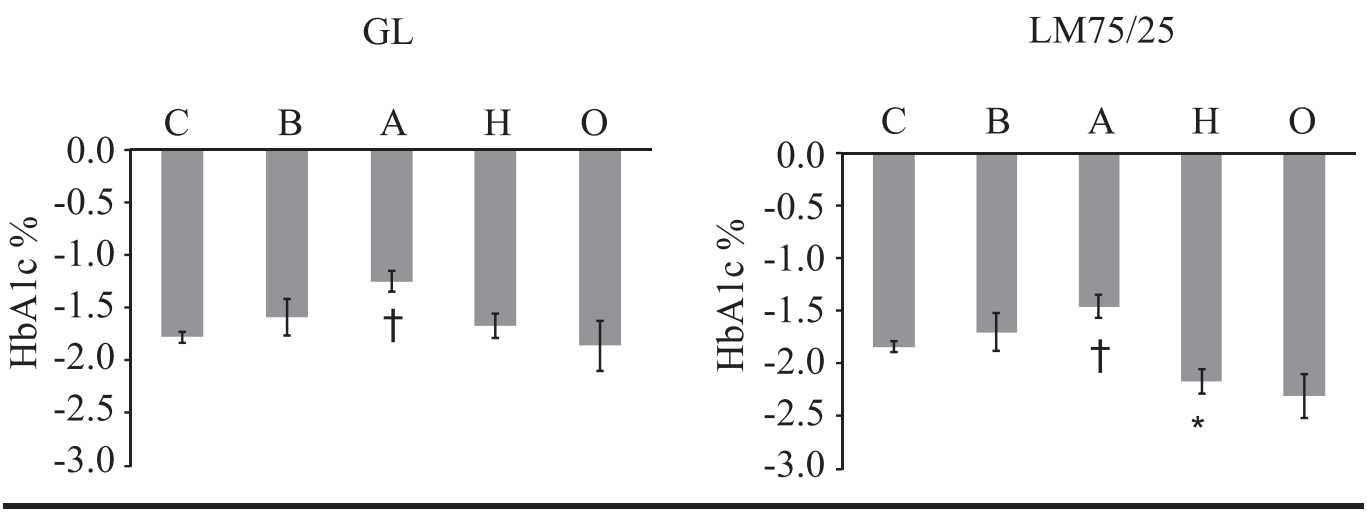

Fig 1. Change in HbA1c (%) from baseline to endpoint by race/ethnicity and by treatment arm. Abbreviations in this figure include: B, Black (African descent); A, Asian (mix of East, Southeast and Western Asians); C, Caucasian; GL, once-daily insulin glargine; H, Hispanic; LM75/25= twice-daily insulin lispro mix 75/25 (LM75/25; 75% lispro protamine suspension, 25% insulin lispro); O, other. *$P<.05$ vs C, †$P<.01$ vs C

therapy gained the most weight in the shortest period of time.[12] Because the majority of patients with T2DM are already overweight, the weight gain associated with insulin therapy may delay insulin initiation. In addition, weight gain itself may have deleterious metabolic and health consequences. The cardiovascular risk profile and obesity are often positively correlated.[13] In our retrospective analysis, we found that weight gain was similar between Caucasians, Blacks and Hispanics within each treatment arm and remained so when corrected for baseline. Despite Asians having lower weight gain with insulin treatment, the percent weight gain was similar after correcting for baseline weight. However, this finding in Asians may be especially significant as increases in weight over time have been found to be more harmful in Asians than in the other ethnic groups.[14] Studies have reported that for every 11 pounds Asians gain as adults, they increase their risk of T2D by 84 percent.[10] Hispanics, Blacks, and Whites who gained weight also had higher diabetes risks, but to a lesser degree than Asians.[10] Several other studies have found that at the same BMI, Asians have higher risks of comorbidities such as hypertension and cardiovascular disease than Whites.[15,16]

Daily insulin use of GL was lower among Asian and African patients, but

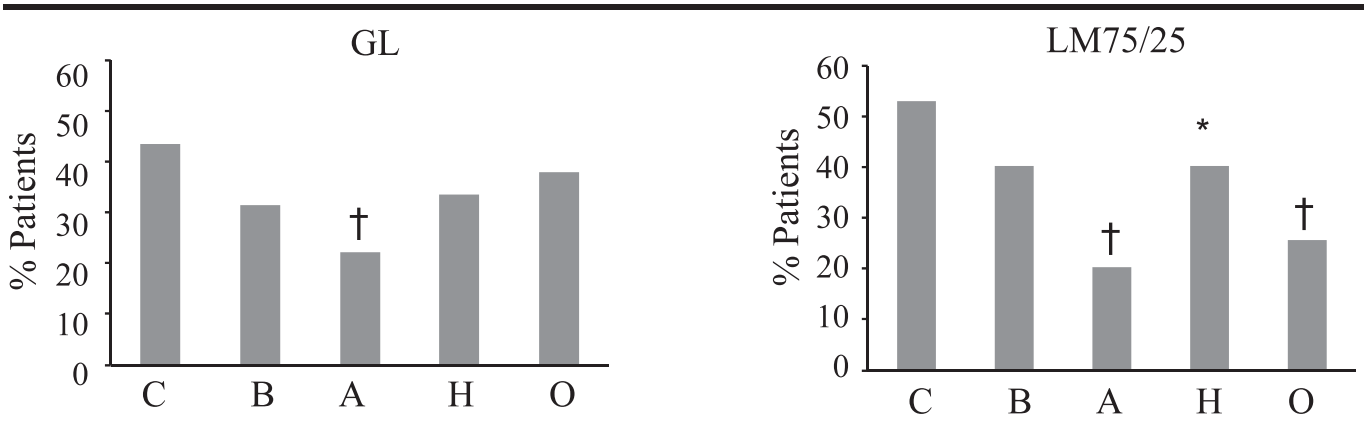

Fig 2. Percentage of patients achieving HbA1c target <7% at endpoint by race/ethnicity and by treatment arm. Abbreviations in this figure include: B, Black (African descent); A, Asian (mix of East, Southeast and Western Asians); C, Caucasian; GL, once-daily insulin glargine; H, Hispanic; LM75/25= twice-daily insulin lispro mix 75/25 (LM75/25; 75% lispro protamine suspension, 25% insulin lispro); O, other. *$P<.01$ vs C, †$P<.001$ vs C

Table 4. Hypoglycemia at endpoint

Characteristic	GL					LM75/25				
	C	B	A	H	O	C	B	A	H	O
Overall hypoglycemia rate[d]	23 ± 1	21 ± 4	15 ± 2[b]	20 ± 3	25 ± 6	33 ± 1	26 ± 5	17 ± 3[b]	22 ± 3[a]	38 ± 6
Nocturnal hypoglycemia rate[d]	13 ± 1	8 ± 3	8 ± 2	9 ± 2	14 ± 5	9 ± 1	9 ± 3	7 ± 2	10 ± 2	14 ± 3
Overall severe hypoglycemia rate[d]	.04 ± .01	.07 ± .04	.00 ± .02	.00 ± .03	.00 ± .06	.13 ± .06	.08 ± .22	.01 ± .13	.07 ± .14	.21 ± .26
Overall hypoglycemia incidence, n(%)	535(80)	45(64)[b]	100(61)[c]	80(69)[b]	25(86)	560(86)	44(71)[b]	97(62)[c]	94(69)[c]	31(80)
Nocturnal hypoglycemia incidence, n(%)	247(37)	18(26)	40(25)[b]	36(31)	10(35)	233(36)	15(24)	40(26)[a]	45(33)	15(39)
Overall severe hypoglycemia incidence, n(%)	11(2)	1(1)	0(0)	0(0)	0(0)	14(2)	2(3)	1(1)	4(3)	1(3)

Data are presented as percentages or absolute LS mean ± SE at endpoint unless otherwise indicated.

B, Black (African descent); A, Asian; C, Caucasian; GL, once-daily insulin glargine; H, Hispanic; LM75/25, twice-daily insulin lispro mix 75/25 (LM75/25; 75% lispro protamine suspension, 25% insulin lispro); O, other.

For continuous variables, *P*s are from pairwise comparisons of each racial/ethnic group to the Caucasian group using Dunnett's test.

[a] $P<.05$.

[b] $P<.01$.

[c] $P<.001$.

[d] Events/patient/year.

when weight-adjusted, insulin dose was lower for African patients and higher for Asians. These findings could suggest that insulin needs are less for African patients due to greater TZD use and more for Asians because of less TZD use. Consistent with similar PPG levels across racial/ethnic groups within the LM75/25 arm, insulin doses were similar across racial/ethnic groups within the LM75/25 arm, with the exception of higher doses in Asians, which could suggest adequate postprandial coverage among a high-carbohydrate consuming racial group. Collectively, these findings differ slightly from the posthoc analysis of pooled data from 11 multinational clinical trials by Davidson and colleagues - there were no differences in insulin dose (total and weight-adjusted) across racial/ethnic groups in patients treated with basal insulin, whereas weight-adjusted insulin dose was higher for Asians and Latino/Hispanics treated with LM75/25.[3]

Black and Hispanic patients demonstrated similar HbA1c reduction with LM75/25 as compared to Caucasians. However, Asians showed consistently lower HbA1c reduction with both regimens and clearly had less individuals achieving HbA1c <7%.

Despite significant racial/ethnic differences in endpoint HbA1c, there were less marked differences in endpoint plasma glucose profiles. At endpoint, FPG levels were similar among the groups in both arms, whereas PPG with GL was lower for Black patients post-breakfast and post-dinner which could be attributable to a higher percentage of patients using 3 OAMs including a higher percentage of TZD/MET use. With the exception of lower PPG post-breakfast in Hispanic patients compared with Caucasians, there were no differences in PPG across racial/ethnic groups in the LM75/25 arm. The similar HbA1c change with lower PPG levels among Africans vs Caucasians with GL treatment may be attributed to differences in background OAM use. The greater HbA1c change along with lower hypoglycemic rates in Hispanic patients treated with LM75/25 may reflect leaner body mass and greater adherence to titration of insulin dose to reach target PPG level goals. Still, less Hispanic patients reached HbA1c goal vs Caucasians despite greater average HbA1c reduction, a discordance that would be explained by the significantly higher baseline HbA1c level in this group.

The reduced glucose-lowering efficacy observed in Asians vs Caucasians (higher endpoint HbA1c level; lower HbA1c change), along with higher weight-adjusted insulin dose in both arms, less hypoglycemia with LM75/25 and lower HbA1c change to insulin dose ratio, raise numerous questions about the response to either basal or premixed insulin in this population. Asian populations have a higher percentage of body fat at lower BMIs compared to Caucasians,[17,18] and increased insulin resistance.[19] The greater insulin requirements in Asians vs Caucasians in this study could be a result of increased insulin resistance in this population. Yet, glycemic improvement was lower for Asians than Caucasians, suggesting that other factors may have impacted treatment response and management of hyperglycemia among Asians. In the DURABLE trial, insulin dose titration was protocol-driven with programmed weekly adjustments to reach targeted FPG and PPG levels for the first 6 weeks, followed by 2-week intervals for the next 6 weeks, and then adjusted every 3 months.[4,5] Perhaps, the West Asians (Indians), who were the major Asians in this study, did not adjust appropriately or were restricted in some way.

There are some limitations to the present analysis. The DURABLE trial was not specifically designed to assess the effects of race/ethnicity on the aforementioned efficacy and safety outcomes and did not control for equal enrollment of different racial/ethnic groups. Furthermore despite racial origin, participants resided in multiple countries thus it was not possible to adequately control for the impact of cultural factors, such as diet and exercise, access to medical care, socioeconomic factors, and patient adherence to medical regimens; nor can we make any inference to environment.

The greatest limitation of this posthoc analysis may be the self-reporting of race/ethnicity. The use of self-reported race and ethnicity (SRE) in genetic and epidemiologic studies is controversial. Some researchers have called for elimination of SRE in favor of genetic testing whereas some studies have found SRE to be closely related to an individual's genetically estimated ancestry proportions.[20,21] Others have stated that while SRE may be sufficient to predict the continent or subcontinent on which an individual's ancestors were born, genetic markers provide a finer genetic ancestry measure capable of capturing more subtle variation within ethnic groups. Most investigators for large epidemiologic studies currently rely on a genetic measure of an individual's ancestral background as a control variable against confounding due to population stratification and admixture in genetic association tests instead of the SRE. A recent study focused on the utility of SRE as a control variable in genetic and epidemiologic studies using data collected for evaluation of heart function.[22] This group observed a high degree of agreement between SRE and two genetic based measures of ancestry computed using genotyped ancestry informative markers. They noted that the self-reported Hispanic-Americans were by far the most heterogeneous group represented in this dataset and stated the result is not surprising given the current definition of the term Hispanic which refers to a group of individuals who are culturally and genetically quite diverse. It is now well accepted that the ancestry distribution of self-reported Hispanics reflects, at different degrees, the genetic contribution of the three ancestral populations Africans, Europeans and Native American.[23]

Despite these limitations, the DURABLE trial does provide a large number of measurements in patients with T2D collected in a standardized fashion, and thus the power to detect differences between the racial/ethnic groups was relatively robust.

In conclusion, this posthoc analysis reveals significant differences in racial/ethnic patterns at baseline; as well as observed differences in efficacy and safety outcomes among racial/ethnic groups in the DURABLE trial of patients with T2D initiating insulin. Further studies are needed to examine the differences and identify contributing factors, but these results highlight the need to tailor insulin treatment by race/ethnicity to maximize efficacy and safety.

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REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 5th ed. Brussels, Belgium: International Diabetes Federation. http://www.idf.org/diabetesatlas/5e/the-global-burden. 2011.
2. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988–2006. *Diabetes Care*. 2010;33(3):562–568.
3. Davidson JA, Lacaya LB, Jiang H, et al. Impact of race/ethnicity on the efficacy and safety of commonly used insulin regimens: a post hoc analysis of clinical trials in type 2 diabetes mellitus. *Endocr Pract*. 2010;16(5):818–828.
4. Buse JB, Wolffenbuttel BH, Herman WH, et al. DURAbility of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results: safety and efficacy of insulin lispro mix 75/25 versus insulin glargine added to oral antihyperglycemic drugs in patients with type 2 diabetes. *Diabetes Care*. 2009;32(6):1007–1013.
5. Fahrbach J, Jacober S, Jiang H, Martin S. The DURABLE trial study design: comparing the safety, efficacy, and durability of insulin glargine to insulin lispro mix 75/25 added to oral antihyperglycemic agents in patients with type 2 diabetes. *J Diabetes Sci Technol*. 2008;2(5):831–838.
6. Fritsche A, Schweitzer MA, Haring HU. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. *Ann Intern Med*. 2003;138(12):952–959.
7. Hirsch IB, Bergenstal RM, Parkin CG, Wright EJ. A real-world approach to insulin therapy in primary care practice. *Clin Diab*. 2005;23:78–86.
8. Buse JB, Wolffenbuttel BH, Herman WH, et al. The DURAbility of Basal versus Lispro mix 75/25 insulin Efficacy (DURABLE) trial: comparing the durability of lispro mix 75/25 and glargine. *Diabetes Care*. 2011;34(2):249–255.
9. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157–163.
10. Shai I, Jiang R, Manson JE, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. *Diabetes Care*. 2006;29(7):1585–1590.
11. Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. *J Adv Nurs*. 2005;49(6):616–623.
12. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):854–865.
13. Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. *J Am Coll Nutr*. 2003;22(5):331–339.
14. Misra A, Khurana L. The metabolic syndrome in South Asians: epidemiology, determinants, and prevention. *Metab Syndr Relat Disord*. 2009;7(6):497–514.
15. Ni Mhurchu C, Rodgers A, Pan WH, Gu DF, Woodward M. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. *Int J Epidemiol*. 2004;33(4):751–758.
16. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann N Y Acad Sci*. 2013;1281:64–91.

17. Deurenberg P, Durenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes Rev*. 2002;3(3): 141–146.
18. Nakagami T, Qiao Q, Carstensen B, et al. Age, body mass index and Type 2 diabetes-associations modified by ethnicity. *Diabetologia*. 2003;46(8):1063–1070.
19. Chiu KC, Chuang LM, Yoon C. Comparison of measured and estimated indices of insulin sensitivity and beta cell function: impact of ethnicity on insulin sensitivity and beta cell function in glucose-tolerant and normotensive subjects. *J Clin Endocrinol Metab*. 2001;86(4): 1620–1625.
20. Liu XQ, Paterson AD, John EM, Knight JA. The role of self-defined race/ethnicity in population structure control. *Ann Hum Genet*. 2006;70(Pt 4):496–505.
21. Tang H, Quertermous T, Rodriguez B, et al. Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. *Am J Hum Genet*. 2005;76(2):268–275.
22. Divers J, Redden DT, Rice KM, et al. Comparing self-reported ethnicity to genetic background measures in the context of the Multi-Ethnic Study of Atherosclerosis (MESA). *BMC Genet*. 2011;12:28.
23. Bertoni B, Budowle B, Sans M, Barton SA, Chakraborty R. Admixture in Hispanics: distribution of ancestral population contributions in the continental United States. *Hum Biol*. 2003;75(1):1–11.

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