Prognostic value of admission hyperglycaemia in black Africans with acute coronary syndromes: a cross-sectional study

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Abstract

Aim: The aim of the study was to determine the relationship between acute hyperglycaemia and in-hospital mortality in black Africans with acute coronary syndromes (ACS).

Methods: From January 2002 to December 2017, 1,168 patients aged ≥ 18 years old, including 332 patients with diabetes (28.4%), consecutively presented to the intensive care unit of the Abidjan Heart Institute for ACS. Baseline data and outcomes were compared in patients with and without hyperglycaemia at admission (> 140 mg/dl; 7.8 mmol/l). Predictors for death were determined by multivariate logistic regression.

Results: The prevalence of admission hyperglycaemia was 40.6%. It was higher in patients with diabetes (55.3%). In multivariate logistic regression, acute hyperglycaemia (hazard ratio = 2.33; 1.44–3.77; p < 0.001), heart failure (HR = 2.22; 1.38–3.56; p = 0.001), reduced left ventricular ejection fraction (HR = 6.41; 3.72–11.03; p < 0.001), sustained ventricular tachycardia or ventricular fibrillation (HR = 3.43; 1.37–8.62; p = 0.008) and cardiogenic shock (HR = 8.82; 4.38–17.76; p < 0.001) were predictive factors associated with in-hospital death. In sub-group analysis according to the history of diabetes, hyperglycaemia at admission was a predictor for death only in patients without diabetes (HR = 3.12; 1.72–5.68; p < 0.001).

Conclusion: In ACS patients and particularly those without a history of diabetes, admission acute hyperglycaemia was a potentially threatening condition. Appropriate management, follow up and screening for glucose metabolism disorders should be implemented in these patients.

Keywords: hyperglycaemia, diabetes, acute coronary syndrome, sub-Saharan Africa

Studies in the West have shown that elevation of blood glucose is a common condition during the early phase of acute coronary syndrome (ACS), even in the absence of a history of diabetes mellitus (DM). There is no uniform definition at present, but the 140 mg/dl (7.8 mmol/l) threshold has often been considered. The prevalence of acute hyperglycaemia > 140 mg/dl ranged from 39 to 58%.

In addition to established prognostic factors (left ventricular systolic dysfunction, heart failure, ventricular arrhythmias), acute elevation of blood glucose level was associated with an increase in in-hospital stay, and 30-day and long-term mortality rate, and there is evidence that the risk of mortality is higher in patients without a history of DM. There is a linear relationship between acute glycaemic levels and outcomes. Pathophysiological mechanisms are uncertain, but acute hyperglycaemia may be an epiphenomenon of the stress response, or the trigger of complex underlying mechanisms, leading to severe complications and poor outcomes.

In sub-Saharan Africa, data on ACS are scarce, particularly on the prevalence and outcomes of patients with acute hyperglycaemia. The aim of this study was to assess the prognostic value of hyperglycaemia at admission in ACS patients in our practice.

Methods

Our study was carried out at the Abidjan Heart Institute (Ivory Coast). We conducted a cross-sectional, observational study between 1 January 2002 and 31 December 2017, including patients aged ≥ 18 years who presented to the intensive care unit (ICU) of Abidjan Heart Institute for ACS. These patients were divided into two groups according to their blood glucose level at admission: admission hyperglycaemia (AH) (blood glucose > 140 mg/dl; 7.8 mmol/l) and absence of admission hyperglycaemia (NAH) (blood glucose ≤ 140 mg/dl). The
blood glucose level considered was the first venous plasma glucose level obtained at admission or within the first 24 hours, and before any glucose-lowering therapy was given during hospitalisation.

The exclusion criteria were: ACS patients with incomplete medical records or who declined to participate in the study, patients with suspected ACS in whom the clinical course and explorations had excluded the diagnosis of ACS, and patients transferred to another department outside the Abidjan Heart Institute during their hospitalisation.

Consent was obtained from each patient participating in this study. Based on our selection criteria, 1,168 patients were included in our study.

Data were collected using a standardised survey form. The parameters investigated were: (1) socio-demographic data (age, gender) as well as clinical data (cardiovascular risk factors and history, clinical presentation); (2) ECG (diagnosis of ACS) and cardiac ultrasound data (left ventricular ejection fraction (LVEF) < 40% or ≥ 40%); (3) biological data: troponin Ic and cardiac enzymes, (4) coronary angiography findings: number of epicardial vessels affected (one-, two- and three-vessel disease), (5) management: dual antiplatelet therapy (DAPT), percutaneous coronary intervention (PCI), and (6) in-hospital evolution: atrial fibrillation, sustained ventricular tachycardia/ventricular fibrillation, cardiacogenic shock, death.

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, measured three times during hospitalisation or treatment of previously diagnosed hypertension. DM was defined according to the American Diabetes Association as one of the following criteria: glycated haemoglobin ≥ 6.5%, fasting plasma glucose ≥ 1.26 g/l (6.99 mmol/l) on two occasions, two-hour plasma glucose ≥ 2 g/l (11.1 mmol/l) after 75-g oral glucose tolerance test (OGTT), random plasma glucose ≥ 2 g/l (11.1 mmol/l), or patients on glucose-lowering therapy on admission. Active smoking was defined as current or interrupted smoking for less than three years.

Dyslipidaemia was defined as total cholesterol concentration > 2.40 g/l (6.22 mmol/l) and/or high-density lipoprotein (HDL) cholesterol < 0.40 g/l (1.04 mmol/l) in males and < 0.50 g/l (1.3 mmol/l) in females and/or low-density lipoprotein (LDL) cholesterol > 1.60 g/l (4.14 mmol/l), or triglyceride levels > 1.5 g/l (1.70 mmol/l). Familial history of coronary artery disease (CAD) was defined as the occurrence of a myocardial infarction or sudden death: before the age of 55 years in the father or in a first-degree male relative; and before the age of 65 years in the mother or in a first-degree female relative. Symptom–admission delay was the time between the onset of symptoms and admission to the Abidjan Heart Institute.

ST-segment elevation myocardial infarction (STEMI) was defined as the presence of symptoms or signs of myocardial ischaemia, persistent ST-segment elevation or newly diagnosed bundle branch block, and an increase in cardiac biomarkers beyond the 99th percentile. Non-ST-elevation ACS (NSTE-ACS) was defined as the presence of symptoms or signs of myocardial ischaemia, absence of persistent ST-segment elevation, and elevation (non-Q-wave myocardial infarction) or no elevation (unstable angina) of cardiac biomarkers beyond the 99th percentile. Left ventricular systolic dysfunction was defined for a LVEF < 40%.

Statistical analysis
Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical data are presented as numbers and proportions. Statistical comparisons between groups used the Student’s t-test or Mann-Whitney test for continuous variables, and the chi-squared test or Fisher’s exact test for categorical variables. A receiver operating characteristics (ROC) curve was performed to determine the admission glycaemic threshold level predictive of death in our population.

Univariate and multivariate backward stepwise logistic regressions were used to assess predictors of in-hospital death, with an inclusion threshold of p < 0.20 in the multivariate analysis. The candidate variables considered were selected according to available data in the literature. The Wald (or Fisher) test was used to assess the significance of hazard ratio (HR) and their 95% confidence interval (95% CI). We defined statistical significance using a two-sided p-value < 0.05. We used RStudio statistical software version 1.1.383 (Boston, MA, USA).

Results
Table 1 summarises the patients’ general characteristics and outcomes according to blood glucose status at admission. Among the 1,168 patients included in our study, 474 had AH, with a prevalence of 40.6%. The average age of our study population was 56.0 ± 11.6 years (range 21–91). Patients in the AH group were significantly older than those in the NAH group (57.9 ± 11.0 vs 54.7 ± 11.8 years, p < 0.001). Patients over 60 years old frequently had acute hyperglycaemia (40.7 vs 31.7%, p = 0.001). The male gender was predominant (80.7%) with a ratio of male to female of 4.2. Patients in the NAH group were more likely to be female, with no significant difference (Table 1). According to cardiovascular risk factors and history, AH patients had significant increases in hypertension (p < 0.001) and DM (p < 0.001). Smoking was frequently reported in the NAH group (p = 0.002).

The median symptom–admission delay was 19 hours (5–48). There was no difference concerning blood glucose levels at admission (p = 0.37). Heart failure often occurred in AH patients (35.4 vs 20.7%, p < 0.001). AH patients presented with increased blood pressure and heart rate. In AH patients, peaks in troponin Ic (p = 0.004), creatine phosphokinase (CPK) (p < 0.001) and creatine kinase-MB (CK-MB) levels (p < 0.001) were higher. Coronary angiography was performed in 564 patients (48.3%). Although there was no significant difference (p = 0.51), three-vessel disease was more common in AH patients (Table 1). Two hundred and twenty patients underwent PCI (18.8%). Dual antiplatelet therapy (aspirin + clopidogrel) was given to 782 patients (67.0%). No differences were reported between the groups.

Over the study period, 800 STEMI patients out of 1,138 (68.5%) were admitted to ICU. Thrombolysis was performed in 93 patients, in most of the cases with Alteplase (77/93, 82.8%). PCI procedures started on 27 April 2010. One hundred and fifty-one STEMI patients underwent PCI.

Cardiogenic shock occurred significantly in patients with acute hyperglycaemia (p < 0.002). Atrial fibrillation and severe ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation) were more frequent in the AH group, without significant difference. Overall in-hospital mortality rate
was 9.1% (106/1168). It was higher in AH patients (15.2%, p < 0.001) (Table 1).

In multivariate analysis, heart failure (HR = 2.22; 1.38–3.56; p = 0.001), LVEF < 40% (HR = 6.41; 3.72–11.03; p < 0.001), acute hyperglycaemia (HR = 2.33; 1.44–3.77; p < 0.001), sustained ventricular tachycardia or ventricular fibrillation (HR = 3.43; 1.37–8.62; p = 0.008) and cardiogenic shock (HR = 8.82; 4.38–17.76; p < 0.001) were the risk factors associated with in-hospital death. PCI (HR = 0.35; 0.16–0.79; p = 0.01) and dyslipidaemia (HR = 0.48; 0.27–0.84; p = 0.01) were identified as protective factors (Tables 2, 3).

The sub-group analyses according to the history of DM emphasised cardiogenic shock (HR = 23.75; 7.60–74.27; p < 0.001 and HR = 9.05; 3.66–22.33; p < 0.001, respectively) in both AH and NAH populations as risk factors (Tables 4, 5). In patients without a history of DM, only hyperglycaemia was associated with in-hospital death (HR = 3.12; 1.72–5.68; p < 0.001) (Table 5).

We carried out a second analysis over two periods: 2002–2010 and 2011–2017. Admission hyperglycaemia was a predictive factor only from 2011–2017 (HR = 2.57; 1.52–4.32). (Tables 6, 7).

The blood glucose threshold of 151 mg/dl (8.8 mmol/l) was the one with the best sensitivity and specificity (area under the curve = 0.636; sensitivity 61%, specificity 67%; p < 0.001) (Fig. 1). Considering the value of 140 mg/dl (7.8 mmol/l), we found similar sensitivity and specificity (sensitivity 62%, specificity 60%).

### Table 1. Patient characteristics according to glycaemia status at admission

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AH</th>
<th>NAH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), m ± SD</td>
<td>57.9 ± 11.0</td>
<td>54.7 ± 11.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>193 (40.7)</td>
<td>220 (31.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>312 (65.8)</td>
<td>377 (54.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>262 (55.3)</td>
<td>70 (10.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Active smoking</td>
<td>113 (23.8)</td>
<td>222 (32.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Troponin Ic peak (µg/l), m (IQR)</td>
<td>13.1 (5.2–30.0)</td>
<td>4.9 (1.4–15.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>CPK peak (UI/l), m (IQR)</td>
<td>1083 (436–2680)</td>
<td>714 (245–1900)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table 2. Predictors of in-hospital death. Univariate analysis

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Alive at discharge (n = 1062)</th>
<th>Death during hospitalization (n = 106)</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>361 (30.4)</td>
<td>52 (49.1)</td>
<td>1.87</td>
<td>1.25–2.79</td>
<td>0.002</td>
</tr>
<tr>
<td>Female gender</td>
<td>195 (38.4)</td>
<td>30 (28.3)</td>
<td>1.75</td>
<td>1.12–2.75</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>619 (58.3)</td>
<td>70 (66.0)</td>
<td>1.39</td>
<td>0.91–2.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>388 (77.8)</td>
<td>44 (41.5)</td>
<td>1.91</td>
<td>1.27–2.87</td>
<td>0.002</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>342 (66.0)</td>
<td>23 (20.8)</td>
<td>0.63</td>
<td>0.38–1.02</td>
<td>0.06</td>
</tr>
<tr>
<td>History of MI</td>
<td>92 (8.7)</td>
<td>8 (7.5)</td>
<td>0.86</td>
<td>0.40–1.82</td>
<td>0.69</td>
</tr>
</tbody>
</table>

### Table 3. Predictors of in-hospital death. Multivariate analysis

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Initial model</th>
<th>Final model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>1.68</td>
<td>0.95–2.70</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.84</td>
<td>0.47–1.51</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.88</td>
<td>0.51–1.32</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.50</td>
<td>0.25–1.05</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>0.58</td>
<td>0.32–1.05</td>
</tr>
</tbody>
</table>

HR: hazard ratio. 95% CI: 95% confidence interval. MI: myocardial infarction. PCI: percutaneous coronary intervention.
Mortality at 30 days and one year evolved linearly with blood studies. The Cooperative Cardiovascular Project is the most patients hospitalised for ACS has been established in numerous.

Discussion
Whereas estimation of the prevalence of DM in ACS patients
ranges from 39 to 58%. However, the blood glucose cut-off
with available data in the literature in wealthy countries, where
the prevalence of hyperglycaemia (40.6%) was higher than the prevalence of DM
in-hospital mortality in our practice. The prevalence of admission
blood glucose levels at admission and their prognostic value on
our knowledge this is the first study reporting the prevalence of
71% of ACS patients had acute hyperglycaemia.3

Table 5. Predictors of in–hospital death in patients without diabetes.

Predictors HR 95% CI p-value
Age > 60 years 2.39 1.27–4.49 0.007 2.46 1.35–4.49 0.003
Female gender 0.77 0.37–1.6 0.48
Hypertension 1.17 0.60–2.25 0.65
Dyslipidaemia 0.53 0.24–1.16 0.11
History of MI 0.15 0.02–1.32 0.09
Congestive heart failure 1.44 0.76–2.74 0.27
LVEF < 40% 8.71 4.05–18.70 0.015 10.18 4.93–21.00 < 0.001
Anterior ACS 1.53 0.78–3.01 0.22
Admission hyperglycaemia 2.65 1.41–4.99 0.002 3.12 1.72–5.68 < 0.001
STEMI 1.34 0.54–3.30 0.99
SVT/VF 3.59 1.21–10.64 0.021
Cardiogenic shock 7.33 2.81–19.08 < 0.001 9.05 3.66–22.33 < 0.001
PCI 0.27 0.09–0.83 0.022 0.29 0.10–0.86 0.02
HR: hazard ratio. 95% CI: 95% confidence interval. MI: myocardial infarction.
ACS: acute coronary syndrome. LVEF: left ventricular ejection fraction. ACS:
acute coronary syndrome. STEMI: ST-segment elevation myocardial infarction.
SVT/VF: sustained ventricular tachycardia/ventricular fibrillation. PCI: percuta-
neous coronary intervention.


Predictors HR 95% CI p-value
Diabetes mellitus 4.79 1.86–12.36 0.001
Congestive heart failure 4.51 1.74–11.70 0.001
Cardiogenic shock 6.10 1.61–23.05 0.008
HR: hazard ratio. 95% CI: 95% confidence interval.


Predictors HR 95% CI p-value
Admission hyperglycaemia 2.57 1.52–4.32 < 0.001
Congestive heart failure 3.40 2.05–5.64 < 0.001
Cardiogenic shock 14.41 6.82–30.42 < 0.001
HR: hazard ratio. 95% CI: 95% confidence interval.

In patients without a history of DM, raised blood glucose may correspond to a pre-diabetic state unmasked under a stressful, acute post-ACS phase. In the GAMI trial, OGTT was systematically performed in the follow up of 181 patients with acute myocardial infarction, no history of DM and an admission blood glucose level < 11.0 mmol/l. This study found 67% of new cases of DM and impaired glucose intolerance (IGT). The potential mechanisms involved with acute hyperglycaemia

Discussion
Whereas estimation of the prevalence of DM in ACS patients
ranges from 39 to 41%, to our knowledge this is the first study reporting the prevalence of blood glucose levels at admission and their prognostic value on in-hospital mortality in our practice. The prevalence of admission hyperglycaemia (40.6%) was higher than the prevalence of DM (28.4%). This high rate of acute hyperglycaemia is consistent with available data in the literature in wealthy countries, where the prevalence of hyperglycaemia > 140 mg/dl (7.8 mmol/l) ranges from 39 to 58%. However, the blood glucose cut-off point differs across studies, and it has been reported that up to 71% of ACS patients had acute hyperglycaemia.

The prognostic impact of hyperglycaemia on admission in patients hospitalised for ACS has been established in numerous studies. The Cooperative Cardiovascular Project is the most important registry (n = 141 680) that evaluated the relationship between mortality rate and admission blood glucose after ACS. Mortality at 30 days and one year evolved linearly with blood glucose levels at admission (≤ 110, 110–140, 140–170, 170–240 and ≥ 240 mg/dl) (6.11, 6.11–7.8, 7.8–9.44, 9.44–13.32 and ≥ 13.32 mmol/l). As in our study, the risk of mortality was higher in patients without a history of DM.

In a recent meta-analysis including 214 219 patients, admission hyperglycaemia significantly increased hospital mortality rate (HR = 3.62; p < 0.0001), and this impact persisted at 30 days (HR = 4.81, p < 0.0001) and long term up to 108 months (HR = 2.02, p < 0.0001). In STEMI patients who underwent primary PCI, hyperglycaemia was associated with a higher rate of complications and mortality, including the risk of recurrence of myocardial infarction and heart failure.

In patients without a history of DM, raised blood glucose may correspond to a pre-diabetic state unmasked under a stressful, acute post-ACS phase. In the GAMI trial, OGTT was systematically performed in the follow up of 181 patients with acute myocardial infarction, no history of DM and an admission blood glucose level < 11.0 mmol/l. This study found 67% of new cases of DM and impaired glucose intolerance (IGT). The potential mechanisms involved with acute hyperglycaemia
are still poorly understood, but some hypotheses have been suggested. Hyperglycaemia may be a cause or ‘marker’ of catecholaminergic stress in the post-ACS phase, particularly in relation to the extent of the infarction and the relative alteration of LVEF. Evidence of a reduced mortality rate after lowering blood glucose levels on insulin therapy argues against blood glucose as a simple epiphenomenon of the stress state. Hyperglycaemia is associated with insulin resistance, increased levels of free fatty acids, marked inflammatory response, and endothelial and microvascular dysfunction, leading to myocardial cell vulnerability, ischaemia and hypoxia. This may explain why in our study, patients with blood glucose > 140 mg/dl (7.8 mmol/l) had higher peaks of troponin Ic and cardiac enzymes. Recently, a new concept, glycaemic variability, has been described in a few studies. In patients with acute myocardial infarction, glycaemic variability was associated with the severity of CAD and death.

Patients with acute hyperglycaemia and without a history of DM should undergo close follow up and screening for glucose metabolism disorders. Current recommendations emphasise the use of OGTT and glycated haemoglobin as screening tests. In a study conducted in South Africa among patients with CAD, the rate of IGT measured by OGTT was 30% higher than the rate of DM (20%). This study included a small sample of patients, but highlights the need for screening of glucose metabolism disorders in patients with CAD in our practice.

The other predictors for in-hospital death identified in our study (age, heart failure, left ventricular dysfunction, sustained ventricular tachycardia/ventricular fibrillation) are powerful prognostic factors in ACS patients, consistent with studies in developed countries. Dyslipidaemia appeared to be a protective factor, and this observation has already been reported. It is mainly the influence of previous lipid-lowering drugs in patients with high cardiovascular risk that would have a beneficial effect on mortality rate. Previous treatments in our study were not specified.

PCI was a protective factor in our series but remarkably, only in patients without a history of DM in sub-group analyses. First, the low rate of PCI in our patients with ACS is a potential bias. Second, CAD patients with DM frequently have multi-vessel coronary heart disease (28.9%) and complex lesions (39.7%), as in studies conducted in developed countries. Coronary artery bypass graft surgery is often the technique of choice for complete revascularisation in patients with DM, but is of limited practice in sub-Saharan Africa. Finally, DM patients are often high-risk patients in whom an earlier invasive strategy should be implemented. However, the excessive admission delays determine the low rate of PCI, which would weaken its beneficial effect.

Limitations

Our study has some limitations. Incomplete medical records did not allow us to make a thorough analysis. Glycated haemoglobin was not available for all patients and was not included in our analysis, nor was the evolution of blood glucose levels during hospitalisation. The influence of previous treatments (antidiabetic drugs, statins) and glucose-lowering treatments given during hospitalisation (particularly insulin infusion) have not been specified. Finally, the low rate of coronary angiography did not make it possible to assess the link between blood glucose levels and the severity of CAD.

Conclusion

This study, carried out in a sub-Saharan African population, shows that in the acute phase of ACS, admission blood glucose has a powerful prognostic value on mortality rate, in accordance with studies conducted in the West. In association with conventional treatment of ACS, adequate control of blood glucose is an important treatment target, especially in non-diabetic patients. Routine screening for glucose metabolism disorders and follow up after ACS must be implemented, as recommended. It would be interesting to determine the rate of IGT and DM in ACS patients without a history of DM in the post-discharge phase, and assess the long-term impact of glucose-lowering therapy on morbidity and mortality rates.

References


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