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Original research

A higher blood glucose level pre-breakfast in comparison to bedtime is a contraindication for intensification of prandial insulin therapy in patients with type 2 diabetes – The impact of a negative BeAM value

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ABSTRACT

Aims: The BeAM value refers to the difference between a patient's blood glucose level at bedtime (Be) and the following morning before breakfast (AM). The clinical impact of a negative BeAM value (AM blood glucose reading compared to that taken at bedtime) is unknown.
Methods: T2DM patients of the OPAL and POC trials were pooled and their BeAM values calculated.
Results: From a total of 358 patients, 31 were calculated as having a negative BeAM value at baseline, while 182 had a high value. Patients in the negative BeAM group were younger, had shorter diabetes duration, and lower HbA1c levels. Fasting blood glucose levels were higher in the negative BeAM group, and these increased to a greater extent during the trial periods. No significant differences in hypoglycaemia occurrence were observed. Multivariate adjusted analysis indicated no association between a negative BeAM value and achievement of HbA1c < 7%, or composite endpoints that additionally included no hypoglycaemia and no weight gain.
Conclusions: Supplementation of BOT with prandial insulin is not beneficial for patients who have a higher blood glucose reading before breakfast in comparison to before bedtime. Further investigation into the cause of the high morning reading in these patients is indicated.

Introduction

The progressive nature of type 2 diabetes mellitus (T2DM) necessitates gradual intensification of treatment so as to maintain adequate glycaemic control [1,2]. While oral antidiabetic drugs (OADs) are often sufficient in early stages of the disease, insulin will ultimately be required [3]. Though there are many insulin regimes available in clinical practise, one well-established approach is injection of a long acting basal insulin such as glargine (Lantus®, Sanofi) in combination with OADs (basal-supported oral therapy; BOT). This has been shown to effectively lower blood glucose, but may not be sufficient to preclude postprandial hyperglycaemia in certain patients [4,5]. In order to control such excursions, BOT may be supplemented with prandial insulin (basal-plus approach) such as glulisine (Apidra®, Sanofi) [6,7]. However, those who are most likely to benefit from this approach are not always clear, and further titration of basal insulin alone may be more suitable for some patients [8].

We have recently developed a simple protocol for identifying patients for whom the basal-plus approach is most appropriate [9]. By subtracting a patient́s morning (AM) blood glucose level from that measured at bedtime (Be) the previous night, a numerical value is obtained that can be used by the treating physician when considering the addition of prandial insulin to BOT. A high BeAM value is suggestive of a) postprandial glucose (PPG) excursions during the day leading to a high bedtime value, and b) well-controlled fasting blood glucose (FBG) resulting in a low morning measurement [9]. A high BeAM value is therefore an indicator for prandial insulin supplementation, whereas a medium/low BeAM value suggests this may be of little benefit [9]. Surprisingly, a subset of T2DM patients were recently found to have a higher glucose level pre-breakfast than at bedtime the night before;

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resulting in a negative BeAM value (< 0 mg/dl) [9]. The present study was carried out to assess the characteristics of such patients, and to determine the safety and efficacy of adding a single daily injection of prandial insulin to their basal regimen.

Materials and methods

Study design and patients

A retrospective evaluation of data obtained during two randomised, multi-centre clinical trials OPAL and POC was carried out [10,11] (Supplementary Table 1). A total of 358 T2DM patients on routine insulin glargine BOT therapy who began pre-meal injection of insulin glulisine at baseline were included. The BeAM value was calculated for each patient (bedtime blood glucose minus pre-breakfast blood glucose), before sub-devision into three groups: negative BeAM value (< 0 mg/dl), medium BeAM value (0–50 mg/dl), and high BeAM value (> 50 mg/dl).

Details of the inclusion and exclusion criteria have been previously reported [10,11]. Briefly, in the OPAL trial, patients with more than two FBG readings of > 120 mg/dl in the five consecutive days before baseline were excluded. While in the POC trial, the dose of insulin glargine was optimised via titration against FBG over a period of three months to achieve a target value of ≤100 mg/dl at baseline. Patients were only included in the BeAM analysis if they had available HbA1c measurements at both the start and end of the trial. Any patients with an HbA1c value ≤7% after insulin glargine optimisation were excluded. During the two clinical trials, insulin glulisine was titrated to give a 2-hour PPG level of ≤135 mg/dl or a pre-meal blood glucose level of 100–120 mg/dl (POC trial only).

Documentation

Characteristics of all patients at baseline were pooled for analysis. These included HbA1c level, FBG level, PPG level, age, gender, weight, body mass index (BMI), diabetes history, diabetes treatment history, and dosages of insulin glargine and insulin glulisine. A mean 7-point daytime blood glucose profile (prior to and 2 h following each meal) was constructed by combining those recorded just prior to baseline. The same factors were recorded at the end of the two trials.

Hypoglycaemic events that occurred during the follow-up periods were classified as symptomatic (blood glucose < 60 mg/dl with symptoms), severe (blood glucose < 36 mg/dl), or nocturnal.

Study endpoints

The primary aim of the analysis was to determine the efficacy and safety of adding a single daily injection of insulin glulisine to BOT in patients who were calculated to have a BeAM value < 0 mg/dl. Changes in PPG, HbA1c, FPG, weight, and BMI were recorded at the start and end of each study, along with incidents of hypoglycaemia that occurred throughout. In addition, 6 composite endpoints (HbA1c < 7%; HbA1c < 7% plus no symptomatic hypoglycaemia; HbA1c < 7% plus no severe hypoglycaemia; HbA1c < 7% plus no weight gain; HbA1c < 7% plus no symptomatic hypoglycaemia and no weight gain; and HbA1c < 7% plus no severe hypoglycaemia and no weight gain) were evaluated.

Statistical analysis

Patient demographics and clinical characteristics were assessed using descriptive statistics. Categorical variables are reported as percentages of the total. Continuous variables are reported as means and standard deviations (SD). Efficacy and safety outcomes were measured and described using descriptive statistics. Associations between BeAM value, composite endpoints and the incidence of hypoglycaemia were evaluated via logistic regression and reported as odds ratios (OR), 95% confidence intervals (95%CI) and, p-values. The SAS® 9.3 software was used for all statistical analyses.

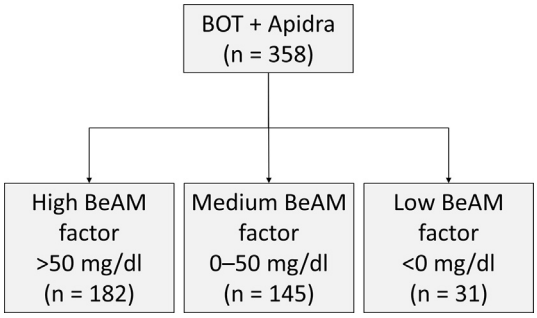

Fig. 1. Patient flow. Legend: BOT, basal-supported oral therapy; BeAM, bedtime minus morning (AM) blood glucose level.

Results

Baseline patient characteristics

At baseline, 31 of the 358 patients included in the OPAL and POC trials (8.7%) were found to have a negative (< 0 mg/dl) BeAM value and 182 (50.8%) were found to have a high BeAM value (> 50 mg/dl; Fig. 1). Negative BeAM patients were slightly younger than high BeAM patients (60.5 ± 9.5 yrs and 63.9 ± 9.0 yrs, respectively; Table 1) and a higher proportion were female (54.8% vs. 44.5%, respectively). Both weight and BMI were greater in the negative BeAM group, while mean diabetes duration was shorter (negative: 9.6 ± 6.3 yrs, high: 11.5 ± 7.4 yrs). Accordingly, the former patients had been treated with OADs and insulin for shorter periods of time.

In terms of glycaemia, negative BeAM patients had lower mean levels of HbA1c (7.2 ± 0.9 vs. 7.5 ± 0.7) and PPG (157.0 ± 28.8 vs. 201.8 ± 47.9 mg/dl) at baseline compared to high BeAM patients. In contrast, the mean FBG level was comparatively greater in negative BeAM patients (114.6 ± 13.4 mg/dl vs. 105.6 ± 16.0 mg/dl, respectively). The 7-point glucose profiles, which were constructed from the mean values recorded just prior to baseline, clearly demonstrate the large differences in daytime blood glucose levels between the negative and high BeAM groups (Fig. 2). For the high BeAM patients, the mean pre-breakfast blood glucose reading was within the recommended prepprandial range (104.0 ± 19.9 mg/dl)[12]. However, this value rose gradually over the course of the day and was significantly elevated at bedtime (199.9 ± 39.7 mg/dl). In contrast, the mean pre-breakfast

Table 1
Patient characteristics at baseline.

	Negative BeAM value (n = 31)	High BeAM value (n = 182)
Age (years)	60.5 (9.5)	63.9 (9.0)
Male (%)	45.2	55.5
Weight (kg)	93.1 (16.1)	87.7 (17.0)
BMI (kg/m^2)	32.8 (5.1)	30.7 (5.1)
HbA1c level (%)	7.2 (0.9)	7.5 (0.7)
FBG (mg/dl)	114.6 (13.4)	105.6 (16.0)
PPG (mg/dl)	157.0 (28.8)	201.8 (47.9)
Diabetes duration (years)	9.6 (6.3)	11.5 (7.4)
OAD treatment duration (years)	6.7 (4.4)	9.7 (6.7)
Insulin treatment duration (years)	2.0 (2.0)	2.3 (2.3)

Negative BeAM value is < 0 mg/dl; high BeAM value is > 50 mg/dl. BMI, body mass index; HbA1c, glycated haemoglobin; FBG, fasting blood glucose; PPG, postprandial glucose; OAD, oral antidiabetic drug.

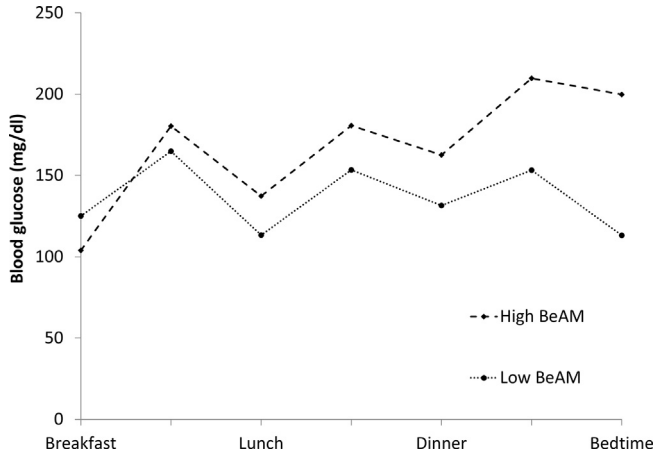

Fig. 2. Variation in daytime blood glucose levels at baseline. Legend: Blood glucose measurements were taken before and 2 h after each meal.

glucose reading for the negative BeAM patients was higher than that of the high BeAM patients (125.0 ± 18.6 mg/dl; p < 0.0001) and levels fell gradually over the day. Accordingly, the bedtime reading was lower than that recorded before breakfast (113.1 ± 17.8 mg/dl), and significantly lower than that noted for the high group at bedtime (mean difference of 86.8 mg/dl; p < 0.0001).

Changes in patient characteristics during the studies

During the OPAL and POC study periods, negative BeAM patients experienced a slight, non-significant decrease in weight and BMI (−0.8 ± 3.7 kg; p = 0.25 and −0.3 ± 1.3 kg; p = 0.29, respectively), while these factors both increased in high BeAM patients (+0.9 ± 2.8 kg and +0.3 ± 1.0 kg, respectively; p < 0.0001) (Table 2).

Between baseline and trial completion, mean HbA1c levels remained constant in the negative BeAM group (from 7.2 ± 0.9% to 7.2 ± 1.1%; p = 0.93), but decreased slightly in the high BeAM group (from 7.5 ± 0.7 to 7.2 ± 0.8%; p < 0.0001) (Table 2). Mean FBG levels increased significantly in both groups (negative BeAM: from 114.9 ± 13.8 to 131.3 ± 32.7 mg/dl [p = 0.022]; high BeAM: from 105.6 ± 16.0 to 114.3 ± 25.6 mg/dl [p < 0.0001]). Conversely, mean PPG decreased in both groups, though was only statistically significant in the high BeAM patients (from 201.8 ± 47.9 to 143.1 ± 40.6 mg/dl; p < 0.0001).

Both insulin glargine and insulin glulisine were continually titrated during the trials. At baseline, the dosage of both insulins was lower in the negative BeAM group in comparison to the high (4.0 ± 1.6 vs. 5.1 ± 1.8 units for insulin glulisine; 33.0 ± 30.9 vs. 37.8 ± 25.8 units for insulin glargine, respectively) (Table 2). By the end of the trials, all dosages had increased significantly (p < 0.0001 for all groups and insulins), with values reaching similar levels in the negative and high BeAM groups (12.5 ± 7.5 and 12.3 ± 6.7 units for insulin glulisine; 43.1 ± 32.8 and 44.7 ± 31.8 units for insulin glargine, respectively)

Table 3
Frequency of composite endpoint achievement and incidence of hypoglycaemia during the study periods.[‡]

	Negative BeAM value (n = 31)	High BeAM value (n = 182)
Composite endpoints		
HbA1c < 7%	41.9	39.0
HbA1c < 7% and no symptomatic hypoglycaemia[*]	29.0	23.6
HbA1c < 7% and no severe hypoglycaemia[†]	41.9	38.5
HbA1c < 7% and no weight gain	25.8	19.8
HbA1c < 7% and no symptomatic hypoglycaemia and no weight gain[*]	19.4	12.1
HbA1c < 7% and no severe hypoglycaemia and no weight gain[†]	25.8	19.2
Incidence of hypoglycemia		
Symptomatic hypoglycaemia[*]	2.2 (4.5)	5.2 (11.8)
Nocturnal hypoglycaemia	0.2 (0.8)	1.0 (3.1)
Severe hypoglycaemia[†]	0.1 (0.4)	0.03 (0.3)

Data are given as mean (SD). Negative BeAM value is < 0 mg/dl; high BeAM value is > 50 mg/dl.
[‡] Events per patient year.
[*] Symptomatic hypoglycaemia is defined as blood glucose < 60 mg/dl.
[†] Severe hypoglycaemia is defined as blood glucose ≤36 mg/dl.

Endpoint achievement

Symptomatic hypoglycaemia occurred less frequently in negative BeAM patients in comparison to high BeAM patients (2.2 ± 4.5 and 5.2 ± 11.8 events per patient yr, respectively) (Table 3). The same trend was found for nocturnal and severe hypoglycaemia, although the incidence of such events was low. A slightly greater proportion of negative BeAM patients achieved an HbA1c level < 7% (41.9% vs. 39.0%). This trend was also evident for the composite endpoints. A negative BeAM value was found to be an independent predictor for meeting the HbA1c < 7% endpoint (OR: 0.57 [95%CI: 0.23 – 1.45]) though this was not the case for the composite endpoints or the occurrence of hypoglycaemia (Table 4).

Discussion

While a high BeAM value is indicative of the need for BOT supplementation with prandial insulin, the benefits of such treatment in patients with a negative BeAM value have been unclear up until now.

Table 2
Change in patient characteristics during the study period.

	Negative BeAM value			High BeAM value		
	Baseline (mean ± SD)	Endpoint (mean ± SD)	p-value	Baseline (mean ± SD)	Endpoint (mean ± SD)	p-value
Weight (kg)	93.1 (16.1)	92.3 (14.6)	0.2501	87.7 (17.0)	88.6 (17.1)	< 0.0001
BMI (kg/m^2)	32.8 (5.1)	32.6 (4.7)	0.2948	30.7 (5.1)	31.1 (5.1)	< 0.0001
HbA1c level (%)	7.2 (0.9)	7.2 (1.1)	0.9324	7.5 (0.7)	7.2 (0.8)	< 0.0001
FBG (mg/dl)	114.9 (13.8)	131.3 (32.7)	0.0224	105.6 (16.0)	114.3 (25.6)	< 0.0001
PPG (mg/dl)	157.0 (28.8)	144.1 (43.1)	0.1367	201.8 (47.9)	143.1 (40.6)	< 0.0001
Insulin glargine dose (units)	33.0 (30.9)	43.1 (32.8)	< 0.0001	37.8 (25.8)	44.7 (31.8)	< 0.0001
Insulin glulisine dose (units)	4.0 (1.6)	12.5 (7.5)	< 0.0001	5.1 (1.8)	12.3 (6.7)	< 0.0001

Negative BeAM value is < 0 mg/dl; high BeAM value is > 50 mg/dl. BMI, body mass index; HbA1c, glycated haemoglobin; FBG, fasting blood glucose; PPG, postprandial glucose; SD, standard deviation.

Table 4
Endpoint predictors for negative vs. high BeAM value groups.

	Odds ratio	Wald 95% confidence limits		p-value
		Lower limit	Upper limit	
Symptomatic hypoglycaemia*	0.618	0.257	1.483	0.2810
Nocturnal hypoglycaemia	0.477	0.104	2.195	0.3417
Severe hypoglycaemia†	2.616	0.219	3.130	0.4477
HbA1c < 7%	0.574	0.228	1.450	< 0.0001
HbA1c < 7% and no symptomatic hypoglycaemia*	0.933	0.366	2.379	0.8853
HbA1c < 7% and no weight gain	0.832	0.306	2.262	0.7182
HbA1c < 7% and no symptomatic hypoglycaemia and no weight gain*	0.867	0.319	2.355	0.7792

Negative BeAM value is > 0 mg/dl; medium BeAM value is 0–50 mg/dl; high BeAM value is > 50 mg/dl.

* Symptomatic hypoglycaemia is defined as blood glucose < 60 mg/dl.

† Severe hypoglycaemia is defined as blood glucose ≤ 36 mg/dl.

We carried out a retrospective analysis of data collected in two clinical trials, both of which included T2DM patients who had prandial insulin added to their BOT at baseline [9]. Patients were stratified according to their calculated BeAM value, and their baseline and endpoint characteristics were compared.

Study population

The majority of patients included in the two trials presented with a high BeAM value; however a proportion had a negative BeAM value (< 0 mg/dl), corresponding to a pre-breakfast blood glucose level that was higher than that at bedtime the night before. In general, these patients were younger, had shorter diabetes durations and lower HbA1c levels than those with high BeAM values.

Changes in patient characteristics relative to baseline

During the study periods, there was no significant change in HbA1c levels for negative BeAM patients. This is to be expected, given that these patients had a mean baseline HbA1c close to that of the recommended < 7% target [13,14], indicating good glycemic control and the need only for on-going maintenance. Conversely, those with a high BeAM value experienced a slight decrease in HbA1c over the study period, reflecting a marginally higher baseline HbA1c and the need for improved management. A similar trend was seen for PPG levels, with a more marked decrease in the high BeAM group. This is in line with previous findings which suggest the addition of insulin glulisine to BOT is beneficial for improving glycaemic control in patients with a high BeAM value [9]. However, the analysis presented here demonstrates that there is no glycemic benefit in supplementing BOT with insulin glulisine in negative BeAM patients.

Further evidence for this arose from the analysis of FBG levels. In the negative BeAM group, baseline mean FBG values were already higher compared to the high BeAM group, and increased to a relatively greater degree over the duration of the trial. This may be explained by the idea that currently implemented titration algorithms demand an increase in insulin dosage where a higher FBG level is present, even though HbA1c levels suggest that existing insulin levels are adequate. Accordingly, a greater degree of titration was seen in the negative BeAM group compared to the high BeAM group (+10.1 vs. +6.9 units for insulin glargine and +8.5 vs. +7.2 units for insulin glulisine, respectively), potentially resulting in hyperinsulinaemia. It has been suggested that in response to excessive insulin levels, myocytes take up an increased amount of glucose [15]. If there is no energy demand on the muscle, acetyl-coA and NADH accumulate and reduce the action of pyruvate dehydrogenase, thus increasing the concentration of pyruvate in the tissue. This is then converted to lactate and secreted into the blood, where it is taken up by the liver and converted to glucose, resulting in higher blood glucose levels [16]. This phenomenon is known as the Somogyi effect. Supposing that excessive insulin was administered to the negative BeAM patients in the present study, the low energy demand on muscle tissue during the night could therefore have resulted in increased lactate secretion and liver gluconeogenesis, leading to the observed elevated FBG levels. Lending further support to this hypothesis is the fact that negative BeAM patients had a shorter diabetes duration at baseline, which may correspond to higher basal insulin secretion and a greater probability of fasting hyperinsulinaemia. As there is evidence that hyperinsulinaemia is a contributory factor for insulin resistance, the addition of insulin glulisine to BOT in negative BeAM patients may not only be non-beneficial, but also potentially damaging [17,18].

However, the Somogi effect has been largely refuted by more recent studies. An alternative explanation for a higher morning FBG level compared to that recorded the previous night is the commonly observed late-night eating habits of T2DM patients. In previous studies, between 3.8 and 42% of patients have been documented as consuming a significant number of calories after their evening meal, and this appears to be country-dependent [19–21]. Intake of foods that are high in carbohydrate and fat content can lead to up to 9 h of postprandial hyperglycemia [22], meaning that if patients consumed snacks fitting this description after the evening blood glucose levels had been recorded in the present analysis, morning FBG levels would be comparatively elevated. In further support of this concept, the negative BeAM patients in the present study had higher BMIs compared to the high BeAM patients; a factor that has been associated with T2DM patients who eat large, late-night meals [23]. Further studies determining whether patients with negative BeAM values have this eating behaviour are merited. If this is the case, lifestyle modification may be more beneficial than addition of insulin glulisine in negative BeAM patients.

The proportion of patients experiencing hypoglycaemic events was low in both negative and high BeAM groups throughout the study, and multivariate analysis suggested that BeAM value was not an independent predictor for this rate. These findings are echoed by a previous study comparing medium and high BeAM patients; further strengthening the idea that BeAM value cannot be used as a tool for predicting hypoglycemia [9].

A slightly higher proportion of negative BeAM patients achieved HbA1c < 7% than high BeAM patients. Multivariate analysis did not identify a negative BeAM value as an independent predictor for this endpoint, nor any of the composite endpoints. This is surprising, as negative BeAM patients had a baseline HbA1c level which was closer to the < 7% target; implying a greater ease of attainment. Indeed, a medium BeAM value was shown by a previous study to be predictive of a higher HbA1c < 7% achievement rate relative to a high BeAM value ($p = 0.027$), as well as the composite endpoint of HbA1c < 7% with no symptomatic hypoglycaemia ($p = 0.025$) [9]. A possible explanation for the lack of this finding in the present study may be the inappropriate use of insulin in the negative BeAM group.

Limitations

Firstly, as a retrospective study, inherent limitations such as patient number could not be controlled. This resulted in only a small number of patients being included in the negative BeAM group, reducing the statistical power of the analysis and meaning that small differences may not have been detected. Secondly, as the data were pooled from two independent trials, some differences between study protocols may have introduced errors into our analysis. The most notable discrepancy is

that the POC trial included optimisation of insulin glargine during a run-in period while the OPAL study did not [11]. Also, detailed information on concomittant OAD use was not available. Furthermore, the observation periods of the two trials were relatively short, with follow-up lasting 6 months in the OPAL trial and only 3 months in the POC trial [6,10]. This poses the question of whether the maximal effects of the therapy had been achieved in such a short time frame, and whether longer observation periods may demonstrate a more significant difference in blood glucose levels and hypoglycaemia rates between BeAM groups.

Conclusions

These retrospectively analysed data suggest that patients with a negative BeAM value do not benefit from supplementation of BOT with prandial insulin. Furthermore, it is possible that such an increase in insulin may actually be less safe, indicating a need for additional investigation into the treatment regimen of such patients. Further studies including a larger negative BeAM cohort and measurement of caloric intake and blood insulin levels may help to validate the current findings, and explain the elevated FBG levels in conjunction with apparently good glycaemic control.

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Conflict of interest statement

Thorsten Siegmund (TS), Ariel Zisman (AZ), Peter Bramlage (PB) and Stephan Kress (SK) declare to have received research funding and/or consultancy fees from Sanofi. Anja Borck (AB) is an employee of Sanofi.

Author contributions

TS, AB, AZ and SK contributed to the conception and design of this study. PB interpreted the data. TS and PB drafted the first version of the manuscript which all other authors revised for important intellectual content. All authors approved the final manuscript and can be held responsible for its content.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2018.10.002.

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