Efficacy of acarbose in different geographical regions of the world: analysis of a real-life database

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Abstract

Introduction: Although alpha-glucosidase inhibitors (aGIs), including acarbose, are recommended in several international guidelines, they are not widely used worldwide due to a perception that they are less effective in Caucasians than Asians. A study was undertaken to investigate whether differences between ethnicity/region populations exist.

Methods/design: We pooled data from 10 non-interventional and post-marketing studies from 21 countries, provinces and country groups from the launch of acarbose to 2011. The effects of acarbose on glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) were analyzed for four major ethnicity/region groups: Caucasians from Europe and Asians from East, South East and South Asia.

Results: The efficacy population included 62,905 patients, with 59,090 patients from the four groups of interest. At the 3-month visit, mean HbA_{1c} had decreased by –1.12±1.31% from 8.4% at baseline (n=32,692), FPG by 37.59±47.26 mg/dl from 170.2 mg/dl (n=45,102), and PPG by 70.00±65.30 mg/dl from 238.2 mg/dl (n=43,290) (p<0.0001 for all comparisons). Reductions in HbA_{1c}, FPG and PPG were larger in patients with higher baseline values regardless of ethnicity and region. Data from 30,730 patients from the four groups with non-missing baseline and 3-month HbA_{1c} data, age and sex were analyzed by multivariable ANCOVA. After adjustment for relevant baseline confounding factors, South East and East Asians had slightly better responses to acarbose than South Asians and European Caucasians; however, the differences were numerically small (e.g. relative difference of ~2.2% for baseline HbA_{1c} of 7.2%; ~3.4% for baseline HbA_{1c} of 9.2%). In the safety population (n=67,682), acarbose was well tolerated, with few episodes of hypoglycemia (0.03%) and gastrointestinal adverse events (2.76%).

Conclusion: Acarbose was effective in European Caucasians and Asians; however, after adjustment for baseline confounding factors, South East and East Asians had slightly better responses to acarbose than South Asians and European Caucasians.

Introduction

- Acarbose, the most widely prescribed of the currently available alpha-glucosidase inhibitors (aGIs), has been used in the management of hyperglycemia for more than 20 years[1, 2]
  - Acarbose acts non-systemically to slow down carbohydrate digestion and attenuates high levels of post-prandial plasma glucose (PPG), which is:[2-9]
    - an important manifestation in the early course of type 2 diabetes mellitus (T2DM)
    - a critical target for achieving glycemic control
    - a contributing factor in the pathogenesis of cardiovascular disease
  - Acarbose indirectly optimizes glucose metabolism during the day through adaptation of insulin secretion[2]
- Numerous studies have shown beneficial effects of acarbose as a 1st-, 2nd- and 3rd-line treatment option,[10-28] for which it is recommended by both the International Diabetes Federation (IDF) and American Association for Clinical Endocrinologists (AACE)[29, 30]
- However, prescribing of acarbose varies around the world due to a perception that efficacy is limited in some ethnic and regional groups
- We therefore analyzed pooled data from acarbose post-marketing studies (PMS) and non-interventional studies (NIS) to examine whether differences between patients of European Caucasian and Asian ethnicity exist based on a large body of evidence

Methods

- Data from 10 PMS and NIS from 21 countries, provinces and country groups across the world from the launch of acarbose to 2001 were pooled in a single database
- Data on PPG, fasting blood glucose (FBG), glycosylated hemoglobin (HbA_{1c}), and/or body weight collected at baseline and post-treatment visits were used to assess the efficacy of acarbose
- Bivariate analysis of covariance (ANCOVA) models were used to assess the relative reduction in HbA_{1c} versus baseline HbA_{1c}, with adjustment for baseline HbA_{1c}, subgroup of interest and baseline HbA_{1c} by subgroup interaction
- Multivariable ANCOVA was used to compare HbA_{1c} response to acarbose in terms of relative change in HbA_{1c} at 3 months versus baseline, with adjustment for baseline HbA_{1c}, ethnicity/region and ethnicity/region group interactions (baseline value, ethnicity/region subgroup, pretreatment, disease duration, baseline HbA_{1c} by subgroup, disease duration by subgroup, dose category, body mass index (BMI) group, and sex)

Results

Patient population

- 67,682 patients were included in the safety population
- After excluding patients who were retrospectively documented, did not take acarbose, did not have follow-up visits, were younger than 18 years and did not have at least two measurements of FPG and PPG, the efficacy population comprised data from 62,905 patients from 21 countries, provinces and country groups
- The analysis population for four major subgroups included 59,090 patients:
  - East Asian Asians from China, Hong Kong, Taiwan, Japan and South Korea (n=29,756; 50%)
  - European Caucasians from Bosnia and Herzegovina, Germany, Poland and Russia (n=15,971; 27%)
  - South Asian Asians from India and Pakistan (n=8,738; 15%)
  - South East Asian Asians from Cambodia, Indonesia, Malaysia, Philippines, Singapore, Vietnam and Thailand (n=4,625; 8%)
  - After restriction of the original efficacy population to the four major ethnicity/region groups and additional exclusions, including patients with missing baseline and/or post-treatment HbA_{1c} data, 30,730 subjects were considered for the multivariable ANCOVA
- Mean follow up (±SD) for the efficacy population with non-missing post-treatment FPG or PPG value(s) was 12.2±4.8 (range 0.1–108.9) weeks

Patient characteristics

- Gender percentages were balanced, except for a higher percentage of men in the South Asian group (58.2%)
- Elderly patients were more common in the European and East Asian groups (median age 63 and 61 years, respectively) than South East Asian and South Asian groups (median age 55 and 49 years, respectively)
- Patients were heavier in Europe and South Asia (median weight 84 and 74 kg, respectively) than in East Asia and South East Asia (median weight 67 and 65 kg, respectively)
- The proportion of obese patients (using the Western standard definitions for European Caucasians and the Asia Pacific standard for Asians) was higher for South Asians (61.9%) and South East Asians (47.7%), but more patients in the European group were overweight (39.0%)
- Hypertension and dyslipidemia were more common in European patients (71.6% and 48.7%, respectively)
- Cerebrovascular accident/stroke was more common in East Asian (11.0%) and European (8.2%) patients than South East Asian (2.4%) and South Asian (1.8%) patients
- Microvascular comorbidities did not differ greatly between ethnicity/region groups (range 6% to 12%)
- Table 1 summarizes the baseline values for HbA_{1c}, FPG and PPG for the efficacy population overall and the four ethnicity/region groups under evaluation

Table 1:
Baseline glycemic values for overall efficacy population and four ethnicity/region groups.

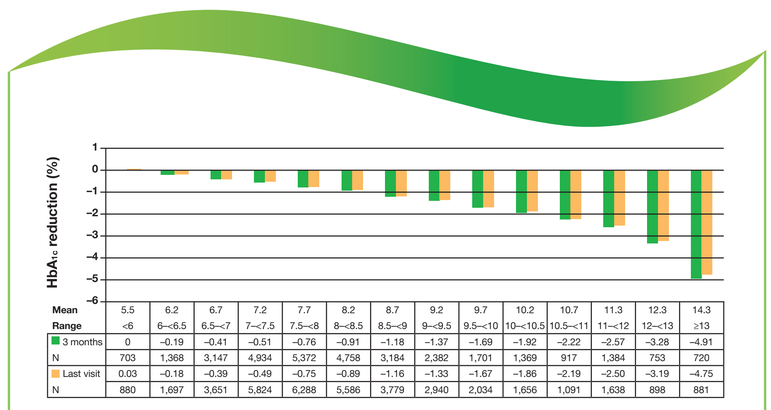
Baseline (±SD) glycemic value	Efficacy population	European Caucasians	Asians		
			East Asian	South East Asian	South Asian
HbA_{1c} (%)	8.4±1.7 (n=47,786)	8.1±1.4 (n=11,798)	8.5±1.9 (n=28,223)	8.4±1.7 (n=2,500)	8.4±1.5 (n=3,421)
FPG (mg/dl)	171.5±55.8 (n=57,285)	168.0±49.4 (n=15,474)	167.4±57.0 (n=26,795)	183.0±63.7 (n=4,332)	176.5±50.6 (n=8,098)
PPG (mg/dl)	240.0±71.6 (n=54,316)	207.6± 54.0 (n=14,332)	247.4±74.3 (n=25,865)	252.4±80.0 (n=3,649)	261.9±65.0 (n=8,214)

- Poster Number: P 495

Changes in glycemic parameters at follow up:

HbA_{1c}

- Mean HbA_{1c} in the total population decreased from 8.4±1.7% at baseline (n=47,786) to 7.3±1.3% at both the 3-month visit (n=34,571) and the last visit (n=41,247)
  - Absolute reductions in patients with baseline and post-treatment HbA_{1c} data were –1.12±1.31% at 3-month visit (n=32,692) and –1.09±1.31% at the last visit (n=38,843) (p<0.0001 for both)
  - Relative reductions were baseline dependent and greater at higher baseline HbA_{1c} (Fig. 1)



Mean	5.5	6.2	6.7	7.2	7.7	8.2	8.7	9.2	9.7	10.2	10.7	11.3	12.3	14.3
Range	<6	6–<6.5	6.5–<7	7–<7.5	7.5–<8	8–<8.5	8.5–<9	9–<9.5	9.5–<10	10–<10.5	10.5–<11	11–<12	12–<13	≥13
3 months	0	–0.19	–0.41	–0.51	–0.76	–0.91	–1.18	–1.37	–1.69	–1.92	–2.22	–2.57	–3.28	–4.91
N	703	1,368	3,147	4,934	5,372	4,758	3,184	2,382	1,701	1,369	917	1,384	753	720
Last visit	0.03	–0.18	–0.39	–0.49	–0.75	–0.89	–1.16	–1.33	–1.67	–1.86	–2.19	–2.50	–3.19	–4.75
N	880	1,697	3,651	5,824	6,288	5,586	3,779	2,940	2,034	1,656	1,091	1,638	898	881

Fig. 1: *Mean change in HbA_{1c}, after 3 months of treatment with acarbose by baseline category.*

- A descriptive plot of change in HbA_{1c} versus baseline HbA_{1c} showed similar results regardless of ethnicity/region group (Fig. 2)

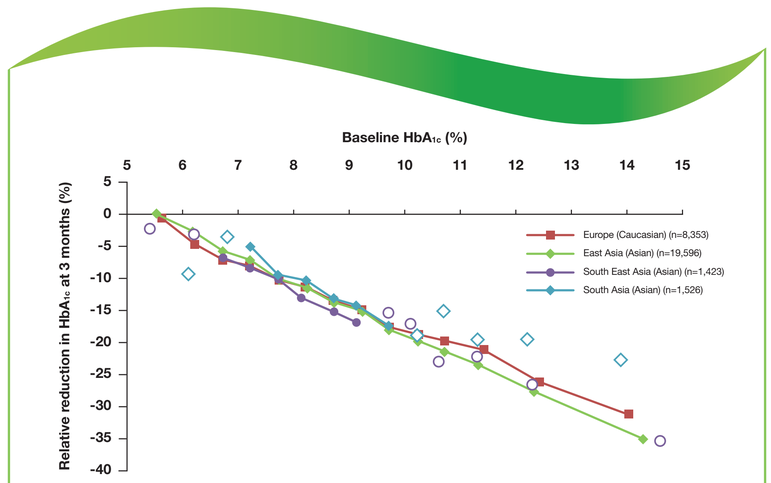


Fig. 2: *Mean relative reduction vs mean baseline HbA_{1c} by ethnicity/region group and baseline HbA_{1c} category. Open symbols indicate n<70; baseline categories are as in Fig. 1.*

- Regression lines for HbA_{1c} change at 3 months versus baseline HbA_{1c} in each ethnicity/region group indicated some differences in the observed efficacy of acarbose between ethnicity/region groups
  - Relative reductions in HbA_{1c} ranged from 10.95% for South Asians to 12.98% for South East Asians for mean baseline HbA1c 8.4% (p<0.0001) (Fig. 3)

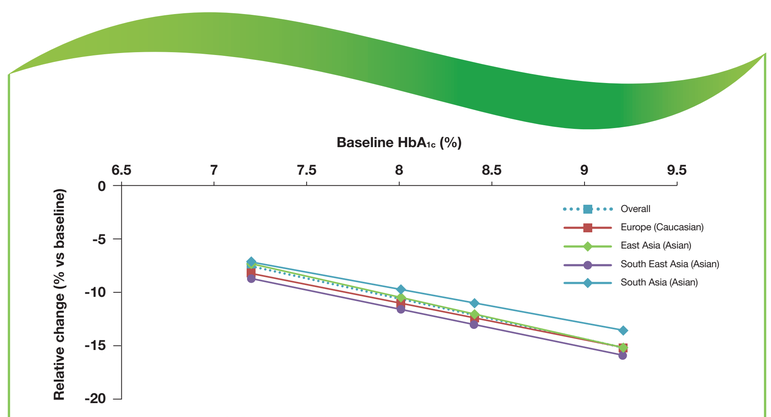


Fig. 3: *Least square (LS) means for relative HbA_{1c} reduction at lower quartile, mean, median and upper quartile of baseline HbA_{1c} by ethnicity/region group by bivariate ANCOVA.*

- The mean relative changes at 3 months from baseline after multivariable adjustments showed:
  - South East Asians and East Asians had, overall, a better response to acarbose than South Asians and European Caucasians
  - East Asians had a significantly steeper slope (p<0.001 versus the other three groups) (Fig. 4)
- A similar analysis based on data from the last visit, which had a larger sample size (n=36,508) confirmed these trends

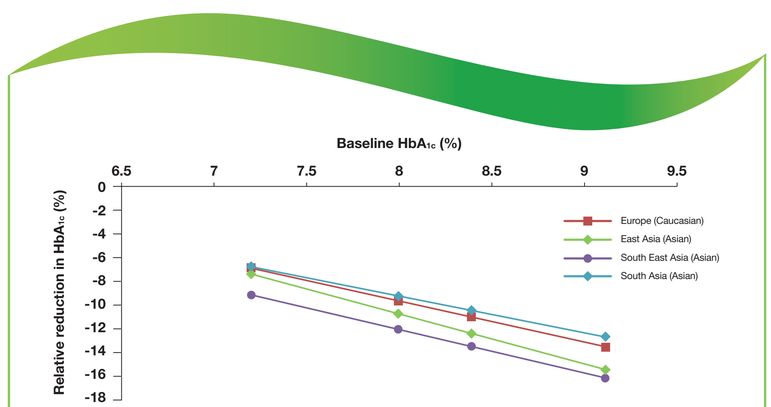
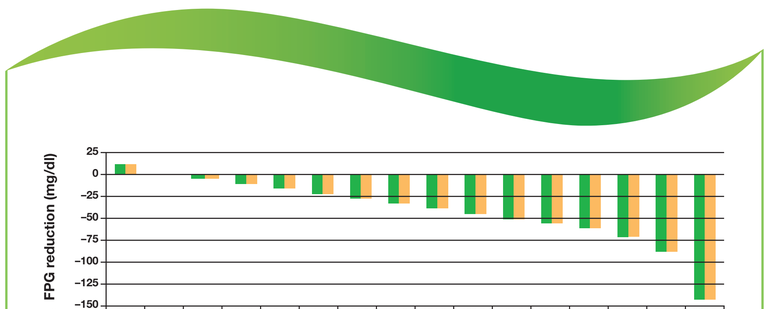


Fig. 4: *Least square (LS) means for relative HbA_{1c} reduction at lower quartile, mean, median and upper quartile of baseline HbA_{1c} by ethnicity/region group by multivariable ANCOVA. *p<0.0001 versus European Caucasian and South Asian Asian; $p<0.0001 versus East Asian Asian; #p=0.0241 versus East Asian Asian; †p=0.0319 versus South Asian Asian.*

FPG

- 45,102 patients had non-missing baseline and 3-month data for FPG
- At the 3-month visit, FPG had decreased by 37.59±47.26 mg/dl from 170.2 mg/dl at baseline (p<0.0001)
- Reductions in FPG were larger in patients with higher baseline FPG (Fig. 5)

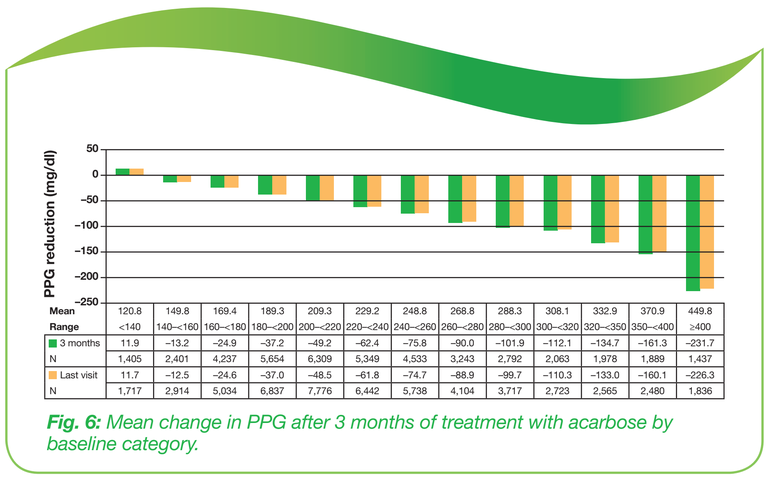


Mean	88.4	105.3	114.7	125.2	134.5	144.1	154.3	164.0	174.2	183.7	194.2	203.8	214.0	228.7	257.0	323.5
Range	<100	100–<110	110–<120	120–<130	130–<140	140–<150	150–<160	160–<170	170–<180	180–<190	190–<200	200–<210	210–<220	220–<230	240–<280	≥280
3 months	11.5	–0.2	–4.8	–10.7	–15.7	–22.0	–26.9	–32.8	–38.5	–44.9	–51.2	–55.5	–61.0	–71.3	–87.8	–142.3
N	1,374	1,864	2,350	4,379	4,018	5,509	3,697	3,754	2,769	2,918	2,116	1,658	1,667	2,109	2,643	2,277
Last visit	11.7	0.2	–4.7	–10.7	–15.4	–21.9	–26.9	–33.1	–38.9	–45.1	–51.8	–55.5	–61.2	–70.1	–87.4	–142.0
N	1,660	2,227	2,854	5,253	4,999	6,725	4,594	4,809	3,552	3,749	2,828	2,128	2,141	2,657	3,440	3,056

Fig. 5: *Mean change in FPG after 3 months of treatment with acarbose by baseline category.*

PPG

- 43,290 patients had non-missing baseline and 3-month data for PPG
- At the 3-month visit, PPG had decreased by 70.00±65.30 mg/dl from 238.2 mg/dl at baseline (p<0.0001)
- Reductions in PPG were larger in patients with higher baseline PPG (Fig. 6)



Mean	120.8	149.8	169.4	189.3	209.3	229.2	248.8	268.8	288.3	308.1	332.9	370.9	449.8
Range	<140	140–<160	160–<180	180–<200	200–<220	220–<240	240–<260	260–<280	280–<300	300–<320	320–<350	350–<400	≥400
3 months	11.9	–13.2	–24.9	–37.2	–49.2	–62.4	–75.8	–90.0	–101.9	–112.1	–134.7	–161.3	–231.7
N	1,405	2,401	4,237	5,654	6,309	5,349	4,533	3,243	2,792	2,063	1,978	1,889	1,437
Last visit	11.7	–12.5	–24.6	–37.0	–48.5	–61.8	–74.7	–88.9	–99.7	–110.3	–133.0	–160.1	–226.3
N	1,717	2,914	5,034	6,837	7,776	6,442	5,738	4,104	3,717	2,723	2,565	2,480	1,836

Fig. 6: *Mean change in PPG after 3 months of treatment with acarbose by baseline category.*

Safety

- Acarbose was well tolerated with a low adverse event rate (3.70%)
- Patients experienced very few episodes of hypoglycemia (0.03%)
- The most frequently reported adverse events, as expected, were gastrointestinal (GI) disorders (2.76%)

Study limitations

- Our analysis includes individual patient data, and we were able to adjust for confounding factors in individual patients, including baseline HbA_{1c}, which is well known to affect the effect size with acarbose[31, 32]
- This is the first study to analyze differences in outcomes in clinical practice rather than data from clinical trials, and reflects the change in HbA_{1c} from baseline that physicians and patients can expect to see in real life
- Due to the nature of NIS, there was no control population (placebo group) for comparison
- As a wide time span existed between the first and the last NIS and as different case report forms were used, some data were missing

Discussion/conclusion

- This analysis of a large database of pooled data from real-life practice in diverse patients from all over the world show that acarbose is effective across all ethnicities and regions examined, although the effects are more pronounced in some populations, such as South East Asians and East Asians
- The relative reduction in HbA_{1c} with acarbose is more pronounced in patients with higher baseline HbA_{1c} values; this trend is more prominent in East Asians than other ethnicity/region groups
- South East Asians and East Asians have slightly but significantly better responses to acarbose than South Asians and Caucasians from Europe after adjustment of relevant baseline confounding factors
- Overall, acarbose has good efficacy regardless of ethnicity and region

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