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Blood glucose on admission and mortality in patients with venous thromboembolism

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ABSTRACT

Aims: Evaluate association between admission blood glucose (ABG) and mortality in patients with or without diabetes mellitus (DM) hospitalized for venous thromboembolism (VTE).
Methods: Observational data derived from the electronic records of hospitalized patients ≥18 years, admitted for VTE (including deep vein thrombosis and pulmonary embolism) between January 2011 and December 2013. ABG levels were classified to categories: ≤70 (low), 70–110 (normal), 111–140 (mildly elevated), 141–180 mg/dl (moderately elevated) and > 180 mg/dl (markedly elevated). Main outcome was all-cause mortality at the end of follow-up. We had complete follow-up data at 12 months for all patients; median follow-up time was 1126 days.
Results: Cohort included 567 patients, 137 with (mean age 73, 45% male), and 430 without DM (mean age 65, 40% male). There was a significant interaction between DM, ABG and mortality ($p \le 0.05$). In patients without DM there was a significant association between ABG and mortality: [hazard ratios 1.6, 2.3, and 4.7 respectively for mildly, moderately and markedly elevated ABG ($p \le 0.01$)]. A significant association between ABG and mortality persisted following multivariable analysis only in patients with markedly elevated ABG (HR = 2.3 95% CI 1.2–4.5). Similar results were evident in patients with deep vein thrombosis or pulmonary embolism. In patients with DM there was no significant association between ABG and mortality.
Conclusion: In patients without DM hospitalized for VTE, markedly elevated ABG is associated with increased mortality.

1. Introduction

Hyperglycemia is associated with elevated coagulation factors and impaired fibrinolysis, and previous studies reported association of hyperglycemia with an increased risk of venous thromboembolism (VTE) (Lemkes et al., 2010). The estimated incidence rate of VTE is 75–269 cases per 100,000 individuals in Western Europe, North America, Australia, and Southern Latin America, and pulmonary embolism represents one third of all VTE cases (Raskob, Angchaisuksiri, Blanco, et al., 2014).

Elevated admission blood glucose (ABG) levels during acute illness is common and is associated with poor outcomes among patients with and without diabetes following admission for several conditions including ischemic or hemorrhagic stroke (Capes, Hunt, Malmberg, Pathak, & Gerstein, 2001), surgery (Golden, Linda, & Frederick, 1999), trauma (Yendamuri, Fulda, & Tinkoff, 2003), heart failure (Barsheshet, Garty, Grossman, et al., 2007; Kosiborod, Inzucchi, Spertus, et al., 2009), pneumonia (Akirov & Shimon, 2016; Falciglia et al., 2009; Foltran, Gregori, Caropreso, Pagano, & Bruno, 2013; Gamble, Eurich, Marrie, & Majumdar, 2010) and acute myocardial infarction (Capes, Sarah, & Hertzel, 2000; Timmer, van der Horst, Ottervanger, et al., 2004; Yang, Song, Bin, et al., 2013).

ABG values are readily available for most hospitalized patients, and may predict the short and long-term outcomes of patients hospitalized for VTE. Our objective was to evaluate the association between ABG levels in patients with and without DM and all-cause short and long-term outcomes following hospitalization for VTE.

2. Methods

Historical prospective data were extracted from the electronic medical records of all patients who were admitted to the medical wards in Rabin Medical Center, Israel, between January 1, 2011 and December 31, 2013. Inclusion criteria were age ≥18 years with a principal discharge diagnosis of pulmonary embolism (PE) or deep

The authors report no conflict of interest.

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vein thrombosis (DVT). Diagnosis of PE/DVT was based on medical history, physical examination, laboratory results and imaging studies, including Doppler ultrasound, computed angiography, or, in rare cases, lung ventilation/perfusion scan. We did not include cases of superficial vein thrombosis. In case of a recurrent admission for VTE, the first admission in that time period was considered the index hospitalization and the recurrent admission was excluded from the data analysis. Patients without documented ABG levels were excluded.

Rabin Medical Center, encompassing Beilinson and Golda-Hasharon campuses, is a tertiary-care facility with more than 1300 beds. Most of the admissions to the 10 medical wards are through the emergency department, and all patients' data are recorded in electronic medical charts, based on the same database platform used in community primary care facilities. Mortality data were obtained from the hospital's mortality database, updated from the Ministry of the Interior Population Registry. We collected mortality data until June 1, 2015.

Patients were stratified into those with pre-existing DM, if their medical record included a diagnosis of DM or use of any oral hypoglycemic agent, glucagon-like peptide agonist, or insulin at the time of admission, and those without DM.

ABG levels, defined as the blood glucose level closest to the patient's admission and, within the first 24 h of the admission date, were classified into the following five categories: <70, 70 to 110, 111 to 140, 141–180, and > 180 mg/dl. These categories were chosen in accordance with the American Diabetes Association guidelines, which recommend initiating insulin therapy for treatment of persistent hyperglycemia starting at a threshold of 180 mg/dl and above, aiming at a target glucose range of 140–180 mg/dl for critically and non-critically ill patients (American Diabetes Association, 2016).

Blood glucose measurements were based on serum glucose levels derived from venous blood samples.

We have collected data regarding co-morbidities, according to diagnoses as defined in the medical records, including: malignancy, hyperlipidemia, hypertension, ischemic heart disease, chronic heart failure, chronic renal failure, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, interstitial lung disease, and inflammatory bowel disease.

2.1. Statistical analysis

The statistical analysis was generated using SAS Software, version 9.4 of the SAS System for PC, Copyright 2002–2012. SAS Institute Inc. and all other SAS Institute Inc. products or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Continuous variables were presented by mean ± SD; categorical variables were presented by (n, %). T-Test was used to compare the value of continuous variables between study groups and Chi-Square was used to value of categorical variables between study groups. Normal distribution of continuous variables (age, BMI) was confirmed using and parametric (Kruskal–Wallis) and nonparametric (Wilcoxon) and nonparametric tests. Cox proportional hazards model was used to assess the effect of study variables on survival, including age, gender, smoking, alcohol, malignancy, chronic renal failure, ischemic heart disease, congestive heart failure, hypertension, and cerebrovascular disease, as well as for interaction between DM and glucose levels. Since this interaction was significant ($p \leq 0.05$), the Cox model was rerun by DM groups. This analysis proved a significant association between ABG levels and mortality risk in patients without DM, but in the group of patients with DM there was no significant association ($p > 0.05$). Subsequently, we focused our data analyses on the group of patients without DM.

We had complete data for all the study variables, other than BMI and smoking. No imputation for missing data was done because missing at random cannot be assumed.

Due to the small number of patients with low ABG levels, we did not analyze the data for this group.

3. Results

3.1. Study cohort

Amongst 35,340 patients admitted to the medical wards during the study period, including 24,159 without DM (68%) and 11,181 with DM (32%), the final cohort comprised 567 patients admitted with VTE, including 295 cases with deep vein thrombosis (DVT), 277 cases with pulmonary embolism (PE), including 5 cases with both DVT and PE (Fig. 1).

Mean ± SD age of the cohort was 67 ± 18 years (range 19–99 years), 232 were men (41%) and 430 (76%) did not have pre-existing DM. Data on DM type were available for 100 of the 137 (73%) patients with DM, and all had type 2 DM. In the remainder, type 2 DM was likely in most cases but this could not be confirmed. Compared with patients without DM, those with DM were older (mean age 65 ± 19 vs. 73 ± 12, $p < 0.001$). Malignancy rates were comparable in patients with and without DM (30% vs., 26%, $p > 0.05$). Rates of hypertension, hyperlipidemia, ischemic heart disease and cerebrovascular disease were significantly higher in the group of patients with pre-existing DM (Table 1). As expected, malignancy rates were much higher in the group of patients with VTE (151/567, 27%) compared with hospitalized patients without VTE (5,080/34,773, 15%).

Most patients without DM had normal ABG levels (52%) or mildly elevated ABG levels (31%), while markedly elevated ABG levels were much less common (5%). However, most of the patients with DM had markedly elevated ABG levels (44%), or moderately elevated ABG levels (24%). The total number of patients with low ABG levels was very small (4 patients without DM and 3 patients with DM (Fig. 1).

We had complete follow-up data at 12 months for all patients, with first patient censored after 519 days. Median follow-up time was 1126 days.

In-hospital mortality rates were 6%, with mortality rates of 13% at 30-days after discharge, 26%, 31% and 34% mortality rates 12-, 24- and 36-months after discharge. Mortality rates were higher in the group of patients with DM, compared with patients without DM throughout the follow-up period (Fig. 2). At the end of follow up mortality rates were 39% (223/567 patients). Mortality rates were highest in the group of patients with markedly elevated ABG levels and lowest in the group of patients with normal ABG levels, compared with all other ABG categories (Fig. 3).

In the group of patients with DM there was no significant association between ABG levels and mortality rates ($p > 0.05$). In patients without DM, there was a statistically significant association between ABG and mortality risk ($p < 0.0001$ for all comparisons).

Unadjusted hazard ratios (95% CI) of all-cause mortality at the end of follow-up, compared with normal ABG levels were 1.6 (1.1–2.4) for mildly elevated ABG levels, 2.3 (1.4–3.7) for moderately elevated ABG, and 4.7 (2.7–8.1) for markedly elevated ABG levels.

Following adjustment for age, gender, smoking, alcohol, malignancy, ischemic heart disease, congestive heart failure, hypertension, chronic renal failure and cerebrovascular disease, the adjusted hazard ratios (95% CI) of all-cause mortality, compared with normal ABG levels were 1.0 (0.7–1.5) with mildly elevated ABG levels, 1.6 (0.9–2.7) with moderately elevated ABG levels and 2.3 (1.2–4.5) with markedly elevated ABG.

Survival analysis at the end of follow-up demonstrated the highest survival rates following discharge for patients with normal or mildly elevated ABG levels, and lowest in patients with markedly elevated ABG levels ($p < 0.001$) (Kaplan–Meier analysis of patient survival following admission as time until death is shown in Fig. 4).

3.2. DVT

Our cohort included 295 patients with DVT, most of them without DM (224 patients, 76%). Rates of DVT during the study period were 0.8% (0.9% in patients without DM and 0.6% in patients with DM).

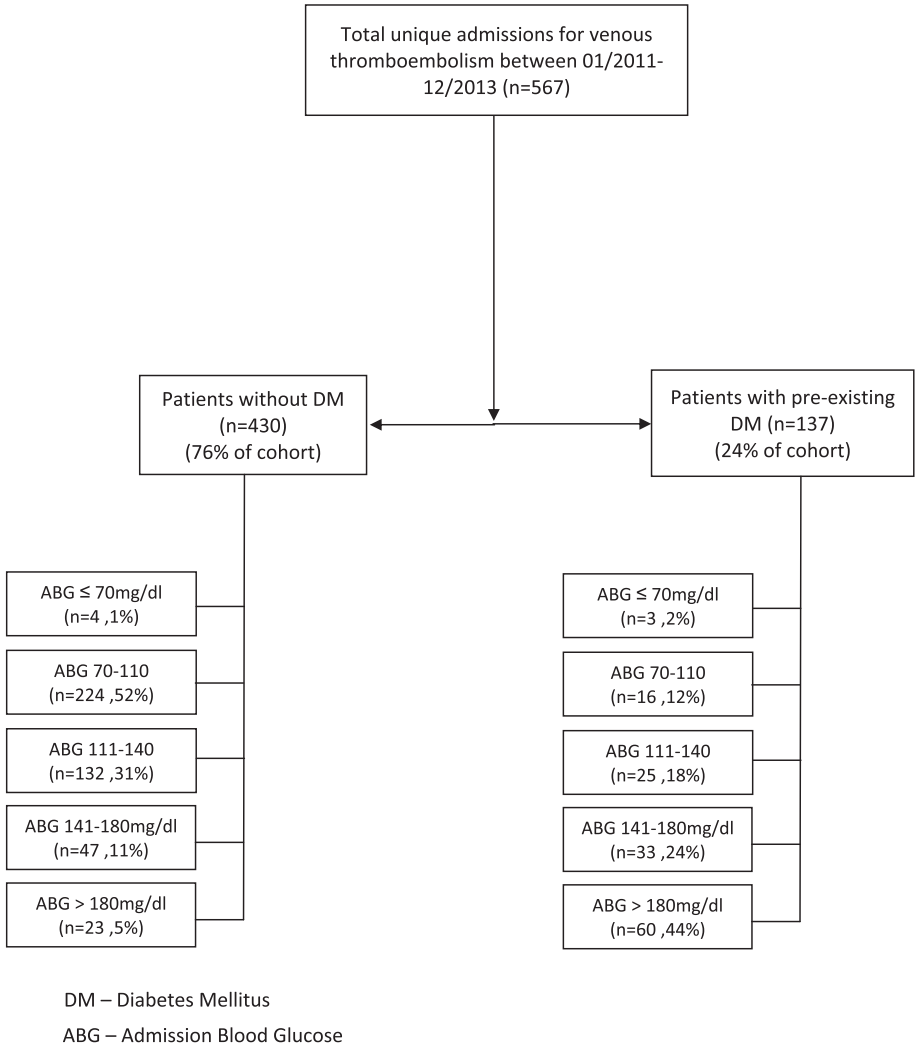

Fig. 1. Patient flow diagram.

Similar to the entire cohort of patients with VTE, there was an interaction between DM, ABG and mortality at the end of follow up in patients with DVT.

In patients with DM there was no statistically significant association between ABG and mortality at the end of follow-up. However, in patients without DM, the unadjusted hazard ratios of mortality, compared with normal ABG levels, were 1.4 (0.7–2.6, p = NS) with mildly elevated ABG, 2.3 (1.2–4.6, $p < 0.05$) with moderately and 8.3 (3.8–18.3, $p < 0.001$) with markedly elevated ABG levels. Following adjustment for age, gender, smoking, alcohol, malignancy, ischemic heart disease, congestive heart failure, hypertension, chronic renal failure and cerebrovascular disease, adjusted hazard ratios were compared between groups for the entire follow-up, indicating a statistically significant difference in overall survival between patients

Table 1
Baseline characteristics of patients with and without diabetes mellitus.

	Patients without diabetes mellitus (n = 430, 76%)	Patients with diabetes mellitus (n = 137, 24%)	p-value
Patient Characteristics			
Age, mean (median)	65 ± 19 (68, IQR 51–79)	73 ± 12 (75, IQR 65–82)	$p < 0.05$
Men, n (%)	171 (40%)	61 (45%)	P = NS
Smoking (%)	54 (14%)	8 (7%)	$P < 0.05$
Alcohol (%)	9 (2%)	2 (2%)	p = NS
BMI, mean	26 ± 4 (IQR 24–29)	29 ± 4 (IQR 26–31)	p = NS
Co-morbidities, n (%)			
Malignancy	110 (26%)	41 (30%)	p = NS
Hypertension	157 (37%)	80 (58%)	$p < 0.05$
Hyperlipidemia	95 (22%)	43 (31%)	$p < 0.05$
Ischemic Heart Disease	47 (11%)	29 (21%)	$p < 0.05$
Congestive Heart Failure	17 (4%)	7 (5%)	p = NS
Cerebrovascular Disease	23 (5%)	15 (11%)	$p < 0.05$
Chronic Renal Failure	10 (4%)	10 (7%)	p = NS
Chronic Obstructive Pulmonary Disease	7 (2%)	2 (1%)	p = NS

BMI = Body Mass Index.

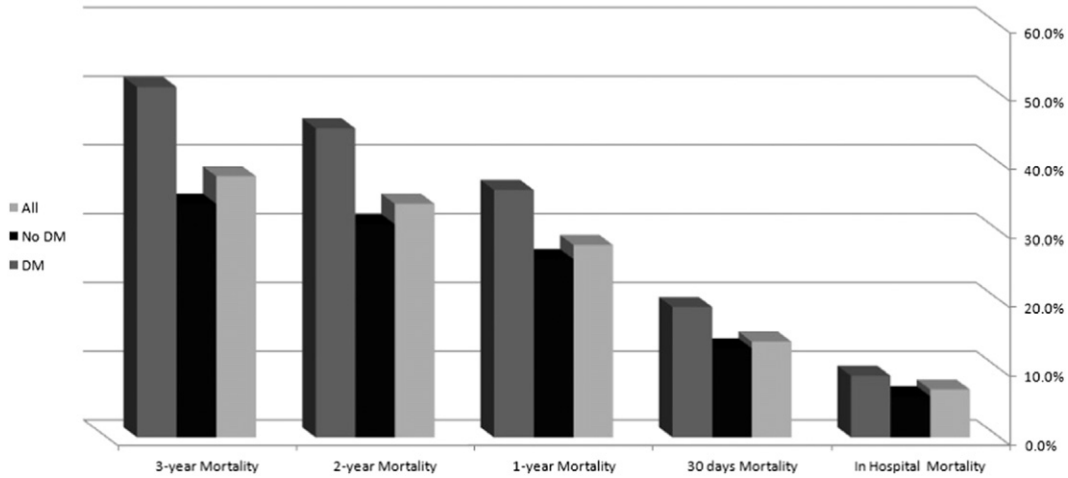

Fig. 2. Short- and long-term mortality according to pre-existing diabetes mellitus.

with normal ABG levels and markedly elevated ABG (aHR = 2.4, 95% CI = 1.2–4.5, $p < 0.05$). However, the difference between normal ABG levels and mildly or moderately elevated ABG levels did not reach statistical significance

3.3. PE

Our cohort included 277 patients with PE, most of them without DM (209 patients, 75%). Rates of PE during the study period were 0.8% (0.9% in patients without DM and 0.6% in patients with DM).

Similar to the entire cohort of patients with VTE, there was an interaction between DM, ABG and mortality at the end of follow up in patients with DVT.

In patients with DM there was no statistically significant association between ABG and mortality at the end of follow-up. However, in patients without DM, the unadjusted hazard ratios of mortality, compared with normal ABG levels, were 1.5 (0.9–2.5, p = NS) with mildly elevated ABG, 2.2 (1.1–4.2, $p < 0.05$) with moderately and 3.0 (1.4–6.4, $p < 0.001$) with markedly elevated ABG levels. Following adjustment for age, gender, smoking, alcohol, malignancy, ischemic heart disease, congestive heart failure, hypertension, chronic renal failure and cerebrovascular disease, adjusted hazard ratios were compared between groups for the entire follow-up, indicating a statistically significant difference in overall survival between patients with normal ABG levels and markedly elevated ABG (aHR = 2.4, 95% CI = 1.2–4.5, $p < 0.05$). However, the difference between normal ABG levels and mildly or moderately elevated ABG levels did not reach statistical significance

4. Discussion

In non-diabetic patients admitted for VTE, glucose levels above 180 mg/dl on admission had a significant impact on short- and long-term mortality rates. Compared with normal ABG levels, markedly elevated ABG levels were associated with 2.4 fold increase in mortality rates. Similar results were evident when analyzing the data for patients with DVT and for patients with PE. In diabetic patients there was no association between ABG levels and mortality.

As there was no association between ABG levels and mortality in DM patients at any time point, we focused on the group of patients without DM.

Our results are in line with previous studies. Scherz et al. reported higher risk of 30-day mortality with hyperglycemia at the time or presentation in patients without a diagnosis of DM hospitalized with acute PE. In patients with known DM there was no similar association between ABG and mortality (Scherz, Labarère, Aujesky, & Méan, 2012). Previous reports suggested that in diabetic patients with chronic hyperglycemia, the acutely increased glucose levels do not cause the same toxic effects evident in patients without pre-existing diabetes (Schuetz, Friedli, Grolimund, et al., 2014).

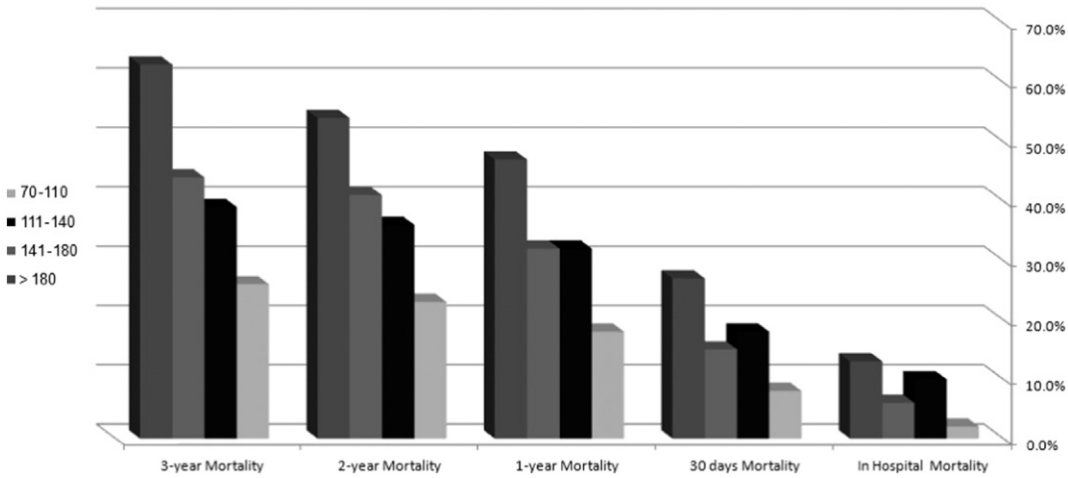

Fig. 3. Short- and long-term mortality according to admission blood glucose.

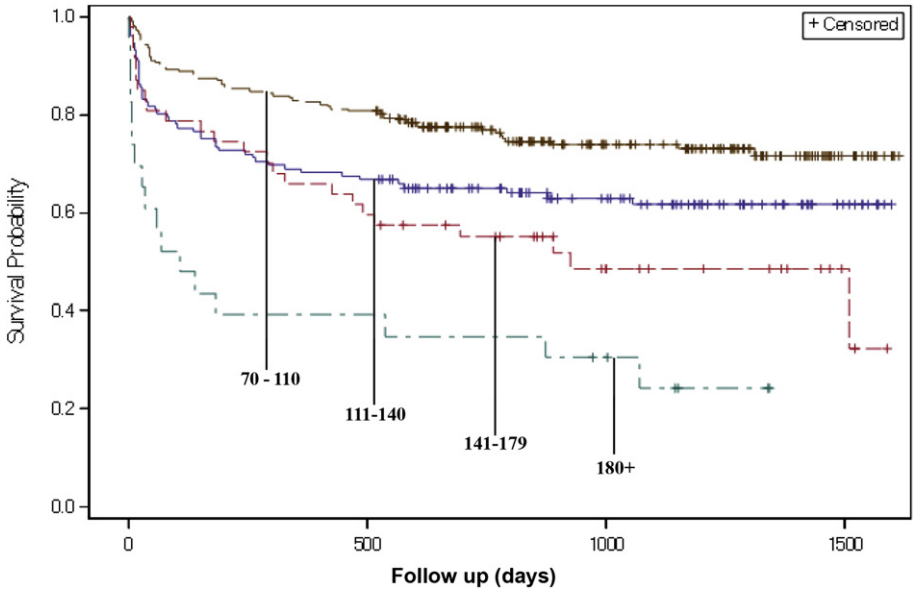

Fig. 4. Kaplan–Meier analysis of patients without diabetes mellitus following admission. Analysis of patient survival following admission as time until death.

A recent study reported that ABG is a simple, inexpensive and available laboratory parameter for predicting in-hospital mortality in patients with PE (Bozbay, Uyarel, Avsar, et al., 2016).

Explanations for the association between ABG and mortality in patients without DM hospitalized for VTE include a possible procoagulant effect and decreased fibrinolysis as a result of increased glucose or insulin levels (Lemkes et al., 2010; Scherz et al., 2012; Vaidyula et al., 2006). Furthermore, as ABG levels were associated with increased mortality following hospitalization for various causes, it may be possible that this is a marker of increased stress and severity of illness. Tichelaar et al. suggested that increased ABG levels in patients with VTE are at least partially the result of an acute phase reaction (Tichelaar, Lijfering, Ter Maaten, Kluin-Nelemans, & Meijer, 2011). A previous study reported that stress hyperglycemia, elevated blood glucose levels in patients who do not have DM, is associated with higher mortality risk, compared with hyperglycemia among patients with DM (Cheung, Li, Ma, & Crampton, 2008).

In patients with DM, the change in blood glucose levels may be more significant and occur earlier due to the abnormal glucose metabolism, whereas the drug treatment for DM may blunt the expected change in blood glucose levels and reflect an exogenous effect (Akirov & Elis, 2016). Hence, in patients without DM admitted for VTE, ABG is a prognostic factor for all-cause mortality, but in patients with DM, ABG levels has no prognostic significance.

The current study has several limitations. First, due to the inherent limitation of the study design, we did not address question of whether treatment for hyperglycemia may reduce mortality associated with hyperglycemia in patients without DM and treatment was left to the discretion of the physicians. This study design is unable to establish a causal relation as it is possible that ABG is a marker of diminished health status. Furthermore, we did not distinguish between fasting and non-fasting glucose values.

Our study focused on the importance of ABG levels on short- and long-term mortality rates specifically in patients with and without DM, hospitalized for VTE. The major strengths of our study are the large cohort and long-term follow-up, representing the real-life scenario of patients admitted to medical wards. Further studies are needed in order to determine whether controlling blood glucose levels has any impact on survival in patients without DM.

In conclusion, in patients without DM admitted for VTE, hyperglycemia on admission was identified as an independent risk factor for short- and long-term mortality. There is no evidence that high glucose levels on admission in diabetic patients with VTE are associated with excess mortality.

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