Obstructive Sleep Apnea Affects Hospital Outcomes of Patients with non-ST-Elevation Acute Coronary Syndromes

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Study Objective: We aimed to test the hypothesis that clinically suspected obstructive sleep apnea (OSA) independently predicts worse in-hospital outcome in patients with non-ST-elevation acute coronary syndromes.

Design: At admission, individuals were evaluated for clinical probability of OSA by the Berlin Questionnaire. Primary cardiovascular endpoint was defined as the composite of death, nonfatal myocardial infarction, or refractory angina during hospitalization.

Setting: Coronary care unit.

Patients: There were 168 consecutive patients admitted with unstable angina or non-ST-elevation acute myocardial infarction.

Measurements and Results: During a median hospitalization of 8 days, the incidence of cardiovascular events was 13% (12 deaths, 4 nonfatal myocardial infarctions, and 6 refractory anginas.) Incidence of the primary endpoint was 18% in individuals with high probability of OSA, compared with no events in individuals with low probability (P = 0.002). After logistic regression adjustment for the Global Registry of Acute Coronary Events (GRACE) risk score, anatomic severity of coronary disease, and hospital treatment, probability of OSA remained an independent predictor of events (odds ratio [OR] = 3.4; 95% confidence interval [CI] = 1.3 – 9.0; P = 0.015). Prognostic discrimination of the GRACE score, measured by a C-statistic of 0.72 (95% CI = 0.59-0.85), was significantly improved to 0.82 (95% CI = 0.73-0.92) after inclusion of OSA probability in the predictive model (P = 0.03).

Conclusion: Considering the independent prognostic and incremental value of suspected OSA, this condition may represent an aggravating factor for patients with non-ST-elevation acute coronary syndrome.

Keywords: Acute coronary syndromes, myocardial infarction, obstructive sleep apnea, prognosis, unstable angina

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive interruption of ventilation during sleep, commonly present in 20% of the population. It is associated with a worse prognosis in individuals with ischemic heart disease, with higher incidences of death, myocardial infarction, and cerebrovascular events. This interaction between OSA and adverse events is probably driven by biologic mechanisms such as hypoxia, sympathetic activation, enhanced inflammation, impairment of endothelial function, thrombosis activation, and oxidative stress.

During acute coronary syndromes (ACS), patients are especially vulnerable to ischemic complications because of plaque instability, endothelial dysfunction, and thrombosis activation. Thus, the presence of OSA during the acute phase may have a synergistic effect with the pathophysiologic processes of ACS. However, there is a paucity of data regarding the association between OSA and prognosis of patients with ACS.

To test the hypothesis that clinically suspected OSA at admission independently predicts worse hospital outcomes in non-ST elevation ACS, 168 consecutive patients with unstable angina or non-ST-elevation myocardial infarction were assessed for OSA by the Berlin Questionnaire and recurrent ischemic events were recorded during hospitalization.

METHODS

Study Population

Consecutive patients admitted to the coronary care unit of our hospital due to unstable angina pectoris or non-ST elevation acute myocardial infarction between February 2008 and September 2009 were considered candidates for the study. In this regard, every patient admitted in the hospital with suspected ACS was primarily admitted in this coronary care unit and all were consecutively screened to the protocol. Inclusion criteria were defined as rest onset of typical chest discomfort in the previous 48 hr, absence of ST-segment elevation and at least one of the following objective criteria: (1) positive serum marker of myocardial necrosis, defined as troponin T ≥ 0.04 μg/L or troponin I ≥ 0.035 μg/L, which corresponds to the values above the 99th percentile in a healthy reference population and with total imprecision of 10%5; (2) electrocardiographic ischemic changes consisting of transient ST-segment depression (≥ 0.05 mV) or T wave inversion (≥ 0.1 mV); and (3) previous documentation of coronary artery disease, defined as a definitive history of myocardial infarction or coronary obstruction ≥ 50% at angiography.

Exclusion criteria were defined as physical or mental inability to answer questions regarding OSA activity, inability to stand up for weight measurement, or lack of desire to participate in the study. Once fulfilling criteria for entering the study,
patients provided written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institution’s human research ethics committee.

**Determination of OSA Probability**

Assessment of OSA probability was obtained during the first 24 hr of hospitalization by applying the Berlin Questionnaire. This is a validated tool to estimate probability of OSA, with 88% sensitivity and 77% specificity, taking a respiratory disturbance index > 5 during sleeping monitoring as the reference standard.

The questionnaire consists of three categories: I, nighttime category: snoring or apnea during sleep; II, daytime category: drowsiness or fatigue during daily activities; and III, clinical conditions such as body mass index > 30 kg/m² or previous diagnosis of hypertension. Category I consists of five questions, category II has three questions, and category III has two questions. Categories I and II are defined as positive when at least two questions are positive. Category III is positive when either body mass index > 30 kg/m² or hypertension is present. Body mass index was defined as the ratio of weight in kilograms by squared height in meters. Weight was measured by the research team with the patient in the standing position. The questionnaire was primarily completed by the patient, sometimes with family assistance. This assistance was not required by the protocol, but was allowed and took place spontaneously in some instances. The evaluation is considered positive for OSA (high probability) when at least two categories are positive. The complete Berlin Questionnaire is depicted in the Appendix.

**Clinical and Laboratory Assessment**

To assess risk of recurrent events by clinical information, the GRACE score was used. The GRACE calculation was based on admission data and performed as previously validated. The GRACE score consists of eight variables – five semiquantitative (age, systolic blood pressure, heart rate, plasma creatinine level, Killip class) and three dichotomic variables (positive necrosis markers, ST-segment deviation, and cardiac arrest at admission). Points are attributed according to the values of each variable and the sum of all variables corresponds to a previously defined risk level.

Plasma biomarkers were measured upon patient arrival to the hospital. Plasma C-reactive protein was assessed by the commercially available high-sensitivity method of nephelometry (Dade-Behring, Newark, Delaware, USA). In the first 84 patients Cardiac Troponin T was used as the necrosis marker, measured by chemiluminescence immunoassay (Roche Diagnostics Corporation, Indianapolis, Indiana, USA). In the other half of the patients, because of hospital policy, a second-generation VITROS Cardiac Troponin I chemiluminescence immunoassay (Ortho-Clinical Diagnostics, Rochester, NY, USA) was used as a necrosis marker. Positive serum marker of myocardial necrosis, defined as troponin T ≥ 0.04 μg/L or troponin I ≥ 0.035 μg/L, which correspond to the values above the 99th percentile of a healthy reference population and with total imprecision of 10%.4,5

**Endpoints Definition**

Cardiovascular events were adjudicated by investigators, independent of physician impression. As the primary endpoint, major cardiovascular events during hospitalization were defined as the composite of death, nonfatal acute myocardial infarction, or refractory unstable angina. Myocardial infarction as an outcome endpoint was defined as either a new Q-wave or troponin elevation during hospitalization despite normal values during the first 24 hr. For patients with infarction at admission, a new peak of mass creatine kinase-MB (> 50% the previous value and above the normal value) was required for diagnosis of reinfarction. Infarction secondary to percutaneous coronary intervention or surgery revascularization did not count as an event. Refractory angina during hospitalization was defined as recurrent chest pain at least twice, despite nitrates and antiangina therapy ensuring controlled oxygen consumption.

**Data Analysis and Statistical Methods**

First, the incidence of cardiovascular events was compared between individuals defined as high or low OSA probability by the Berlin Questionnaire, using the Pearson χ² test. In addition, events were compared among three groups defined by the number of positive categories in the Berlin Questionnaire (zero to one category, two categories, or three categories), by the Mantel-Haenszel χ² linear-by-linear association test. Clinical characteristics and treatment were compared between high and low OSA probability by Pearson χ² test or Fisher exact test for categorical variables and Student’s t test for numeric variables. In search for confounding factors, the variables associated with high OSA probability by a significance level < 0.20 were also compared between patients with and without events. In this analysis, variables with a significance level < 0.10 were defined as potential confounding. The independent predictive value of OSA in relation to cardiovascular events was assessed by logistic regression analysis, in which OSA was entered as a three-level variable, according to the number of positive categories in the Berlin Questionnaire. In this analysis, independent predictors were defined by a significance level < 5%. Finally, the additional predictive value of OSA in relation to the GRACE score was assessed by comparison of the C-statistics (areas under the receiver operator characteristics curve of the predictive model). Using the predicted probabilities of the logistic regression model containing both GRACE score and OSA, the C-statistics were calculated and compared with the C-statistic of the GRACE score by the method proposed by Hanley and McNeil. The differences between these two areas measured how much additional value OSA input provided to the GRACE score and statistical significance was defined as a P value < 0.05. SPSS Statistical Software (Version 9.0, SPSS Inc., Chicago, IL, USA) and MedCalc Statistical Software (Version 9.3.2.0, MedCalc Software, Mariakerke, Belgium) were used for data analysis.

**RESULTS**

**Sample Characteristics**

The sample population consisted of 168 patients, age 70 ± 12 yr, 54% male, body mass index of 26 ± 5.2 kg/m². Fifty-seven percent of the individuals were admitted with non-ST elevation acute myocardial infarction and the remaining with unstable angina. The GRACE score averaged 134 ± 37, indicating an intermediate risk population. Of those who underwent coronary angiography, 42% presented with severe extension.
of coronary atherosclerosis (triple-vessel or left main disease). During a median hospitalization of 8 days (interquartile range = 6–15 days), the incidence of cardiovascular events was 13% (22 patients), resulting in 12 deaths, 4 nonfatal myocardial infarctions, and 6 refractory anginas.

**OSA and Cardiovascular Events**

During hospitalization, the incidence of combined cardiovascular events as the primary endpoint was 18% in individuals with a high probability of OSA, compared with no events in individuals with a low probability (P = 0.002). A dose-response relationship was observed as the number of positive categories in the Berlin Questionnaire increased: no events in patients with zero to one positive category, incidence of 15% in those with two positive categories and 25% in patients with three positive categories (P for trend = 0.001; Figure 1). This observation was the result of differences in death (0% vs. 7.2% vs. 15%, respectively, P = 0.008), nonfatal myocardial infarction (0% vs. 4.8% vs. 0%, P = 0.12) and refractory angina (0% vs. 2.4% vs. 10%, P = 0.015).

When components of the Berlin Questionnaire were analyzed, patients who developed events had a positive nighttime category more frequently, compared with those free of events (96% vs. 67%, P = 0.006). Seemingly, daytime positive category was more common in patients with events, compared with patients without events (55% vs. 29%, P = 0.015). In contrast, body mass index (26.3 ± 5.2 kg/m² vs. 26.7 ± 5.2 kg/m², P = 0.76) and history of hypertension (92% vs. 86%, P = 0.37) was similar in patients with and without events, respectively. In summary, it is the clinical presentation of OSA that is related to events, instead of risk factors such as increased body weight and hypertension.

**Independent and Additional Prognostic Value of OSA**

As expected, a number of clinical characteristics differed between patients with high or low clinical probability of OSA, defining potential confounding factors. The GRACE score tended to be higher (128 ± 37 vs. 116 ± 34, P = 0.08), and severe anatomic disease (triple vessel or left main) tended to be more common (46% vs. 31%, P = 0.16) in individuals with high probability, indicating a group with a worse risk profile. In addition, body mass index was greater in the high probability group (27 ± 5.6 kg/m²) compared with those with low probability (25 ± 3.4 kg/m², P = 0.01) and systemic hypertension was more common in the high probability group (95% vs. 73%, P < 0.001). Hospital treatment tended to be more aggressive in patients with high OSA probability, according to the frequency of beta-blockers, coronary angioplasty, and surgical revascularization (Table 1).

To evaluate which of these variables could be acting as confounding factors, we compared them among patients with and without events (Table 2). As expected, the GRACE score was higher (P < 0.001) and severe disease was more frequent in those with events (P = 0.005), compared with patients without events. Also, coronary angioplasty (P = 0.038) and surgical revascularization (P = 0.006) were more frequent in patients with events. The remaining variables were similar between the two groups. Therefore, the association of OSA and events were adjusted for these four potential confounding variables.

In the logistic regression model, OSA by Berlin Questionnaire was entered as a three-level variable (zero to one positive category, two positive categories, or three positive categories). After adjustment, OSA remained an independent predictor of events (OR = 3.4; 95% CI = 1.3 – 9.0; P = 0.015). In addition, the GRACE score and surgical revascularization remained significant, whereas severe anatomic disease and coronary angioplasty lost significance (Table 3).

As a predictor of hospital events, the GRACE score had a C-statistic of 0.72 (95% CI = 0.64–0.72). When OSA probability was incorporated into the GRACE score, a significant improvement in predictive value was observed (C-statistic = 0.82; 95% CI = 0.76–0.88); P = 0.03 for comparison between the two curves (Figure 2).

Table 1—Comparison of clinical characteristics and treatment between patients with high and low probability of OSA according to Berlin Questionnaire

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low</th>
<th>High</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>45</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>69 ± 14</td>
<td>71 ± 12</td>
<td>0.32</td>
</tr>
<tr>
<td>Male</td>
<td>25 (56%)</td>
<td>65 (53%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 3.4</td>
<td>27 ± 5.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>33 (73%)</td>
<td>117 (95%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (22%)</td>
<td>42 (34%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt; 45%</td>
<td>4/37 (11%)</td>
<td>18/114 (16%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Three-vessel or left main disease</td>
<td>8/26 (31%)</td>
<td>43/93 (46%)</td>
<td>0.16</td>
</tr>
<tr>
<td>GRACE score</td>
<td>116 ± 34</td>
<td>128 ± 37</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**In-Hospital Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>High</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>45 (100%)</td>
<td>122 (99%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>39 (89%)</td>
<td>108 (88%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>41 (91%)</td>
<td>109 (89%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>25 (56%)</td>
<td>83 (68%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>40 (91%)</td>
<td>112 (93%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>8 (18%)</td>
<td>35 (29%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Surgical revascularization</td>
<td>2 (4.4%)</td>
<td>16 (13%)</td>
<td>0.11</td>
</tr>
</tbody>
</table>
our analysis showed it was not the case. We tested the association between each category of the Berlin Questionnaire and events: the two categories related to clinical symptoms of OSA (snoring or breath interruption during sleep and daytime sleepiness) were clearly associated with events. In contrast, body mass index and hypertension did not differ between those with and without events. This suggests that the relationship is mediated by the OSA itself, as opposed to its risk factors.

Table 2—Comparison of potential confounding factors (characteristics associated with obstructive sleep apnea probability) between patients with and without hospital events (death, nonfatal infarction or refractory angina)

<table>
<thead>
<tr>
<th></th>
<th>No Event</th>
<th>Event</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>189</td>
<td>24</td>
<td>0.76</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.7 ± 5.2</td>
<td>26.3 ± 5.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>185 (86%)</td>
<td>24 (92%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>68 (32%)</td>
<td>9 (35%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Three-vessel or left main disease</td>
<td>54/146 (37%)</td>
<td>14/20 (70%)</td>
<td>0.005</td>
</tr>
<tr>
<td>GRACE score</td>
<td>120 ± 33</td>
<td>159 ± 48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>148 (69%)</td>
<td>16 (62%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>44 (21%)</td>
<td>10 (39%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Surgical revascularization</td>
<td>16 (7.4%)</td>
<td>7 (27%)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Table 3—Multivariate logistic regression analysis of obstructive sleep apnea effect on hospital outcomes (death, nonfatal infarction and refractory angina), adjusted for GRACE score and other potential confounding variables not present in this score

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive sleep apnea</td>
<td>3.4 (1.3 – 9.0)</td>
<td>0.015</td>
</tr>
<tr>
<td>GRACE score</td>
<td>1.03 (1.01 – 1.04)</td>
<td>0.001</td>
</tr>
<tr>
<td>Three-vessel or left main disease</td>
<td>1.5 (0.42 – 5.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>2.4 (0.7 – 8.5)</td>
<td>0.16</td>
</tr>
<tr>
<td>Surgical revascularization</td>
<td>4.6 (1.2 – 17)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

DISCUSSION

In the current study, we demonstrated that patients with clinical manifestation of OSA have higher risk for cardiovascular complications during the acute phase of unstable angina or non-ST elevation acute myocardial infarction. In addition, adjustment for confounding variables indicated the independent nature of this association.

The clinical assessment of OSA was performed using the Berlin Questionnaire, a validated tool with reasonable diagnostic accuracy. As components of Berlin Questionnaire diagnostic criteria, body mass index was higher and hypertension was more frequent in patients with high OSA probability. Thus, one natural concern is whether the predictive ability of OSA assessment was dependent on these risk factors, instead of OSA itself. Our analysis showed it was not the case. We tested the association between each category of the Berlin Questionnaire and events: the two categories related to clinical symptoms of OSA (snoring or breath interruption during sleep and daytime sleepiness) were clearly associated with events. In contrast, body mass index and hypertension did not differ between those with and without events. This suggests that the relationship is mediated by the OSA itself, as opposed to its risk factors.

Because classic risk factors for atherosclerosis are commonly associated with OSA, a greater extension of patients with coronary disease with higher OSA probability is expected. In fact, angiographic extension of atherosclerosis, severity of clinical presentation according to the GRACE score, and treatment during hospitalization were different between the groups of OSA probability. As potential confounding variables, these characteristics could have an intermediate association with OSA and cardiovascular risk. Therefore, we carefully adjusted for confounding variables, showing OSA as an independent and strong predictor of cardiovascular events. Finally, when clinical probability of OSA was added to the GRACE score, there was a large improvement in prognostic accuracy, indicated by a C-statistic absolute increment of 0.10. It should be emphasized that such magnitude of increment is not commonly observed when novel risk predictors are evaluated in prognostic studies of ACS. Even so, it should be recognized that this large increment might be mediated in part by the fact that recurrent angina was part of the composite endpoint and the GRACE score was not specifically calibrated for it.

Only one previous study evaluated the association between clinically suspected OSA and hospital prognosis in ACS. In that pioneering research, Jesus and colleagues used the Berlin Questionnaire to assess OSA and found a threefold increased risk in patients with high OSA probability, an association that proved to be independent in multivariate analysis. Our data confirm this previous evidence and adds some originality. First, we adjusted for anatomic severity for coronary disease, a potentially important confounding factor. Second, we chose the approach of controlling the predictive ability of OSA for the GRACE score, the most accurate prognostic tool in ACS. Third, we reported not only independent prediction
but also incremental prognostic value, by C-statistic analysis. Finally, our study was the first to specifically study non-ST elevation ACS.

The biologic plausibility of OSA and ACS prognosis is supported by a number of pathologic mechanisms. The hypoxia that these individuals experience during sleep probably diminishes oxygen delivery to the myocardium, whereas sympathetic activation related to OSA may increase oxygen demand. The combination of these factors aggravates myocardial ischemia. In parallel, plaque stabilization might be delayed as OSA enhances inflammation and thrombosis and worsens endothelial function. These theoretical mechanisms suggest that OSA may be causally linked with events. However, a final criterion will be necessary to definitely validate the causal nature of this relationship: experimental evidence that treatment of OSA in the acute phase improves outcomes of ACS patients.

As future studies confirm our findings, a diagnosis of OSA may have implications in ACS management. Possibly, individuals with high probability of OSA should receive special surveillance regarding nocturnal hypoxia, which once detected should trigger initiation of therapy during hospitalization. In patients with stable coronary disease, it has been demonstrated that continuous positive airway pressure diminishes angina and myocardial ischemia measured by ST-segment depression. However, this documentation has not been extended to patients with ACS and the beneficial effect of such strategy is still hypothetical.

The chief limitation of the current study is that assessment of OSA was based on clinical probability as opposed to routine sleep studies. The Berlin Questionnaire has a reasonable accuracy in the general population, but it is not validated in individuals with acute coronary syndromes. Thus, we cannot guarantee its accuracy in our target population. Therefore, this study should be considered preliminary evidence. A second limitation of our study is the lack of information regarding the timing of event during the day. Future studies should evaluate if events take place predominantly during the night, which would increase the strength of a causal association. Finally, statistical adjustment with the GRACE score probably cannot fully adjust for the difference in the complexity of patients with or without a positive Berlin Questionnaire.

In conclusion, the current study provides preliminary evidence that clinical suspicion of OSA has an independent and incremental prognostic value in patients with ACS. It suggests that OSA is a relevant condition during ACS and emphasizes the need for further investigation directed toward the interaction between OSA and ACS.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

REFERENCES


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Appendix—Berlin Questionnaire

**Category 1**

1. Do you snore?
   a. Yes
   b. No

2. Your snoring is:
   a. Slightly louder than breathing
   b. As loud as talking
   c. Louder than talking
   d. Very loud—can be heard in adjacent rooms

3. How often do you snore?
   a. Nearly every day
   b. 3–4 times a week
   c. 1–2 times a week
   d. 1–2 times a month
   e. Never or nearly never

4. Has your snoring ever bothered other people?
   a. Yes
   b. No
   c. Don’t know

5. Has anyone noticed that you quit breathing during your sleep?
   a. Nearly every day
   b. 3–4 times a week
   c. 1–2 times a week
   d. 1–2 times a month
   e. Never or nearly never

**Category 2**

6. How often do you feel tired or fatigued after your sleep?
   a. Nearly every day
   b. 3–4 times a week
   c. 1–2 times a week
   d. 1–2 times a month
   e. Never or nearly never

7. During your waking time, do you feel tired, fatigued, or not up to par?
   a. Nearly every day
   b. 3–4 times a week
   c. 1–2 times a week
   d. 1–2 times a month
   e. Never or nearly never

8. Have you ever nodded off or fallen asleep while driving a vehicle?
   a. Yes
   b. No

**Category 3**

9. History of arterial systemic hypertension

10. Body mass index > 30 kg/m²