

Cerebrovascular Diseases

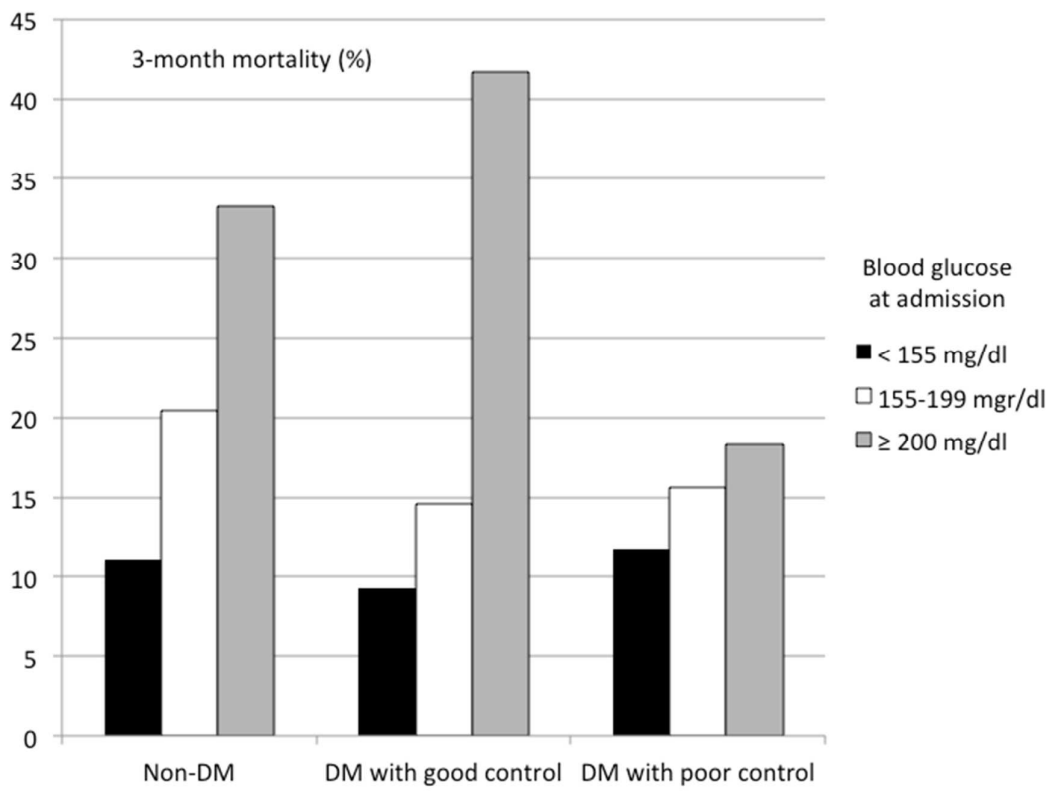
Glycated hemoglobin value combined with initial glucose levels for evaluating mortality risk in patients with ischemic stroke.

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Figure 1



View Only

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4 **Glycated hemoglobin value combined with initial glucose levels for evaluating mortality risk in**
5 **patients with ischemic stroke.**
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36 **Short title:** Glycemia, HbA1c and stroke mortality.
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40 **Key words:** Ischemic stroke, diabetes, hyperglycemia, HbA1c, Mortality
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Background: Hyperglycemia is a marker of poor outcome in acute ischemic stroke (IS) patients. We aimed to evaluate the effect of combined HbA1c and first glucose measurement values on 3-month mortality prediction.

Methods: In a prospective analysis, 1317 first-ever IS patients with HbA1c values were classified by first glycemia value (<155 mg/dl, 155-199 mg/dl, \geq 200 mg/dl). Three-month mortality was analyzed by glycemia category in nondiabetics, diabetics with good previous glucose control (PGC) (HbA1c<7%), and diabetics with poor PGC (HbA1c \geq 7.0%).

Results: Mortality at 3 months was 13.1%, with no differences ($p=0.339$) between non-DM (12.3%), good PGC-DM (12.4%), and poor PGC-DM (15.6%) patients. The unadjusted relative risk of 3-month mortality for patients with glucose \geq 200 mg/dl was 3.76 (95%CI: 1.48-9.56) in non-DM, 6.10 (95% CI: 1.76-21.09) in good PGC-DM, and 1.44 (95% CI: 0.77-2.69) in poor PGC-DM. Glycemia cutoffs most highly correlated with mortality increased as PGC declined: 107 mg/dl in non-DM, 152 mg/dl in good PGC-DM, and 229 mg/dl in poor PGC-DM patients. Glycemia correlated with stroke severity in nondiabetics and diabetic patients with good PGC, but not in those with poor PGC.

Conclusions: HbA1c determination combined with first measured glucose value is useful to stratify mortality risk in IS patients: hyperglycemia is a poor prognostic marker in non-DM and DM patients with good PGC; results are inconsistent in poor PGC-DM patients. Our data suggest the relationship between hyperglycemia and poor outcome reflects stress response rather than a deleterious effect of glucose.

Introduction

Hyperglycemia in the acute phase of ischemic stroke (IS) is a well-established indicator of poor prognosis[1-4]. However, it remains unknown whether the metabolic changes associated with hyperglycemia increase neuronal damage and result in worse prognosis, or the condition simply reflects greater neurological severity through stress hyperglycemia. Although experimental studies suggest that hyperglycemia may increase neuronal damage in hypoxic brain tissue, all clinical trials that examined the impact on mortality and prognosis of aggressive control of hyperglycemia during the acute phase of stroke returned negative findings[5, 6]. Moreover, the deleterious effect of hyperglycemia in acute conditions, such as IS, seems to be lower in diabetes mellitus (DM) patients than in non-DM patients[2,7,8].

Previous glucose control (PGC) could be relevant in outcome evaluation, mainly in DM patients, and would explain some controversial data regarding the relationship between high glycemia levels and patient outcome during the acute illness phase. Glycosylated hemoglobin (HbA1c) is currently used as a DM diagnostic tool, as well as a marker for average glycemia levels over several[2,3] months prior to the measurement. The hypothesis of this study was that combining HbA1c and glucose values in IS patients would help to stratify the mortality risk prediction related to hyperglycemia.

Methods

From January 2007 to June 2014, a total of 2895 patients with acute stroke were prospectively included in the BASICMAR database[9], an ongoing register of patients with acute stroke at a Barcelona's Hospital del Mar. This is a university tertiary hospital, with a catchment area comprising the 330,000 inhabitants of 3 of the 10 city districts of Barcelona, and is the only public hospital that treats acute stroke in this area. Patients with intracerebral hemorrhage (n=352), transient ischemic attack (n=342), previous stroke (n=552), and unusual cause of stroke (n=106) were excluded. Of the remaining patients (n=1543), 1317 had HbA1c tests during hospitalization (85.4%). Missing HbA1c data were due to early discharge (n=96), early death (n=39), or no test ordered (n=91).

All patients were evaluated at hospital admission by a neurologist to establish initial severity using the National Institutes of Health Stroke Scale (NIHSS) and received a computed tomography (CT) scan in the emergency room. Previously described diagnostic procedures, care methods, and secondary prevention measures[10] were followed, in accordance with the current stroke guidelines, during the hospital admission.

Vascular risk factors, as defined by international guidelines, were obtained from each patient or from relatives, caregivers, or previous medical records. A structured questionnaire was used to record the following: arterial hypertension (evidence of at least 2 raised blood pressure measurements, systolic >140 mmHg or diastolic >90 mmHg, recorded on different days before stroke onset; a physician's diagnosis; or use of medication); diabetes (previous physician diagnosis or use of medication); hyperlipidemia (physician diagnosis, use of medication, serum cholesterol concentration >220 mg/dL, low density lipoprotein cholesterol [LDL-c] >130 mg/dL or serum triglyceride concentration >150 mg/dL); current smoking habits; ischemic heart disease (documented history of angina pectoris or myocardial infarction); and atrial fibrillation (AF) (physician diagnosis, use of medication, or conclusive electrocardiogram data). Body mass index and waist circumference were obtained in 1228 and 1129 patients, respectively. For this study,

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3 patients without previous DM diagnosis but with in-hospital HbA1c>6.5% (n=80) were included in
4 the group of DM patients, even though a DM diagnosis requires a second high value for HbA1c.
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7 Patients were classified into 3 groups: “Non-DM” included patients with no previous history of
8 DM and HbA1c<6.5%; “good PGC” DM patients had HbA1c<7%; and “poor PGC” DM patients
9 had HbA1c \geq 7% [11]. Previously unknown DM patients were included in one of the DM groups
10 according to their HbA1c value. HbA1c determination was obtained from fasting patients on the
11 morning after admission or at some point during the first 7 days of hospitalization. The first
12 glycemia (nonfasting), obtained in the emergency room, was used to classify patients into 3
13 categories: <155 mg/dl, from 155 to 199 mg/dl, and \geq 200 mg/dl. These cut-off levels were chosen
14 because 155 mg/dl was the optimal cutoff for poor outcome at 3 months in the GLIAS study[4],
15 and randomglycemia>200 mg/dl is acurrent criteria used to identify stress hyperglycemia[12].
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19 The main outcome assessed was 3-month mortality. Mortality data were obtained in 100% of cases,
20 from electronic medical records, information from the primary care physician, hospital admission
21 records, or telephone contact with the family.
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24 25 26 27 28 29 30 31 32 33 34 **Statistical analysis**

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36 Age, NIHSS, glycemia at emergency room arrival, HbA1c, body mass index, and waist
37 circumference presented a non-normal distribution and were expressed as medians and interquartile
38 ranges (IQR) 25-75. Categorical data were expressed as counts and percentages. Differences in
39 parametric and nonparametric continuous variables were evaluated using the t test and Mann-
40 Whitney U test, respectively, and the chi square test was used for proportional analysis.
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44 We determined by univariate analysis the factors related to 3-month mortality in the whole series.
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46 Variables with a p-value <0.1 in the univariate analysis were included in the multivariate analysis
47 to analyze the independent predictors of 3-month mortality.
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51 We assessed the relationship between HbA1c (as a continuous variable, and by quartiles), 3-month
52 mortality, and stroke severity by NIHSS.
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3 We compared mortality rates by glycemia classification (<155 mg/dl, 155-199 mg/dl, ≥200 mg/dl)
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5 in the 3 patient groups (non-DM, good PGC-DM, poor PGC-DM) and also in patients with
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7 HbA1c<vs≥7.0%, irrespectively of the diagnosis of DM.

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9 Finally, for the 3 patient groups, the receiver operating characteristic (ROC) curves were
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11 constructed to determine the predictive values of the area under the curve (AUC), with 95%
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13 confidence interval (CI), and the cutoff points for glycemia values that would predict 3-month
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15 mortality. We identified the cutoff point with the best specificity and sensitivity using the Youden
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17 value.

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19 The linear relationship between stroke severity by NIHSS and glycemia levels was analyzed using
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21 the Spearman Rho test. All analyses were 2-tailed. The significance level was set at 0.05.
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24 **Ethics**

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27 The information used in this study was collected from the prospective BASICMAR register, with
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29 the approval of our local ethics committee. All patients gave their informed consent prior to their
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31 inclusion in the study.
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Results

Baseline patient data and variables related to mortality in the univariate analysis are shown in Table 1. The 3-month mortality was 13.1%. Multivariate analysis showed the following predictors related with 3-month mortality for the whole patient series: age ($p<0.0001$; HR 1.06 [95% CI 1.04-1.08]), NIHSS ($p<0.0001$; HR 1.21 [95% CI 1.18-1.24]), glycemia ($p<0.0001$; HR 1.005 [95% CI 1.002-1.008]), and atrial fibrillation ($p<0.006$; HR 1.67 [95% CI 1.15-2.41]).

There was no relationship between HbA1c values and 3-month mortality in the whole series ($p=0.399$), in non-DM patients ($p=0.745$), nor in DM cases ($p=0.939$). There was no relationship between HbA1c quartiles (3.0-5.3%, 5.4-5.8%, 5.9-6.7%, and 6.8-14.8%) and 3-month mortality (12.8%, 10.8%, 13.8%, and 15.1%), respectively ($p=0.403$) or stroke severity by NIHSS ($p=0.110$).

There was no difference in 3-month mortality ($p=0.339$) between non-DM patients (12.3%), good PGC DM patients (12.4%), and poor PGC DM patients (15.6%). Clinical differences between the 3 groups are shown in Table 2.

Mortality increased according to first glycemia values: 10.9%, 16.8%, and 22.0% for patients with first glycemia value <155 mg/dl, 155-199 mg/dl, and ≥ 200 mg/dl, respectively ($p<0.0001$). By DM category, there was a significant relationship between mortality rates and glycemia values in non-DM (11.1%, 20.4%, and 33.3%, respectively; $p=0.002$) and good PGC-DM (9.3%, 14.6%, and 41.7%, respectively; $p=0.004$). However, in the poor PGC-DM category, this relationship was nonsignificant (11.7%, 15.6%, and 18.3%, respectively; $p=0.402$). Figure 1 shows these differences graphically. In the whole patient series, the unadjusted relative risk of 3-month mortality associated with admission glucose level ≥ 200 mg/dl was 2.10 [95% CI: 1.40-3.17], $p<0.001$. By DM category, the unadjusted relative risk was 3.76 [95% CI: 1.48-9.56] in non-DM, 6.10 [95% CI: 1.76-1.09] in good PGC-DM, and 1.44 [95% CI: 0.77-2.69] in poor PGC-DM patients. In the whole patient series, the unadjusted relative risk of 3-month mortality associated with admission glucose level ≥ 155 mg/dl was 1.95 [95% CI: 1.39-2.73], $p<0.0001$. By DM category, the unadjusted relative risk was 2.53 [95% CI: 1.42-4.56] in non-DM, 2.56 [95% CI: 1.07-6.14] in good PGC-DM,

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3 and 1.58 [95% CI: 0.77-3.26] in poor PGC-DM patients.
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6 The best glycemia cutoffs for predicting 3-month mortality in patients with acute IS were
7
8 determined. For the whole series, a glycemia value of 134 mg/dl had a sensitivity of 52.2% and a
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10 specificity of 65.0% (AUC: 0.61[95%CI: 0.59-0.63]); for non-DM patients, a glycemia value of
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12 107 mg/dl had a sensitivity of 73.3% and a specificity of 45.2% (AUC: 0.60[95%CI: 0.57-0.63]);
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14 for good PGC DM patients, a glycemia value of 152 mg/dl had a sensitivity of 54.2% and a
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16 specificity of 74.0% (AUC: 0.66 [95%CI:0.60-0.73]); and for poor PGC DM patients, a glycemia
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18 value of 229 mg/dl had a sensitivity of 42.6% and a specificity of 72.5% (AUC: 0.56 [95%CI:
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20 0.50-0.62]).
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23 The linear relationship between NIHSS stroke severity and glycemia was statistically significant
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25 for non-DM patients ($r= 0.182$, $p=0.006$) and for good PGC DM patients ($r= 0.201$, $p<0.0001$), but
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27 not for poor PGC DM patients ($r= -0.052$, $p= 0.372$).
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Discussion

The present study is, to our knowledge, the first to analyze the combined value of glycemia and HbA1c levels to predict 3-month mortality in a large prospective series of first-ever IS. Our study offers some well-supported observations. First, although the HbA1c value alone had no predictive value for 3-month mortality, measuring HbA1c during the acute IS phase is useful. It differentiates between good and poor PGC in patients with diabetes, and permits the identification of patients with previously undiagnosed DM. Second, the glucose cutoffs associated with 3-month mortality after IS were only weakly correlated (AUC from 0.56 to 0.66) but differed greatly between good (152 mg/dl) and poor PGC-DM patients (229 mg/dl); in non-DM patients, the glycemia cutoff was 107 mg/dl, a strictly normal glycemia value (in our laboratory, normal values are 75-115 mg/dl). Third, hyperglycemia is a marker of poor prognosis in patients with good PCG (non-DM or DM patients), but with inconsistent findings in poor PGC-DM patients. Fourth, in non-DM and in good PGC DM patients, hyperglycemia correlates with NIHSS stroke severity. However, this relationship is not present in poor PGC DM patients.

Moreover, our results agree with previous reports in some aspects. Hyperglycemia in acute IS is a marker of high mortality[1-4]. In non-DM patients, the deleterious effect of hyperglycemia in IS patients is more evident [2,7,8] and the best glycemia cutoffs to predict mortality after IS are much lower [2,13,14], compared to DM patients. Finally, mortality was similar in DM patients and in non-DM patients[4].

As expected, patients with DM had more vascular risk factors than the non-DM cases in our study (Table 2); however, stroke severity and 3-month mortality were similar between non-DM, good PGC-DM, and poor PGC-DM.

Regarding HbA1c determination, current information on its relationship with outcome after IS is controversial: some studies found no association[15] or an inverse relationship[16] and others suggested a deleterious effect for patients with high HbA1c[17-19]. In our study, we found no association with mortality, whether we analyzed the HbA1c as a continuous variable, by quartiles, or using the same cutoff as in other studies[17]. Our data indicate that, by itself, HbA1c has no

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3 effect on 3-month mortality after IS. However, HbA1c testing during the acute IS phase adds
4 relevant information: first, it permits the identification of patients with unknown DM[20,21] in
5 whom hyperglycemia would be explained solely by previously undiagnosed DM; second, it
6 differentiates between good and poor PGC DM patients. This second point is very important
7 because, according to our results, the relationship between hyperglycemia and mortality in DM
8 patients differs according to the PGC: hyperglycemia is a marker of poor outcome only for those
9 patients with good PCG irrespective of DM diagnosis. In non-DM and good PGC-DM patients,
10 glucose values ≥ 200 mg/dl are clearly related with high 3-month mortality (3.76 and 6.10 times
11 higher, respectively), compared to patients with glucose values < 200 mg/dl. In these patients,
12 hyperglycemia probably reflects a stress response related with stroke severity, given that
13 hyperglycemia was well correlated with NIHSS in both groups. In the poor PGC-DM group,
14 despite higher 3-month mortality than in the other two groups, the relationship between glucose
15 values ≥ 200 mg/ml and 3-month mortality was weaker (1.44-fold) and nonsignificant. The lack of a
16 significant relationship between glycemia and mortality, or at least the lower effect, in poor PGC-
17 DM patients would be explained because high glycemia levels in this group likely reflect two
18 different situations: in some cases, only pre-stroke glycemia; in others, an additional stress
19 response. The lack of any relationship between PGC and stroke severity in this group supports this
20 idea. Therefore, our data show that the relationship between hyperglycemia and mortality in acute
21 IS patients cannot be analyzed using only the acute glucose values. Furthermore, the concept that
22 the effect of hyperglycemia in acute IS patients differs in diabetics and nondiabetics[22] must be
23 reconsidered, taking into account that hyperglycemia would have a different meaning in patients
24 with or without previous good glucose control.

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48 Another rather intriguing finding is that the cutoff glycemia value predicting mortality in non-DM
49 patients with acute IS (107 mg/dl) is a normal value. A “deleterious” effect of slight increases
50 in glycemia in non-DM patients with acute IS has been observed in previous studies. In a systematic
51 overview published in 2001[2], an admission glycemia level from 6.1 to 7.0 mmol/L (110 to 126
52 mg/dL) after IS was associated with increased relative risk (RR: 3.28) of in-hospital or 30-day
53 mortality in non-DM patients. It is therefore difficult to explain why—and how—a normal glucose
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3 value (107 mg/dl) would be the best cutoff related with mortality for non-DM patients with acute
4 IS, as shown in our results. Although our study cannot rule out a direct toxic effect of glucose on
5 the ischemic brain, the suggested mechanisms[2,3,12]by which hyperglycemia would produce a
6 deleterious effect (intracellular acidosis, oxidative stress, reduced peripheral uptake of glucose,
7 increased circulating free fatty acids, endothelial dysfunction, mitochondrial dysfunction, etc.) have
8 not definitively proved that hyperglycemia was the causal factor for poor outcome after IS[3].
9 Moreover, it is remarkable that the relationship between stroke severity and hyperglycemia
10 observed in non-DM and good PCG DM patients is not present in poor PGC DM patients (those
11 with the highest admission glycemia).

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13 **Limitations of the study:** We used the HbA1c determination as a DM diagnostic tool, following
14 the ADA criteria (HbA1c>6.5%) in patients with no previous DM diagnosis. However, a new
15 HbA1c was not always ordered, and therefore overdiagnosis of DM is possible; this would have a
16 small effect on the final results. However, we would note that in current practice a second HbA1c
17 during admission is often not ordered in acute stroke care. A second limitation is that we analyzed
18 the first glycemia value obtained in the emergency room. Despite qualifying as a random blood
19 glucose test, it is likely a better reflection of stroke-related acute glycemetic response than a morning
20 (fasting) glucose determination, which would be affected by the use of insulin according to our
21 current hyperglycemia treatment protocols. A third limitation is that, despite the large number of
22 patients studied, there were few outcome events (death) in some subgroups.

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24 We believe that our findings add new information on the intriguing relationship between glucose
25 and stroke, and could have practical clinical implications, especially for future studies on
26 hyperglycemia and stroke outcome. HbA1c determination during the acute stroke phase is useful to
27 interpret the prognostic value of blood glucose with respect to stroke mortality, because
28 hyperglycemia is a marker of poor prognosis in patients with good PCG (non-DM or DM patients),
29 with inconsistent findings in poor PGC-DM patients.
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7 translation and copyediting of the manuscript.
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19 **Disclosures:** The authors have reported no conflicts of interest.
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21 **Author contributions:**

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24 Jaume Roquer: Design, data interpretation, revising the manuscript and final approval.

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26 Eva Giralt-Steinhauer, Georgina Cerdà, Ana Rodríguez-Campello, Elisa Cuadrado-Godia, Jordi
27 Jiménez-Conde, Rosa M Vivanco Hidalgo, Carol Soriano, Irene R Dégano, and Angel Ois
28 contributed to acquisition of data, data interpretation and revising the manuscript, and final
29 approval of the version.
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Table 1: Univariate analysis of variables related with 3-month mortality.

	Total cases (n= 1317)	Survivors (n= 1145)	3-month mortality (n=172)	P	OR (95% CI)
Age, median years(IQR 25,75)	77 (68 83)	76 (65 82)	83 (77 88)	0.0001	
Men/women, n (%)	660(50.1)/657(49.9)	593(89.8)/559(84.0)	67(10.2)/105(16.0)	0.002	1.68 (1.21-2.34)
NIHSS, median (IQR 25,75)	5 (3 12)	5 (3 9)	17 (11 21)	0.0001	
DM diagnosis, n (%)	495 (37.6)	424 (37.0)	71 (41.3)	0.311	0.84 (0.60-1.16)
Arterial hypertension, n (%)	979 (74.7)	848 (74.3)	131 (77.1)	0.508	0.86 (0.59-1.26)
Dyslipidemia, n (%)	594 (45.2)	522 (45.7)	72 (41.9)	0.366	1.17 (0.85-1.62)
IHD, n (%)	170 (13.0)	162 (14.4)	28 (16.5)	0.484	0.84 (0.54-1.31)
PAD, n (%)	112 (8.5)	98 (8.6)	14 (8.2)	1.0	1.06 (0.59-1.89)
AF, n (%)	483 (36.7)	369 (31.9)	114 (66.3)	0.0001	0.24 (0.17-0.34)
Current smoking, n (%)	277 (21.5)	262 (23.3)	15 (9.1)	0.0001	3.04 (1.76-5.26)
Alcohol overuse, n (%)	266 (20.6)	246 (21.9)	20 (12.0)	0.003	2.06 (1.26-3.36)
Glycemia, median (IQR 25,75)	120 (103 155)	119 (101 151)	132 (110 182)	0.0001	
HbA1c, % median (IQR 25,75)	5.8 (5.3 6.7)	5.8 (5.3 6.7)	5.9 (5.3 7.0)	0.334	

IQR, Interquartile Ratio; NIHSS, National Institutes of Health Stroke Scale; DM, Diabetes

Mellitus; IHD, Ischemic Heart Disease; PAD, Peripheral Arterial Disease; AF, Atrial Fibrillation.

Table 2: Clinical characteristics of non-DM, good PGC DM (HbA1c < 7%), and poor PGC DM patients (HbA1c ≥ 7%).

	Non-DM (n= 822)	Good PGC-DM (n=193)	Poor PGC-DM (n=302)	P
Age, median years (IQR 25,75)	77 (67 83)	78 (71 82)	75 (65 82)	0.022
Men, n (%)	406 (49.4)	95 (49.2)	159 (52.6)	0.604
NIHSS, median (IQR 25,75)	6 (3 13)	5 (3 12)	5 (3 10)	0.104
Glycemia, median (IQR 25,75)	110 (98 128)	129 (113 157)	187 (142 241)	0.0001
Arterial hypertension, n (%)	580 (70.9)	157 (82.2)	242 (80.1)	0.0001
Dyslipidemia, n (%)	316 (38.5)	99 (51.6)	179 (59.5)	0.0001
IHD, n (%)	95 (11.6)	37 (19.5)	58 (19.3)	0.001
PAD, n (%)	58 (7.1)	19 (9.9)	35 (11.7)	0.040
AF, n (%)	305 (37.1)	90 (46.6)	88 (29.1)	0.0001
Current smoking, n (%)	187 (23.3)	27 (14.3)	63 (21.2)	0.025
Alcohol overuse, n (%)	101 (12.3)	24 (12.4)	47 (15.6)	0.339
BMI men, median (IQR 25,75)	26.2 (23.7 29.4)	27.1 (24.2 29.4)	27.6 (25.0 30.3)	0.006
BMI women, median (IQR 25,75)	26.7 (24.1 30.3)	28.8 (24.4 32.3)	27.5 (24.9 31.6)	0.028
WC men, median (IQR 25,75)	98 (89 106)	97 (90 106)	102 (94 112)	0.006
WC women, median (IQR 25,75)	98 (88 105)	100 (93 108)	100 (89 110)	0.069
3-month mortality, n (%)	101 (12.3)	24 (12.4)	47 (15.6)	0.339

IQR, Interquartile Ratio; DM, Diabetes Mellitus; PGC, Previous Glucose Control; NIHSS, National Institutes of Health Stroke Scale; IHD, Ischemic Heart Disease; PAD, Peripheral Arterial Disease; AF, Atrial Fibrillation; BMI, Body Mass Index; WC, Waist Circumference.

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5 **Legend, figure 1:**
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10 Fig.1 Relationship between glycemia levels and 3-month mortality in patients without DM
11 $p=0.002$), with DM and previous good control ($p=0.004$), and in DM patients with previous poor
12 control ($p=0.402$). DM, Diabetes Mellitus.
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