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Original Article

Documented hypoglycemia is associated with poor short and long term prognosis among patients admitted to general internal medicine departments

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ABSTRACT

Aim: To study the association of documented hypoglycemia with length of stay, 30-day mortality, and 1-year mortality, among patients with and without diabetes admitted to internal medicine units.
Methods: The electronic medical records of all patients hospitalized in internal medicine departments at E. Wolfson Medical Center, Holon, Israel, between 1/1/2010 and 31/12/2013, were reviewed. Data extracted included all glucose measurements (performed using an institutional blood glucose monitoring system). Patients were considered hypoglycemic if at least one hypoglycemic event was recorded. Regression analysis was used to assess the association between documented hypoglycemia and length of stay, 30-day and one-year mortality. Age, sex, reason for admission, and the Charlson comorbidity index were entered as covariates, and the most conservative model was developed.
Results: The study population included 45,272 patients (mean age 68.9 ± 17.8 years, 49.4% males, 21.0% had diabetes mellitus). The rate of hypoglycemia in the total study population was 7.5% (16.8% among DM patients, 6.0% among patients without diabetes, $p < 0.001$). Patients with documented hypoglycemia had a longer length of hospital stay (9.3 ± 18.7 vs. 3.1 ± 6.4 days, $p < 0.001$), as well as higher risk for both 30-day (23.7% vs. 7.0%, $p < 0.001$) and 1-year mortality (41.6% vs. 15.3%, $p < 0.001$). Cox regression analysis showed that hypoglycemia significantly increased risk death at one year (HR 2.436, 95% CI 2.298–2.582, $p < 0.001$) independent of age, sex, the Charlson comorbidity index, DM status and reason for admission.
Conclusion: Documented hypoglycemia is associated with prolonged length of hospital stay and increased risk for both 30-day and 1-year mortality, regardless of diabetes mellitus status.

1. Introduction

In the community settings, strict glucose control among diabetes mellitus patients is associated with increased risk for hypoglycemia [1]. This in turn leads to increased morbidity and mortality [2,3] and increased treatment costs [4]. In addition, it has been shown that hypoglycemia occurring in the hospital setting is also associated with increased risk of in-hospital mortality in several hospitalized patient populations. Among diabetes patients hospitalized in general medical departments, hypoglycemia was associated with increased mortality [5], and prognosis was also correlated to hypoglycemia severity and number of hypoglycemic events [6].

Hypoglycemia has also been documented among non-diabetes patients. This is more frequent among intensive care unit (ICU) patients where hypoglycemia and hyperglycemia were shown to be associated with worst prognosis [7]. Similar results were found among non-critically ill patients, where glucose variability, rather than hyperglycemia or hypoglycemia per-se, was found to be associated with increased length of stay and higher mortality rates [8]. The etiology of this finding is unknown, but the occurrence of hypoglycemia among non-diabetes patients is considered to be associated with disease severity [9].

For diabetes patients, the occurrence of hyper and/or

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hypoglycemia is considered to be mostly attributed to under/over treatment. However, this is not the case for non-diabetes patients. The hypothesis of this study is that hyper and hypoglycemia during hospitalization is detrimental to health, and carries similar short and long term risk, regardless of etiology and/or diabetes mellitus status. The aim of this study is to analyze the association of hyperglycemia and hypoglycemia incidence and short and long term prognosis among patients admitted to internal medicine departments.

2. Methods

2.1. Study design: historical prospective analysis of medical records

Study population: For this study, electronic medical records of all patients discharged from internal medicine units of Edith Wolfson Medical Center, a 700-bed tertiary government medical center, between January 1st, 2010 and December 31st, 2013, were reviewed. For patients with several admissions, only the first (index) admission was included. Extracted data included patient demographics, co-morbidities, laboratory information, and length of hospital stay and date of death when applicable. Diabetes mellitus (DM) status was defined as the presence of DM as a diagnosis in the discharge letter (ICD9 code 250 and sub codes) and/or glucose lowering medications recorded upon hospital admission. Laboratory information included all glucose measurements performed during the hospitalization period, using an institutional blood glucose monitoring system (IGMS), which consisted of a point-of-care, automated glucometer, and an interactive database [10].

Glucose control and hypoglycemia definitions: A hypoglycemic event was defined as any glucose measurement equal or below 70 mg/dL (3.89 mmol/L), regardless of symptoms or treatment. Patients were considered hypoglycemic if they had at least one documented hypoglycemic event. The number of hypoglycemic events was also recorded for each patient, and an average glucose during the stay was calculated. Patients were considered "controlled" if the average glucose during stay was lower than 180 mg/dL, regardless of the number of glucose measurements.

Statistical analysis: Data were analyzed using SPSS ver. 21.0 (IBM Inc., USA). Continuous variables were compared between patient groups using the *t*-test for independent samples, or ANOVA with Bonferonni post-hoc analysis as appropriate. Associations between nominal variables were assessed using the chi-square test. Logistic regression analysis was used to examine the effect of the number of hypoglycemic events on 30-day and, separately, 1-year mortality. General linear modeling was used to predict length of hospital stay. Cox regression analysis was used to model 30-day and 1-year survival. All tests are two-sided and considered significant at $p < 0.05$.

3. Results

3.1. Hypoglycemic events among diabetes and non-diabetes patients

Table 1 shows patient demographics, co-morbidities and baseline laboratory data across diabetes mellitus and hypoglycemia groups. During the acquisition period, 45,272 patients (mean age 68.9 ± 17.8 years, 49.4% males) were discharged from the hospital. Of the patients discharged, 9507 (21.0%) had DM.

The average glucose levels during stay for diabetes patient were 182 ± 63 mg/dL, and 57.7% were considered controlled with an average below 180 mg/dL. For non-diabetes patients, the average glucose levels during stay were 133 ± 46 mg/dL, and 88.8% were controlled ($p < 0.001$ between diabetes and non-diabetes results). Rate of hypoglycemia was 7.5% of all patients. There were more individuals with documented hypoglycemic events among patients with vs. without diabetes: 16.8% vs. 6.0%, $p < 0.001$. Among patients with any hypoglycemic event, the mean number of events was 2.2 ± 2.6 (median 1 event). There was no clear association between the average glucose and the rate of hypoglycemia. Rate of hypoglycemia was the highest among the first and fifth quintiles of glucose control, regardless of diabetes mellitus status.

In general, hypoglycemic patients were older (73.8 ± 15.5 vs. 68.4 ± 17.9 years, $p < 0.001$), had higher rates of hypoalbuminemia upon admission (58.8% vs. 28.2%. $p < 0.001$) lower cholesterol (150 ± 50 vs. 169 ± 48 mg/dL, $p < 0.001$), lower hemoglobin (11.7 ± 2.2 vs. 12.6 ± 2.0 g/dL, $p < 0.001$) and higher white blood cell counts (12.2 ± 2.0 vs. $10.2 \pm 6.3 \times 10^3$ cells per mm^3, $p < 0.001$). Acute infection was more prevalent as a reason for admission among patients with hypoglycemia (43.7% vs. 35.1%, $p < 0.001$). In addition, hypoglycemic patients were sicker, as indicated by the Charlson comorbidity index (1.9 ± 2.0 vs. 1.0 ± 1.6 arbitrary units, $p < 0.001$). They had higher rates of congestive heart failure (12.6% vs. 8.4%, $p < 0.001$), chronic renal failure (18.9% vs. 7.4%, $p < 0.001$) and dementia (7.6% vs. 4.0%, $p < 0.001$).

3.2. Short- and long-term prognosis of hypoglycemia

In the total study cohort, the mean length of hospital stay was 3.5 ± 8.2 days (median 2 days, Q1-Q3 0–4 days). Rates of 30-day and 1-year mortality were 8.3% and 17.3% respectively. Table 2 shows the length of hospital stay, 30-day and 1-year mortality rates according to hypoglycemia and diabetes mellitus status.

Regardless of diabetes mellitus status, patients with documented hypoglycemia during the hospitalization period had a significantly longer length of hospital stay compared to patients without hypoglycemia (9.3 ± 18.7 vs. 3.1 ± 6.4, $p < 0.001$). Compared to patients without hypoglycemic events, patients with at least one hypoglycemic event had significantly greater 30-day mortality (7.0% vs. 23.7%, $p < 0.001$) and 1-year mortality (15.3% vs. 41.6%, $p < 0.001$).

A logistic regression model was used to examine the effects of the number of hypoglycemic events, and the glucose control status on 30-day, and 1-year mortality. This model showed that an increased number of hypoglycemic events significantly increased odds of both 30-day (OR 1.205, 95% CI 1.173–1.238, $p < 0.001$) and 1-year mortality (OR 1.370, 95% CI 1.327–1.414, $p < 0.001$).

In addition, age (OR 1.071, 95% CI 1.068–1.075, $p < 0.001$) also showed significantly increased odds of 30-day mortality. However, positive diabetes mellitus status (OR 0.733, 95% CI 0.662–0.810, $p < 0.001$) and positive glucose control status (OR 0.443, 95% CI 0.406–0.484, $p < 0.001$) all significantly *reduced* odds of 30-day mortality. Regarding 1-year mortality: Age (OR 1.076, 95% CI 1.073–1.079, $p < 0.001$), male sex (OR 1.154, 95% CI 1.090–1.221, $p < 0.001$) and the Charlson comorbidity index (OR 1.346, 95% CI 1.325–1.367, $p < 0.001$) all significantly increased odds of 1-year mortality. However, positive diabetes mellitus status (OR 0.797, 95% CI 0.737–0.862, $p < 0.001$) and positive glucose control during stay (OR 0.546, 95% CI 0.508–0.586, $p < 0.001$) were both significantly associated with reduced 1-year mortality.

In the total study cohort, general linear modeling showed that age, glucose control, and hypoglycemia occurrence significantly increased length of hospital stay, while sex did not. Findings were robust in analyses performed separately among patients with and without diabetes. In these models, both age and hypoglycemia occurrence significantly increased the length of hospital stay. However, when plotting the estimated marginal means for length of stay according to hypoglycemia, glucose control and diabetes mellitus status, it appears that hypoglycemia was a key parameter

Table 1
Patient demographics, co-morbidities and baseline laboratory data across diabetes mellitus and hypoglycemia groups.

Parameter	Non-diabetes		Diabetes	
	Hypoglycemia		Hypoglycemia	
	No n = 36,433	Yes n = 2321	No n = 5424	Yes n = 1094
Age (years)	67.8 ± 18.5	73.1 ± 16.8[a]	73.3 ± 12.6[b]	75.2 ± 12.3[a b]
Male sex (%)	49.3	49.9	49.8	48.5
Reason for admission				
Acute Cerebrovascular disease (%)	5.3	5.5	5.3	6.0[b]
Exacerbation of congestive heart failure (%)	5.9	7.3[a]	8.9[b]	11.0[a†]
Exacerbation of obstructive lung disease (%)	7.5	7.0	7.5	7.3
Acute coronary syndrome (%)	4.3	4.3	5.2	5.6
Acute infection (%)	36.2	45.8[a]	31.7	41.2[a]
Co-morbidities				
Chronic obstructive lung disease (%)	14.1	14.6	11.4[b]	16.9[a]
Dementia (%)	4.7	7.9[a]	4.1[b]	5.9[a b]
Congestive heart failure (%)	7.7	11.3[a]	11.4[b]	14.4[a b]
Anemia – all types (%)	7.6	11.9[a]	8.7	14.1[a b]
Cerebrovascular disease (%)	4.7	7.6[a]	5.8[b]	7.0
Hyperlipidemia (%)	43.3	37.1[a]	52.0[b]	48.4[a b]
Hypertension (%)	17.1	17.7	74.9[b]	72.5[b]
Ischemic heart disease (%)	8.5	8.5	38.2[b]	40.6[b]
Chronic renal failure (%)	5.1	10.9[a]	5.5[b]	22.8[a b]
Charlson comorbidity index (arbitrary units)	0.8 ± 1.5	1.5 ± 2.0[a]	2.1 ± 1.9[b]	2.6 ± 2.0[a b]
Laboratory data				
Hypoalbuminemia (%)	27.0	58.2[a]	36.2[b]	60.1[a]
Length of stay (days)	3.0 ± 6.4	8.7 ± 18.9[a]	3.6 ± 6.5[b]	10.6 ± 18.2[a b]
Albumin (g/dL)	3.7 ± 0.5	3.3 ± 0.7[a]	3.6 ± 0.5[b]	3.3 ± 0.6[a b]
Creatinine (mg/dL)	1.1 ± 0.8	1.5 ± 1.3[a]	1.4 ± 1.1[b]	1.8 ± 1.5[a b]
Cholesterol (mg/dL)	170 ± 47	151 ± 51[a]	162 ± 51[b]	149 ± 48[a]
Hemoglobin (g/dL)	12.7 ± 2.0	11.9 ± 2.1[a]	12.0 ± 2.1[b]	11.2 ± 2.1[a b]
White blood cell count (cells per mm3x103)	10.1 ± 6.3	12.2 ± 7.5[a]	10.8 ± 6.1[b]	12.2 ± 11.6[a]
Average glucose (mg/dL)	133 ± 46	135 ± 50	184 ± 64[b]	174 ± 56[b]

[a] Significant compared to no hypoglycemia (same diabetes sub-group).
[b] Significant compared to non-diabetes (same hypoglycemia sub-group).

Table 2
Length of hospital stay, 30-day and 1-year mortality rates according to hypoglycemia and diabetes mellitus status.

Parameter	Non-diabetes		Diabetes	
	Hypoglycemia		Hypoglycemia	
	No n = 36,433	Yes n = 2321	No n = 5424	Yes n = 1094
Length of stay (days)	3.0 ± 6.4	8.7 ± 18.9[a]	3.6 ± 6.5[b]	10.6 ± 18.2[a b]
30-day mortality (%)	6.6	25.2[a]	10.0[b]	20.5[a b]
1-year mortality (%)	14.4	42.0[a]	21.6[b]	40.9[a b]

[a] Significant compared to no hypoglycemia (same diabetes sub-group).
[b] Significant compared to non-diabetes (same hypoglycemia sub-group).

to influence length of stay for both diabetes and non-diabetes patients, whereas glucose control during hospitalization was associated with increased length of stay only among diabetes patients. Diabetes mellitus status had no effect on length of stay among patients with well-controlled glucose levels and no documented hypoglycemia (Fig. 1).

Cox regression analysis was used to model 1-year survival including any hypoglycemic event (yes/no), glucose control status (controlled/uncontrolled) and including age, sex and the Charlson comorbidity index as covariates. Hypoglycemia significantly increased risk of 1 year mortality (HR 2.369, 95% CI 2.233–2.513, $p < 0.001$). In addition, age (HR 1.066, 95% CI 1.064–1.068, $p < 0.001$), male sex (HR 1.107, 95% CI 1.057–1.159, $p < 0.001$), and increasing Charlson co-morbidity index (HR 1.218, 95% CI 1.206–1.230, $p < 0.001$) all increased risk of 1 year mortality. Glucose control (HR 0.636, 95% CI 0.603–0.672, $p < 0.001$) was associated with reduced risk of 1-year mortality.

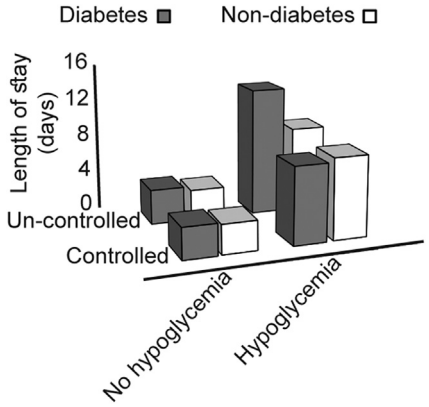

Fig. 1. Estimated marginal means for length of stay across hypoglycemia, glucose control and diabetes subgroups.

The study population was categorized into sub-groups according to hypoglycemia occurrence and the glucose control status, and the Cox regression analysis was used to model 1-year survival for diabetes and non-diabetes patients separately (Fig. 2). The patients with the worst 1-year survival were patients with uncontrolled glucose and with documented hypoglycemia, regardless of diabetes mellitus status.

For non-diabetes patients, adequate glucose control and no hypoglycemia was associated with the best outcome (HR 0.328, 95% CI 0.280–0.383, $p < 0.001$), followed by patients with uncontrolled glucose but no hypoglycemia (HR 0.606, 95% CI 0.512–0.716, $p < 0.001$). No difference in survival was observed for non-diabetes patients subgroup with documented hypoglycemia combined with uncontrolled glucose. In addition, age (HR 1.067, 95% CI 1.064–1.069, $p < 0.001$), male sex (HR 1.123, 95% CI 1.066–1.183, $p < 0.001$) and increasing Charlson comorbidity index (HR 1.226, 95% CI 1.212–1.240, $p < 0.001$) all increased risk of 1 year mortality.

For diabetes patients, adequate glucose control and no hypoglycemia was also associated with the best outcome (HR 0.333, 95% CI 0.284–0.391, $p < 0.001$), followed by diabetes patients with hypoglycemia but controlled glucose (HR 0.565, 95% CI 0.480–0.663, $p < 0.001$), and lastly, patients with uncontrolled glucose but no hypoglycemia (HR 0.700, 95% CI 0.581–0.844, $p < 0.001$). In addition, age (HR 1.067, 95% CI 1.064–1.069, $p < 0.001$) and increasing Charlson comorbidity index (HR 1.226, 95% CI 1.212–1.240, $p < 0.001$) all increased risk of 1 year mortality. Male sex did not affect prognosis.

The study population was then categorized into 4 sub-groups based on the hypoglycemia and diabetes mellitus status, and the Cox model included the patients' sub-groups as well as glucose control status (controlled/uncontrolled), age, sex and the Charlson comorbidity index as covariates. Using the sub-group of neither diabetes nor any hypoglycemic events as references, diabetes patients with hypoglycemia (HR 1.753, 95% CI 1.585–1.938, $p < 0.001$) and non-diabetes patients with hypoglycemia (HR 2.697, 95% CI 2.516–2.891, $p < 0.001$) had a greater risk of 1-year mortality. Interestingly, diabetes patients without documented hypoglycemia had lower one-year mortality (HR 0.915, 95% CI 0.853–0.981, $p = 0.013$). Further, hypoglycemic events in patients without diabetes conferred greater 1-year mortality risk than hypoglycemic events in patients with diabetes as shown in Fig. 3.

In addition, age (HR 1.066, 95% CI 1.064–1.068, $p < 0.001$), male sex (HR 1.110, 95% CI 1.050–1.152, $p < 0.001$), increasing Charlson co-morbidity index (HR 1.226, 95% CI 1.213–1.238, $p < 0.001$) and uncontrolled glucose (HR 1.640, 95% CI 1.551–1.735, $p < 0.001$) all significantly increased risk of 1 year mortality.

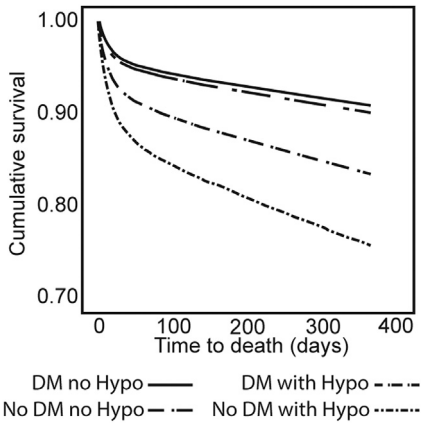

Fig. 3. Cumulative survival of patients across hypoglycemia and diabetes subgroups.

When reason for admission was added to the Cox regression models, the aforementioned predictors remained significant. In addition, only acute infection (HR 1.406, 95% CI 1.333–1.484, $p < 0.001$) increased 1-year mortality risk. Acute coronary syndrome, exacerbation of CHF, acute stroke were not associated with increased mortality in this model. Exacerbation of COPD was associated with reduced 1-year mortality in this model (HR 0.887, 95% CI 0.801–0.983, $p = 0.022$).

4. Discussion

Our data suggest that glucose control is a key factor associated with both short and long term prognosis of patients admitted to internal medicine units, regardless of diabetes mellitus status. Among diabetes mellitus patients, hyperglycemia was associated with both increased length of hospital stay and 30-day and 1-year mortality. Among non-diabetes patients, the effect of hyperglycemia was similar. Hyperglycemia during hospital stay was found to be associated with increased 30-day and 1-year mortality among non-diabetes, but failed to have an impact on length of hospital stay. However, our data also show that the key factor to influence prognosis was hypoglycemia.

Hypoglycemia, regardless of diabetes mellitus status, is

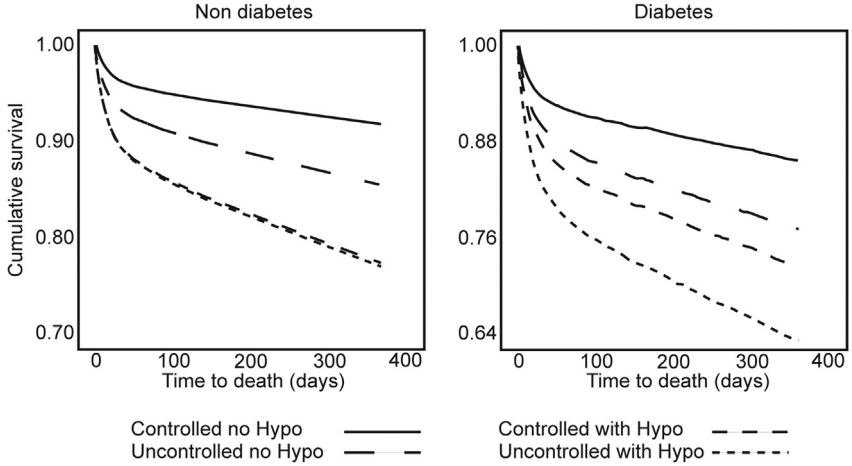

Fig. 2. Cumulative survival of patients across hypoglycemia and glucose control groups for non-diabetes (left panel) and diabetes (right panel) patients.

associated with more than doubling the length of stay and quadrupling the rate of 30-day mortality. There is a significant association between the number of documented hypoglycemic events and the 30-day mortality rates, and each hypoglycemic event increases the chances of 30-day mortality by ~25%. This, again, is true, regardless of diabetes mellitus status, and it persists for all patients, even after controlling for reason of admission and for glucose control.

The occurrence of hypoglycemia among non-diabetes mellitus patients has been documented before, but it is considered rare [11]. Recent data suggests higher rates [12]. We found that 6% of our non-diabetes mellitus patients had at least one documented hypoglycemic event. This finding may be attributable to nurse-initiated glucose measurement, increasing the yield of hypoglycemic events [13].

Interestingly, non-diabetes patients with hypoglycemia have poorer 1-year survival than patients with diabetes and hypoglycemia. It is possible that hypoglycemia among non-diabetes patients reflects severe underlying conditions and comorbidities. The Charlson comorbidity index scores were significantly higher among patients with vs. without diabetes, but this is because diabetes mellitus contributes to the Charlson index. In addition, the index does not take into account other conditions and/or treatments that may affect prognosis. It is possible that, among diabetes mellitus patients, treatment-induced hypoglycemia carries different risk compared to hypoglycemia not associated with medical treatment. This, however, is beyond the scope of the present study, and should be evaluated in further research.

One possible explanation for hypoglycemia common to patients both with and without diabetes is malnutrition. Malnutrition is defined as an imbalance between consumption and expenditure of either energy, protein or any other nutrient that damages body function [14]. This condition is extremely prevalent among patients admitted to internal medicine units [15]. In the present study, patients with documented hypoglycemia had lower albumin levels and lower cholesterol levels than patients without hypoglycemic events, likely indicating malnutrition in these patients. This may also explain the high 1-year mortality rates, similar to rates observed among malnourished patients [16].

It has been shown that severely malnourished individuals may have hypoglycemia and may even exhibit insulin resistance and diabetes mellitus [17]. The association between dysglycemia and severe malnutrition has been shown in developing countries [18], but has not been identified in developed countries to our knowledge. It was shown that patients admitted to the hospital of westernized hospitals consume less than 50% of the calories provided, and that caloric intake is associated with length of hospital stay, re-admission rate and in-hospital mortality [19]. The lack of adequate nutrition, and the possible association of malnutrition and glucose control should be further investigated.

We conclude that documented hypoglycemia carries a high risk for increasing length of hospital stay and 30-day as well as 1-year mortality rates among patients admitted to internal medicine units. This is regardless of diabetes mellitus status, and is regardless of reason for admission.

Conflict of interest

This study received no funding, and all authors declare no conflict of interest.

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