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Research: Treatment

The effect of basal–bolus therapy varies with baseline 1,5-anhydroglucitol level in people with Type 2 diabetes: a *post hoc* analysis

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Abstract

Aims To investigate the impact of baseline 1,5-anhydroglucitol on the treatment effect of basal–bolus therapy in people with Type 2 diabetes.

Methods *Post hoc* analysis of onset 3, an 18-week, randomized, phase 3 trial evaluating the efficacy and safety of fast-acting insulin aspart in basal–bolus therapy (n = 116) vs. basal insulin-only therapy (n = 120) in people with Type 2 diabetes. The estimated treatment difference in change from baseline in HbA_{1c} was investigated for different cut-off values of baseline 1,5-anhydroglucitol (2, 3, 4, 5 and 6 μg/ml).

Results The estimated treatment difference in change from baseline in HbA_{1c} between basal–bolus therapy and basal insulin-only therapy was statistically significantly greater in participants with baseline 1,5-anhydroglucitol ≤3 μg/ml (n = 34) vs. >3 μg/ml (n = 198) [estimated treatment difference (95% CI): −1.53% (−2.12; −0.94) vs. −0.82% (−1.07; −0.57); *P*-value for interaction = 0.03]. The estimated treatment difference became more pronounced when comparing participants with 1,5-anhydroglucitol ≤2 μg/ml (n = 15) vs. >2 μg/ml (n = 217) [estimated treatment difference (95% CI): −2.26% (−3.15; −1.36) vs. −0.85% (−1.08; −0.62); *P*-value for interaction = 0.003]. For cut-off values ≥4 μg/ml, estimated treatment differences were numerically greater below the cut-off compared with above, although the interaction terms were not statistically significant.

Conclusion This analysis indicates that people with Type 2 diabetes with low 1,5-anhydroglucitol have an added treatment benefit with basal–bolus therapy compared with people with higher 1,5-anhydroglucitol. Further research is needed to clarify any clinical utility of these findings.
Clinical Trials Registry No: NCT01850615

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Introduction

Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion, resulting in both fasting and postprandial hyperglycaemia. To control fasting plasma glucose (FPG), treatment guidelines recommend initiating basal insulin when HbA_{1c} targets have not been achieved with oral antidiabetes drugs [1]. While control of FPG is necessary, it is usually insufficient for maintaining appropriate HbA_{1c} targets [2], and many people with Type 2 diabetes will eventually benefit from treatment intensification with drugs that target postprandial plasma glucose (PPG) excursions (e.g. mealtime bolus insulin or glucagon-like peptide-1 receptor analogues). However, determining which people with Type 2 diabetes would benefit from basal–bolus therapy is a challenge facing physicians in clinical practice.

Plasma 1,5-anhydroglucitol (1,5-AG) has been proposed as a marker to assess short-term glycaemic control in people with Type 1 and Type 2 diabetes [3–5]. 1,5-AG is

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What's new?

- The onset 3 trial evaluated the efficacy and safety of adding mealtime fast-acting insulin aspart to basal insulin in people with Type 2 diabetes.
- This *post hoc* analysis of onset 3 indicates that low 1,5-anhydroglucitol is predictive of basal–bolus treatment effect.
- The findings suggest that 1,5-anhydroglucitol measurements may be useful for identifying people with Type 2 diabetes who would most benefit from intensifying insulin therapy, but further research is needed to determine whether 1,5-anhydroglucitol adds clinical utility beyond that of HbA_{1c}.

an endogenous dietary polyol, structurally similar to glucose, that is maintained at a constant steady state in the blood [6]. When blood glucose is in the normal range, 1,5-AG is reabsorbed in the proximal tubules of the kidney and is stable in the range of 6.8–29.3 μg/ml in women and 10.7–32.0 μg/ml in men [4]. When blood glucose exceeds the renal threshold (~180 mg/dl), glucose blocks reabsorption of 1,5-AG and circulating levels decrease. When glycaemic control is restored, 1,5-AG levels recover at a rate of ~0.3 μg/ml per day. Consequently, 1,5-AG responds rapidly to changes in blood glucose, and, in contrast to HbA_{1c}, can reflect glycaemic control over the previous 1–2 weeks [7,8].

The onset 3 trial was an 18-week, multicentre, open-label, randomized phase 3 trial that evaluated the efficacy and safety of fast-acting insulin aspart (faster aspart) in basal–bolus therapy vs. basal insulin-only therapy in people with Type 2 diabetes [9]. Faster aspart is a new formulation of insulin aspart that presents with an earlier onset of appearance, a higher early insulin exposure, and a greater early glucose-lowering effect compared with conventional insulin aspart [10]. In onset 3, as part of basal–bolus therapy, faster aspart significantly reduced HbA_{1c} compared with basal insulin [estimated treatment difference (ETD) 95% confidence interval (CI)]: −0.94% [−1.17; −0.72]; P <0.0001. The reduction in overall mean 2-h PPG and mean PPG increment for all meals [derived from self-measured plasma glucose (SMPG) values], and the increase in 1,5-AG were also statistically significant in favour of basal–bolus therapy compared with basal insulin-only therapy [9].

In the current analysis, it was hypothesized that the treatment effect of basal–bolus therapy would be different in people with Type 2 diabetes and low baseline 1,5-AG compared with people with Type 2 diabetes and high baseline 1,5-AG (i.e. that baseline 1,5-AG would be predictive of the basal–bolus treatment effect). This hypothesis was explored using data from onset 3 to perform a *post hoc* analysis of the treatment differences within subgroups based on baseline 1,5-AG.

Participants and methods

onset 3 design

The onset 3 methodology has been reported previously [9]. The trial compared intensification with faster aspart in a basal–bolus regimen vs. continued basal insulin therapy, both in combination with metformin, in participants aged ≥18 years with a BMI ≤40.0 kg/m^2 diagnosed with Type 2 diabetes for ≥6 months and treated for ≥3 months prior to screening with once-daily basal insulin [insulin detemir, insulin glargine U100 or neutral protamine Hagedorn (NPH)] and metformin ≥1000 mg with or without other oral antidiabetes drugs. Participants had an HbA_{1c} of 59–80 mmol/mol (7.5–9.5%) if taking metformin, or 59–75 mmol/mol (7.5–9.0%) if taking metformin plus other oral antidiabetes drugs at the screening visit.

At the start of an 8-week run-in period, participants continued their once-daily basal insulin and metformin and discontinued all other oral antidiabetes drugs. During run-in, basal insulin dose was optimized using a treat-to-target approach, with weekly adjustments to a pre-breakfast target of 4.0–6.0 mmol/l (71–108 mg/dl). After the run-in period, basal insulin dose was adjusted at the investigator's discretion.

Participants requiring further intensification [i.e. HbA_{1c} 53–75 mmol/mol (7.0–9.0%) following the run-in period] were randomized 1:1 to faster aspart in basal–bolus therapy or to continue basal insulin-only therapy. Randomization was stratified based on the type of basal insulin used (insulin detemir, insulin glargine U100 or NPH). Participants randomized to receive faster aspart self-adjusted the dose by 1-unit increments aiming for a pre-prandial or bedtime target of 4.0–6.0 mmol/l (71–108 mg/dl).

Post hoc analysis population and outcomes

All participants included in the full analysis set were considered for the *post hoc* analysis. Participants were required to have baseline 1,5-AG information available for inclusion (baseline was defined as the randomization visit after basal insulin optimization). As 1,5-AG levels can display substantial variation between individuals, participants were divided into subgroups based on a range of 1,5-AG cut-off values (2, 3, 4, 5 or 6 μg/ml). Treatment differences in change from baseline in HbA_{1c} were estimated for 1,5-AG subgroups below and above each cut-off value.

Statistical analysis

Change from baseline in HbA_{1c} in subgroups above and below each 1,5-AG cut-off value was analyzed using a mixed-effects model for repeated measures (MMRM). All calculated changes in HbA_{1c} from baseline at weeks 6, 12 and 18 were included in the analysis. The model included a

treatment-by-subgroup interaction, alongside the main effects of treatment, subgroup (above/below cut-off value), region (Asia, Europe, North America or South America) and strata (insulin detemir, insulin glargine U100 or NPH), with baseline HbA_{1c} and baseline 1,5-AG as covariates. All effects were nested within visit; an unstructured covariance matrix was used to describe the variability for the repeated measurements for participants. The *P*-value for the interaction term was used to evaluate if the treatment effect was different above vs. below the cut-off value. A *P*-value <0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics in the onset 3 population were similar between the basal–bolus therapy and basal insulin-only treatment groups (Table 1) [9]. 42.4% (n = 100) of participants were from Europe or North America. Of the onset 3 population (n = 236), 234 participants had baseline 1,5-AG information available and were included in the *post hoc* analysis of baseline characteristics (Table 2). Only participants with post-baseline HbA_{1c} data contributed to the MMRM analysis (n = 232).

Table 1 Baseline characteristics of the onset 3 population at randomization [9]

Characteristic, n, FAS	Faster aspart in basal–bolus therapy (n = 116)	Basal insulin-only therapy (n = 120)	Total (n = 236)
Age, years	57.5 (9.9)	57.4 (8.5)	57.4 (9.2)
Gender, n (%)			
Men	55 (47.4)	59 (49.2)	114 (48.3)
Women	61 (52.6)	61 (50.8)	122 (51.7)
BMI, kg/m^2	30.4 (5.0)	31.1 (4.7)	30.8 (4.8)
Body weight, kg	82.2 (16.2)	85.1 (17.3)	83.7 (16.8)
Duration of diabetes, years	10.9* (6.1)	11.8 (7.4)	11.3 (6.3)
HbA_{1c}			
mmol/mol	63 (8)	63 (7)	63 (8)
%	7.9 (0.7)	7.9 (0.7)	7.9 (0.7)
FPG			
mmol/l	7.4 (2.4)	7.7† (2.9)	7.5 (2.6)
mg/dl	132.5 (43.5)	138.9 (51.4)	135.7 (47.7)
1,5-AG, μg/ml	8.2 (5.4)	7.7 (4.7)	7.9 (5.0)

Data are mean (SD) unless stated otherwise.
*n = 115; †n = 119.
The conversion factor used for glucose between mmol/l and mg/dl was 0.0555.
1,5-AG, 1,5-anhydroglucitol; FAS, full analysis set; faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; n, number of participants contributing to the analysis.
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Association between baseline 1,5-AG and change from baseline in HbA_{1c} after 18 weeks of treatment

Figure 1 indicates a separation in HbA_{1c} treatment difference at week 18 between basal–bolus therapy and basal insulin-only therapy at lower baseline 1,5-AG values. The difference between the smoothing curves fitted to the scatter plot demonstrates the larger treatment effect at lower baseline 1,5-AG compared with higher baseline 1,5-AG.

HbA_{1c} treatment difference above vs. below 1,5-AG cut-off values

The ETD in change from baseline in HbA_{1c} between basal–bolus therapy and basal insulin-only therapy was statistically significantly greater in participants with baseline 1,5-AG ≤3 μg/ml (n = 34) vs. >3 μg/ml (n = 198) [ETD (95% CI): −1.53% (−2.12; −0.94) vs. −0.82% (−1.07; −0.57); *P*-value for interaction = 0.03]. The ETD became more pronounced when comparing participants with 1,5-AG ≤2 μg/ml (n = 15) vs. >2 μg/ml (n = 217) [ETD (95% CI): −2.26% (−3.15; −1.36) vs. −0.85% (−1.08; −0.62); *P*-value for interaction = 0.003]. For cut-off values ≥4 μg/ml, ETDs were numerically greater below the cut-off compared with above, although the interaction terms were not statistically significant (Fig. 2).

Baseline characteristics above and below 1,5-AG cut-off values

Baseline characteristics of participants in the 3 μg/ml 1,5-AG cut-off subgroups are shown in Table 2. Baseline characteristics were similar between basal–bolus therapy and basal insulin-only therapy within the two subgroups. Participants in the ≤3 μg/ml subgroup had numerically higher mean HbA_{1c}, FPG and 2-h PPG (SMPG) at baseline compared with participants in the >3 μg/ml subgroup [≤3 (n = 35) vs. >3 μg/ml (n = 199): HbA_{1c}, 68 vs. 62 mmol/mol (8.4 vs. 7.9%); FPG, 8.2 vs. 7.4 mmol/l (147.7 vs. 133.7 mg/dl); 2-h PPG (SMPG), 9.8 vs. 8.7 mmol/l (176.6 vs. 156.8 mg/dl)]. Body weight, BMI and duration of diabetes were similar between the two subgroups. The baseline characteristics of participants in the 2, 4, 5 and 6 μg/ml cut-off subgroups are included in the supporting information for this article (Table S1).

Discussion

In onset 3, addition and titration of mealtime faster aspart in basal–bolus therapy effectively improved glycaemic control in people with Type 2 diabetes, demonstrating the expected superiority to basal insulin-only therapy for HbA_{1c} and PPG control [9]. However, in routine clinical practice, identifying people with Type 2 diabetes who could most benefit from intensifying treatment with basal–bolus therapy, and

Table 2 Baseline characteristics of participants included in the *post hoc* analysis by baseline 1,5-AG ≤3 μg/ml and >3 μg/ml

Characteristic	Baseline 1,5-AG ≤3 μg/ml			Baseline 1,5-AG >3 μg/ml		
	Faster aspart in basal–bolus therapy (n = 19)	Basal insulin-only therapy (n = 16)	Total (n = 35)	Faster aspart in basal–bolus therapy (n = 97)	Basal insulin-only therapy (n = 102)	Total (n = 199)
Age, years	52.2 (10.1)	53.9 (7.4)	52.9 (8.9)	58.5 (9.6)	57.9 (8.3)	58.2 (8.9)
Gender, % men	63.2	56.3	60.0	44.3	48.0	46.2
Body weight, kg	85.3 (17.3)	80.3 (15.6)	83.0 (16.5)	81.5 (16.0)	85.8 (17.6)	83.7 (16.9)
BMI, kg/m^2	29.9 (3.8)	29.6 (5.4)	29.8 (4.5)	30.5 (5.2)	31.3 (4.5)	30.9 (4.9)
Duration of diabetes, years	11.6 (5.2)	11.9 (7.6)	11.7 (6.3)	10.7 (6.3)	11.9 (7.4)	11.3 (6.9)
HbA_{1c}						
mmol/mol	68 (10)	68 (7)	68 (8)	62 (7)	63 (7)	62 (7)
%	8.4 (0.9)	8.3 (0.7)	8.4 (0.8)	7.9 (0.6)	7.9 (0.7)	7.9 (0.6)
FPG						
mmol/l	8.0 (2.8)	8.4 (2.5)	8.2 (2.7)	7.2 (2.3)	7.6 (2.9)	7.4 (2.7)
mg/dl	144.3 (50.3)	151.9 (45.8)	147.7 (47.7)	130.1 (42.0)	137.1 (52.6)	133.7 (47.7)
2-h PPG (SMPG)						
mmol/l	9.8 (2.1)	9.9 (2.1)	9.8 (2.0)	8.5 (1.8)	8.8 (1.7)	8.7 (1.7)
mg/dl	176.6 (37.8)	178.4 (37.8)	176.6 (36.0)	153.2 (32.4)	158.6 (30.6)	156.8 (30.6)
1,5-AG, μg/ml	2.2 (0.6)	2.1 (0.4)	2.1 (0.5)	9.3 (5.1)	8.6 (4.4)	9.0 (4.8)

Data are mean (SD) unless stated otherwise.
The conversion factor used for glucose between mmol/l and mg/dl was 0.0555.
Of the onset 3 population (n = 236), 234 participants had baseline 1,5-AG information available and were included in the *post hoc* analysis.
1,5-AG, 1,5-anhydroglucitol; faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; n, number of patients contributing to the analysis; PPG, postprandial plasma glucose; SMPG, self-measured plasma glucose.

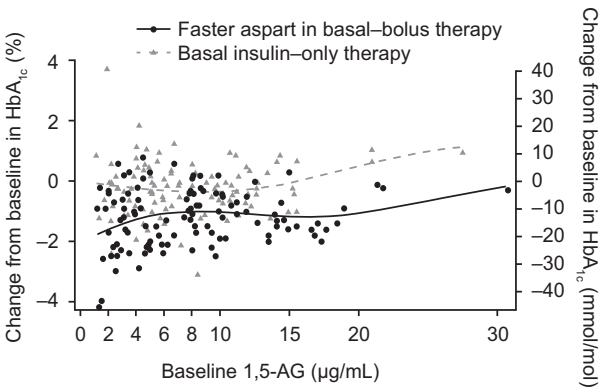


FIGURE 1 Scatter plot of change from baseline in HbA_{1c} after 18 weeks of randomized treatment against baseline 1,5-AG. Penalized B-spline scatter plot smoothing is used to depict the association between change from baseline in HbA_{1c} and baseline 1,5-AG.
1,5-AG, 1,5-anhydroglucitol; faster aspart, fast-acting insulin aspart.

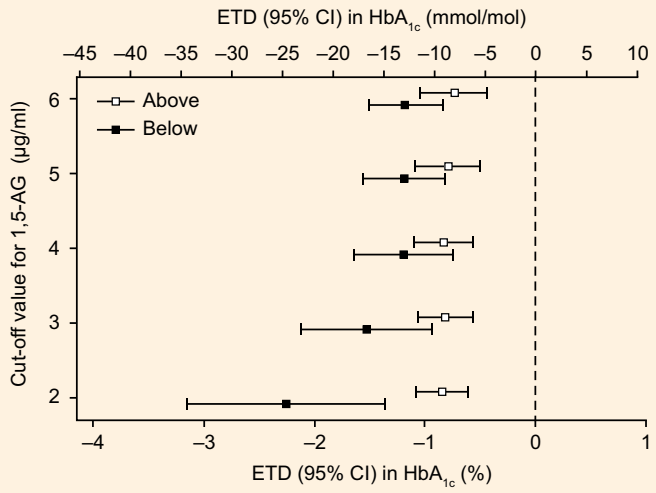
intensifying in a timely manner, is a challenge. Indeed, a recent study showed that only 30.9% of people with Type 2 diabetes with HbA_{1c} ≥59 mmol/mol (≥7.5%) on basal insulin had their treatment intensified after a median 3.7-year delay [11].

This *post hoc* analysis of onset 3 suggests that participants with low baseline 1,5-AG (≤3 μg/ml) experienced an increased benefit in HbA_{1c} reduction with basal–bolus therapy compared with participants with a higher baseline 1,5-AG (>3 μg/ml). Since all statistical models were adjusted for HbA_{1c} at baseline, the results can be interpreted as indicating that if two individuals have similar HbA_{1c} but one has a low 1,5-AG then the latter may experience an increased benefit in HbA_{1c} reduction with basal–bolus therapy. It is important to note that this analysis does not address the question of whether 1,5-AG or HbA_{1c} alone is more useful for predicting response to adding basal–bolus therapy. Instead, the results demonstrate, in a prospective setting, the complementary value of 1,5-AG to HbA_{1c}.

At baseline, participants in the 1,5-AG ≤3 μg/ml subgroup had higher 2-h PPG (SMPG) across all meals compared with participants in the 1,5-AG >3 μg/ml subgroup [SMPG: 9.8 mmol/l (176.6 mg/dl) vs. 8.7 mmol/l (156.8 mg/dl)]. While intensifying insulin therapy based on PPG values is recommended, obtaining information on the prandial component of hyperglycaemia requires frequently sampled blood glucose measurements and relies on patient cooperation. In contrast, 1,5-AG reflects glycaemic control over the previous 1–2 weeks and is more convenient to measure than a full SMPG profile.

A previous *post hoc* analysis of people with Type 2 diabetes and suboptimal control with oral antidiabetes drugs [HbA_{1c} 54–63 mmol/mol (7.1–7.9%)] found that those with baseline 1,5-AG <7.8 μg/ml achieved greater HbA_{1c} reduction with initiation of insulin lispro mix 75/25 compared with insulin glargine [12]. Although the study suggests that 1,5-AG may offer therapeutic insight when starting insulin therapy, it did not find 1,5-AG to be predictive of treatment effect.

While this is the first study to explore the use of 1,5-AG as a predictor of the response to basal–bolus therapy, other studies have shown that 1,5-AG is associated with the



n	ETD (95% CI) (%)	ETD (95% CI) (mmol/mol)	*P*-value
130	–0.73 (–1.04;–0.43)	−8.0 (−11.4;−4.7)	0.060
102	–1.18 (–1.51;–0.84)	−12.8 (−16.6;−9.1)	
147	–0.80 (–1.09;–0.51)	−8.8 (−11.9;−5.6)	0.108
85	–1.19 (–1.56;–0.82)	−13.0 (−17.1;−8.9)	
173	–0.84 (–1.10;–0.57)	−9.1 (−12.1;−6.2)	0.177
59	–1.20 (–1.64;–0.75)	−13.1 (−18.0;−8.2)	
198	–0.82 (–1.07;–0.57)	−9.0 (−11.7;−6.3)	0.031
34	–1.53 (–2.12;–0.94)	−16.7 (−23.2;−10.3)	
217	–0.85 (–1.08;–0.62)	−9.3 (−11.8;−6.7)	0.003
15	–2.26 (–3.15;–1.36)	−24.7 (−34.5;−14.9)	

FIGURE 2 Estimated treatment difference in change from baseline in HbA_{1c} above and below different 1,5-AG cut-off values.
Change from baseline in HbA_{1c} was analysed using an MMRM. The model included a treatment-by-subgroup interaction, alongside main effects of treatment, subgroup (above/below cut-off value), region and strata, with baseline HbA_{1c} and baseline 1,5-AG as covariates. *P*-values for the interaction term were used to evaluate if the ETD was different above vs. below the cut-off values. Only participants with post-baseline HbA_{1c} data contributed to the MMRM analysis (n = 232).
1,5-AG, 1,5-anhydroglucitol; CI, confidence interval; ETD, estimated treatment difference; MMRM, mixed-effects model for repeated measures; n, number of participants contributing to the analysis.

macro- and microvascular complications of diabetes. Analysis of samples from ~10 000 people in the 20-year Atherosclerosis Risk in Communities study found that, after adjustment for HbA_{1c}, 1,5-AG was associated with retinopathy and chronic kidney disease in those with diagnosed diabetes [13]. Additionally, people with diabetes and 1,5-AG <6.0 µg/ml had an increased risk of coronary heart disease, stroke, heart failure or death compared with people with 1,5-AG ≥6 µg/ml and no history of diabetes [14].

A limitation of this *post hoc* analysis is the small number of participants in the baseline 1,5-AG subgroups; this is reflected in the wide confidence intervals in the lower 1,5-AG subgroups. In addition, due to its exploratory nature, the analysis cannot identify an optimal cut-off value for 1,5-AG for predicting response to basal–bolus therapy. Randomized clinical trials are needed to further evaluate 1,5-AG as a useful predictor of response to therapies targeting PPG.

In conclusion, this *post hoc* analysis indicates that people with Type 2 diabetes and low 1,5-AG have an added treatment benefit with basal–bolus therapy compared with those with higher 1,5-AG. This suggests that 1,5-AG may be useful in identifying subgroups of people for whom basal–bolus therapy is a particularly promising treatment option. However, an added advantage of basal–bolus therapy was observed only in a relatively small subgroup of participants with very low 1,5-AG (≤3 µg/ml), and further research is needed to clarify the clinical utility of these findings.

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Competing interests

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics of participants included in the *post hoc* analysis by baseline 1,5-AG—cut-off values of 2, 4, 5 and 6 μg/ml.