Patient Preference and Adherence

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ORIGINAL RESEARCH

A discrete choice experiment evaluation of patients' preferences for different risk, benefit, and delivery attributes of insulin therapy for diabetes management

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Objective: To evaluate patients' preferences for various attributes of insulin treatment, including route of insulin delivery.

Methods: We used a discrete choice experiment (DCE) to quantify patients' preferences. The attributes (and levels) included in the DCE questionnaire were: glucose control, frequency of hypoglycemic events, weight gain, route of administration for the long-acting and the short-acting insulin, and out-of-pocket cost. Data were analyzed using conditional logit regression and segmented models were also developed to evaluate differences in preferences between subgroups.

Results: Two hundred and seventy-four questionnaires were completed. The mean age (SD) of participants was 56.7 (12.9) years. Forty-nine percent of participants were insulin users, and 17% had type 1 diabetes. Overall, patients' ideal insulin treatment would provide better glucose control, result in fewer adverse reactions, have the lowest cost, and be administered orally. Overall, there was a strong positive preference for better glucose control relative to the other attributes. Segmented analyses by insulin use and type of diabetes suggest that there may be an important psychosocial barrier to initiating insulin therapy but that patients tend to adjust to subcutaneous administration once they initiate therapy.

Conclusions: This study illustrates the importance that patients with diabetes place on glucose control and how preferences for insulin therapy differ between subgroups. Specifically, efforts need to be made to overcome the psychosocial barriers to initiating insulin therapy which may lead to improved control through improved treatment acceptance and ultimately improve patients' quality of life and reduce the economic burden of the disease.

Keywords: insulin therapy, patients' preferences, diabetes mellitus, discrete choice experiment (DCE)

Introduction

Approximately 5% of adult Canadians have diabetes and it is suggested that this prevalence[1] may continue to increase. Many patients who could benefit from insulin therapy are either not using subcutaneous insulin at all, or are noncompliant.[2] Lack of diabetes education, inconvenience of repeated daily injections, fear of needles, injection-related anxiety, denial, and feeling that the disease has progressed are often identified as major barriers to initiating insulin therapy.[3]

It is conceivable that alternative routes of insulin delivery systems may become a clinical reality in the future.[4] Two of the most clinically viable routes of delivery that

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have the potential to greatly improve patients' compliance are oral and pulmonary (ie, inhaled) insulin administration.

The most promising oral insulin to date is hexyl-insulin-monoconjugate-2 (HIM-2), a recombinant insulin that has alterations in its physio-chemical characteristics such that it resists enzymatic degradation and facilitates gastrointesintal absorption. Ongoing phase I and II clinical trials suggest that it has an acceptable glucose-lowering effect. In addition, the delivery of oral HIM-2 to the liver through the portal circulation, thereby mimicking the physiological route of insulin secretion, may improve control of glucose excursions and avoidance of peripheral hyperinsulinemia.[5]

Pulmonary delivery of insulin is feasible given the large surface area and high permeability of the lungs where insulin can be effectively absorbed via the pulmonary alveoli.[6] However, Exubera® (Pfizer), approved for use in 2006 as the first available inhaled alternative to injectable insulin, was removed from the market less than 2 years later because of a limited uptake which may have been related to the cumbersome delivery system, safety concerns, and cost.[7] Regardless, attempts to overcome these problems have been made by other companies that are developing their own versions of inhaled insulin,[8] and promising results on patients' acceptance are beginning to emerge. Eliminating injections and providing a more physiologically similar insulin secretory profile may allow for more intensive insulin delivery that will improve glycemic control and reduce complications, while enchancing patient compliance.[4]

Because diabetes is a disease in which a large management component is based on a patients' ability to provide their own daily care, for diabetes care to succeed patients must be able to make decisions about how they will live with their illness.[9] Therefore, for health care providers to successfully facilitate patients' treatment acceptance, which in turn may lead to greater treatment effectiveness, lower burden of disease, and better patient outcomes, they need to consider what patients want to incorporate into their decisions for diabetes management.[10]

Despite newer approaches to insulin administration and diabetes management on the horizon, there is a paucity of information on how patients might "value" alternative, noninjectable insulin. Therefore, finding the insulin-delivery system and the attributes of insulin therapy that patients prefer may lead to improved control through improved treatment acceptance, and ultimately reduce the financial burden of the disease and improve patients' quality of life. In this context, the objectives of this study were to determine patients' preferences for different attributes of insulin therapy and to determine the value that patients with type 1 and type 2 diabetes place on these attributes using a discrete choice experiment (DCE). In addition, differences in preferences for treatment attributes between predefined subgroups, such as type of diabetes and insulin use, were also investigated.

Patients and methods

DCE

One of the most effective and widely used techniques to evaluate patients' preferences in the health care domain is the DCE, a stated preference technique that has evolved from conjoint analysis, and is consistent with economic theory. Conjoint analysis is designed to resemble real life, everyday choices between goods or services with well-defined but varying attributes and costs.[11] In a DCE questionnaire, participants are faced with choices between hypothetical, but realistic scenarios comprising different attributes and levels that are germane to the decision they are making. By asking respondents to make choices between these hypothetical scenarios, they are forced to make trade-offs, thereby revealing their preferences. By understanding how patients choose between treatment options in response to changes in the attribute levels, we can estimate the potential impact that each level of each attribute has on overall treatment preference, and the overall preferences for any combination of attributes and levels, even if the technology is not yet available. In this context, although hypothetical, realistic scenarios of potential insulin delivery systems that are conceivable of being released were used to design the DCE questionnaire.

Study design and patients

We performed a cross-sectional study of 378 patients with established physician-diagnosed diabetes. Participants were eligible for enrolment if they were 18 years of age or older, had physician-diagnosed type 1 or type 2 diabetes, were using oral hypoglycemic agents and/or insulin, were fluent in both reading and writing English, and were able to provide informed consent. Participants were recruited through the diabetes education clinics at Vancouver General Hospital and St Paul's Hospital in Vancouver, Canada.[12]

Ethics approval was obtained from Vancouver General Hospital, Providence Health Care, and the University of British Columbia Behavioral Research Ethics Boards. All patients were required to provide informed consent prior to enrolling in the study and each participant was remunerated C$20 for their time, travel, and parking.

Demographics, socioeconomic status, and diabetes medication use

Each patient was asked to provide sociodemographic and treatment data using a diabetes assessment questionnaire which has been designed previously for use in asthma and rheumatoid arthritis studies.[13,14] Socioeconomic status was measured based on education completed and annual household income. Diabetes history was collected based on type of diabetes, insulin status, date of diagnosis, and current use of diabetes medication. Diabetes control was measured based on patients' most recent HbA_{1c} levels. Number of hypoglycemic events (per month) and self-assessed diabetes control were also collected.

DCE questionnaire development

To develop the DCE questionnaire, we completed a qualitative descriptive study using individual interviews and focus group techniques to identify the most important attributes of insulin therapy from the perspective of patients with diabetes. Two focus groups (4 participants each) and 7 individual interviews were conducted. The sample included both men and women who attended the diabetes education clinic at St Paul's Hospital in Vancouver, B.C. Interviews typically lasted 30 to 50 minutes and all interviews were audio recorded, transcribed, and analyzed. Both insulin naïve and insulin users identified similar attributes of major importance relating to insulin therapy. Based on the results of the qualitative study, published data, and consultation with diabetes educators and clinicians, the attributes identified and included in the DCE questionnaire were: fasting blood glucose control; weight gain in the first year (low [2 kg], moderate [6 kg], and high [10 kg]); route of administration for the long-acting insulin (oral and subcutaneous), administered once daily; route of administration for the short-acting insulin (oral, subcutaneous, and inhaled) administered 3 times daily; and monthly out-of-pocket cost (C$0, C$50, C$100, and C$200).

The attributes and levels defined in Table 1 gave rise to 648 ($2^1 \times 3^4 \times 4^1$) possible combinations of treatment scenarios. Therefore, because the full factorial design of 648 possible scenarios was not feasible, a fractional factorial design was used to reduce the number of scenarios to a more feasible number while still being able to estimate utilities for all combinations of attribute levels.

One strength of this design model is its ability to develop multiple versions of the questionnaire, which significantly increases the statistical efficiency of the study. Thus, 6 fractional factorial designs optimizing D-efficiency (a summary measure of how precisely this design can estimate all parameters of interest with respect to another design) were generated to create a questionnaire with a feasible and practical number of choice sets Each version was designed to present each participant with the same number of scenarios, each with the same attributes, but the levels of all attributes in each questionnaire differed. D-efficiency summarizes how precisely this design can estimate all parameters of interest with respect to another design.

Based on 6 versions of the questionnaire each containing 15 different choice sets, the sample size required for this study was estimated using Sawtooth® software, version 6.4.2 (Sawtooth Software Inc., Sequim, WA, USA). [15] Based on this, we determined that the minimum sample size required was 130 respondents. Accounting for potential missing data and inconsistent responses, a target of 200 participants was selected. Using the CBC/Web module within Sawtooth,

Table 1 Sociodemographic and diabetes-related characteristics of participants (n = 274)

Characteristic	Number (%) or mean (SD)
Mean age	56.7 (12.98)
Gender	
Male	144 (52.55)
Female	130 (47.45)
Most recent HbA_{1c} level	
4%–7%	103 (37.59)
7.1%–10%	125 (45.62)
>10%	24 (8.76)
Do not know	18 (6.57)
Number of hypoglycemic events (per month)[a]	
None	113 (41.24)
1–2	64 (23.36)
3–4	48 (17.52)
5–6	23 (8.39)
7–8	13 (4.74)
>8	9 (3.28)
Type of diabetes	
Type 1	47 (17.15)
Type 2	227 (82.85)
Insulin status[b]	
Insulin users	134 (48.91)
Insulin nonusers	139 (50.73)
Highest education level completed	
Some high school	30 (10.95)
Completed high school	66 (24.09)
Trade/technical college	92 (33.58)
University	60 (21.89)
Masters or doctorate degree	18 (6.57)
Annual income by categories (C$):	
Low (<20,000)	33 (12.04)
Medium (20,001–50,000)	74 (27.01)
High (≥50,001)	120 (43.80)

Notes: [a]4 missing; [b]1 missing.
Abbreviation: SD, standard deviation.

6 different orthogonal designs of 15 choice sets with 2 treatment options each were created. In addition, the validity of responses was assessed by including 2 fixed choice sets in each version in which 1 treatment option was clearly "better", ie, dominant, and thus should be the preferred treatment. Respondents were expected to choose the dominant option if they understood the task; those who "failed" both tests were defined as "inconsistent" (lack of understanding of the questionnaire) and were excluded from the final analysis. Because these fixed scenarios did not require respondents to make any trade-offs, they were not included in the final analysis.

Statistical procedures

Descriptive statistics were performed using the SAS statistical software package, version 9.1 (SAS Institute, Cary, NC).[16] DCE analysis was performed using both Sawtooth® and the SAS statistical software packages. Random utility theory is used to model DCEs.[17]

Response data were analyzed using conditional logit regression. First, a full model including all consistent respondents was developed that allowed for the determination of the overall or mean preferences of the sample. In addition, segmented models were used to evaluate whether patients' preferences differed between subgroups (eg, insulin user or insulin naïve, type 1 or type 2 diabetes). Z-tests were performed to test for significant differences ($P \leq 0.05$) in preferences between the predefined subgroups.

The individual regression coefficients represent the average relative utility, or preference, for that level of that attribute. Both the sign and the magnitude of the regression coefficient for a specific attribute level reveal information about the average relative preference for that level of that attribute in the sample. Specifically, a positive regression coefficient suggests that patients prefer more of that attribute (ie, greater likelihood of benefit), whereas a negative coefficient suggests that, on average, patients prefer to have less of that characteristic (eg, an adverse event).

For the discrete choice data in this study, effect-coded variables were created for each level of all attributes; however, as a linear relationship existed between the levels for the cost attribute, this variable was analyzed as a continuous variable.

Results

Response rate and usable data

Of the 378 questionnaires distributed, 291 (77%) were returned. Of these, 7 returned incomplete questionnaires and 10 "failed" both consistency choice sets and were excluded from the analysis. Therefore, 274 participants completed the questionnaire and were included in the final analysis. Questionnaires versions 1, 2, 3, 4, 5 and 6 were completed by 44, 50, 48, 45, 47, and 43 patients, respectively.

Sample characteristics

Detailed information regarding socioeconomic and diabetes-related factors of the study participants is presented in Table 1. The mean age (SD) of participants was 56.7 (12.9) years, and 53% were men. Two hundred twenty-seven (83%) participants had type 2 diabetes and 134 (49%) were insulin users. Forty-four percent of participants had an annual house income of >C$50,000.

Conditional logit model

The results of the conditional logit model analysis conform to a priori postulated model predictions, validating the theoretical construct of the model. All regression coefficients were statistically significantly associated with treatment choices ($P < 0.05$), except for 4 hypoglycemic events per month compared to none ($P = 0.0532$), and inhaled as the route of administration for the short-acting insulin. Estimated coefficients, standard errors, and P values for the estimated utility equation are shown in Table 2.

Overall, in descending order of importance, patients' ideal insulin treatment would result in better glucose control, fewer hypoglycemic events, be less costly, and both long and short-acting insulin would be administered orally. Participants in this sample showed a strong preference for better glucose control relative to the other attributes investigated. However, in their preferred route of delivery, patients showed a stronger preference for oral administration of the short-acting insulin over both inhaled ($P < 0.001$) and subcutaneous insulin ($P < 0.001$), and they also preferred inhaled over subcutaneous administration ($P < 0.001$). For the long-acting insulin, patients also preferred oral administration to subcutaneous ($P < 0.001$).

Segmented models

Stratification of the sample by insulin use revealed that insulin users preferred oral short-acting insulin to inhaled ($P = 0.006$); however, insignificant differences were observed between oral and subcutaneous ($P = 0.192$), as well as between inhaled and subcutaneous ($P = 0.167$). Conversely, insulin-naïve patients preferred both oral and inhaled short-acting insulin over subcutaneous ($P < 0.001$), but there was no statistically significant difference in their preferences for

Table 2 Relative preferences – full conditional logit model (n = 274)[a]

Treatment attributes	Regression coefficient (SE)[b]
Fasting blood glucose control	
Optimal	0.581 (0.032)
Suboptimal	0.121 (0.027)
Poor	–0.702 (0.034)
Number of hypoglycemia events per month	
None	0.243 (0.030)
4	0.053 (0.027)[d]
8	–0.296 (0.031)
Weight gain in the first year	
Low (2 kg)	0.272 (0.030)
Moderate (6 kg)	0.143 (0.028)
High (10 kg)	–0.416 (0.031)
Route of administration for the long-acting insulin	
Oral	0.054 (0.017)
Subcutaneous	–0.054 (0.017)[c]
Route of administration for the short-acting insulin	
Subcutaneous	–0.171 (0.031)
Inhaled	0.014 (0.029)[e]
Oral	0.156 (0.028)
Cost	–0.004 (0.000)

Notes: [a]Log likelihood function: –2484; McFadden's log-likelihood ratio: 0.123; [b]SE: standard error; [b]$P < 0.001$, except as noted; [c]$P = 0.002$; [d]$P = 0.053$; [e]$P = 0.612$
Abbreviation: SE, standard error.

oral or inhaled insulin ($P = 0.064$). For long-acting insulin, they preferred oral to subcutaneous ($P < 0.001$). Comparing preferences of insulin users versus naïve revealed that insulin-naïve patients had a stronger positive preference for oral long-acting ($P < 0.001$) and short-acting insulin relative to insulin users (Table 3). They also had a stronger preference for inhaled insulin compared to insulin users ($P < 0.001$). In addition, insulin users had a stronger preference for a treatment that would not result in any hypoglycemic events per month ($P = 0.012$) compared to insulin-naïve participants.

Stratification of the sample by type of diabetes revealed that although patients with type 1 diabetes had stronger positive preferences for both oral and subcutaneous short-acting insulin relative to inhaled, the differences in preference between these 3 routes were not statistically significant. Similarly, there was an insignificant difference in their preference for oral and subcutaneous long-acting insulin ($P = 0.083$). On the other hand, patients with type 2 diabetes preferred oral short-acting insulin over both inhaled ($P = 0.001$) and subcutaneous insulin ($P < 0.001$). They also preferred inhaled insulin over subcutaneous ($P = 0.001$). Similarly, they preferred an oral long-acting insulin over subcutaneous ($P < 0.001$). The comparison of patients with type 1 or type 2 diabetes revealed that patients with type 2 diabetes had a stronger preference for the oral route for the long-acting insulin ($P = 0.008$) (Table 4); however, for the short-acting insulin, although patients with type 2 diabetes had a greater preference for an inhaled and an oral insulin than did patients with type 1 diabetes, these differences were not statistically significant. In addition, patients with type 1 diabetes had a stronger preference for subcutaneous short-acting insulin relative to patients with type 2 diabetes ($P = 0.003$). For glucose control, patients with type 1 diabetes had a stronger positive preference for optimal ($P < 0.001$) and suboptimal ($P = 0.034$) control, and a stronger negative preference for poor control ($P < 0.001$).

Discussion and conclusions

Findings from the present study revealed that patients' ideal insulin treatment would provide better glucose control, result in fewer adverse events, have the lowest cost, and be administered orally. Moreover, there was a strong positive preference for better glucose control relative to the other attributes, while route of insulin administration was not as important as hypothesized a priori. Stratification of the sample by insulin use and type of diabetes revealed a strong negative preference for the subcutaneous insulin by insulin-naïve participants and those with type 2 diabetes, while patients with type 1 diabetes and insulin users had stronger positive preference for increased control and fewer adverse events compared with patients with type 2 diabetes and the insulin naïve.

It has been argued that improved diabetes outcomes may be achieved by combining psychosocial support with appropriate medical care.[18] Greater involvement of patients in making decisions about their medication has been advocated and the importance of medication concordance (agreement between the patient and the health care provider that addresses patients' preferences and concerns about whether, when, and how medication is to be taken) has been recognized in the literature.[19,20] Building concordant patient–health care provider relationships may depend on health care providers developing strategies to address patients' preferences for involvement in the treatment decision-making process.[21] In this context, the results of the present study add to the current literature as a formal valuation and quantification of patients' preferences for insulin therapy, and how they may be willing to trade off different attributes of insulin therapy, including route of insulin delivery, for better control or potentially fewer adverse events. However, these results merely provide average preferences over the sample. Therefore, it is essential that an individuals' preferences be explored and considered when making treatment decisions.

Table 3 Relative preferences – segmented model: insulin users vs insulin naïve

Treatment attributes	Insulin users	Insulin naïve	z-test (users × naïve)
	Regression coefficient (SE)	Regression coefficient (SE)	*P* value
Fasting glucose control			
Optimal	0.662 (0.049)	0.535 (0.045)	0.055
Suboptimal	0.109 (0.039)	0.135 (0.038)	0.635
Poor	–0.772 (0.052)	–0.670 (0.048)	0.151
Number of hypoglycemia events per month			
None	0.341 (0.047)	0.183 (0.042)	0.012
4	0.031 (0.039)	0.067 (0.039)	0.518
8	–0.372 (0.047)	–0.250 (0.044)	0.057
Weight gain in the first year			
Low (2 kg)	0.316 (0.044)	0.249 (0.043)	0.278
Moderate (6 kg)	0.170 (0.041)	0.130 (0.039)	0.479
High (10 kg)	–0.486 (0.047)	–0.380 (0.042)	0.092
Route of administration for the long-acting insulin			
Oral	–0.042 (0.025)	0.146 (0.024)	<0.001
Subcutaneous	0.041 (0.025)	–0.146 (0.024)	<0.001
Route of administration for the short-acting insulin			
Subcutaneous	0.002 (0.044)	–0.344 (0.045)	<0.001
Inhaled	–0.083 (0.042)	0.119 (0.041)	<0.001
Oral	0.081 (0.042)	0.225 (0.040)	0.013
Cost	–0.004 (0.000)	–0.005 (0.000)	0.918

Abbreviation: SE, standard error.

No previously published studies in this area[22,23] included an oral route for insulin administration or weight-gain in their evaluation. Oral insulins have been extensively investigated and are on the horizon, and weight gain was commonly raised during the focus group sessions as one of the most disconcerting side effects of insulin therapy. Therefore

Table 4 Relative preferences – segmented model: type 1 vs type 2 diabetes

Treatment attributes	Type 1 diabetes	Type 2 diabetes	z-test (type 1 × type 2)
	Regression coefficient (SE)	Regression coefficient (SE)	*P* value
Fasting glucose control			
Optimal	0.937 (0.095)	0.527 (0.035)	<0.001
Suboptimal	0.262 (0.070)	0.100 (0.029)	0.034
Poor	–1.199 (0.105)	–0.627 (0.037)	<0.001
Number of hypoglycemia events per month			
None	0.409 (0.088)	0.226 (0.033)	0.051
4	–0.046 (0.072)	0.066 (0.030)	0.154
8	–0.363 (0.088)	–0.291 (0.034)	0.449
Weight gain in the first year			
Low (2 kg)	0.340 (0.084)	0.269 (0.033)	0.438
Moderate (6 kg)	0.20 (0.076)	0.142 (0.030)	0.505
High (10 kg)	–0.537 (0.091)	–0.412 (0.033)	0.195
Route of administration for the long-acting insulin			
Oral	–0.057 (0.046)	0.075 (0.019)	0.008
Subcutaneous	0.057 (0.046)	–0.075 (0.019)	0.008
Route of administration for the short-acting insulin			
Subcutaneous	0.041 (0.082)	–0.219 (0.034)	0.003
Inhaled	–0.097 (0.078)	0.037 (0.032)	0.109
Oral	0.056 (0.077)	0.182 (0.031)	0.131
Cost	–0.003 (0.000)	–0.005 (0.000)	0.269

Abbreviation: SE, standard error.

excluding these attributes from decision making will reduce the degree to which the simulated decision process can applied in the real world. Furthermore, we have also evaluated patients' willingness-to-pay to avoid weight gain related to insulin therapy, and we found out that this adverse event was the second most valued attribute in the study.[24]

Undertaking stratified analyses was key, in that it revealed differences in preferences between different types of patients which could not be observed within the full model. We showed that patients with type 1 diabetes, and insulin users, had a stronger preference for better glucose control and avoidance of adverse events compared with type 2 diabetics and insulin-naïve participants, respectively. However, differences in preferences for alternative routes of insulin administration revealed particularly interesting findings. Although previous studies have shown a stronger preference for inhaled over subcutaneous insulin by patients with type 1 diabetes,[25,26] and higher willingness-to-pay for inhaled insulin for those who were dissatisfied with their current insulin therapy, the present study revealed different findings. Specifically, patients with type 1 diabetes were indifferent to the route of insulin administration, while those with type 2 diabetes preferred oral long- and short-acting insulin. Moreover, insulin-naïve participants had a stronger positive preference for both inhaled and oral short-acting insulin and for an oral long-acting insulin relative to insulin users. Therefore, findings from the stratification of the sample by insulin use and type of diabetes suggest that there may be an important barrier to initiating therapy with subcutaneous insulin, but that patients tend to accommodate and accept the subcutaneous route once they start using insulin. Once the initial barriers to insulin use are overcome and treatment is implemented, other aspects of treatment then become more important.

The study findings can be used to guide future directions for drug development, with a focus on increasing the ability to improve glucose control and reduce adverse events. Moreover, one explanation for the low valuation patients placed on route of insulin administration may be the fact that insulin users and patients with type 1 diabetes were more likely to have experienced at least 1 serious adverse event (ie, hypoglycemia), and therefore they may be more concerned about avoiding these adverse events than with the route of insulin delivery. A second explanation is that, as mentioned earlier, patients tend to adjust to subcutaneous administration once they start using insulin. These findings are of great importance since they may be important in helping understand patients' decisions about initiation of various insulin treatment strategies.

This study found that patients were capable of understanding and making decisions based on complex information. The findings also demonstrate that the present study was capable of evaluating and quantifying patients' preferences for insulin therapy, which may provide diabetes educators with useful information for the development of targeted diabetes education and individualized treatment approaches, allowing them to help select management plans more aligned with patients' preferences. Furthermore, findings from the stratification of the sample suggest that efforts need to be made to overcome the barriers to initiating insulin therapy, which may lead to improved control, through improved treatment acceptance, and ultimately reduce the financial burden of the disease and improve patients' quality of life.

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Disclosure

The authors declare no conflicts of interest in this work.

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