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EFFECT OF B-BLOCKERS ON THE RISK OF ATRIAL FIBRILLATION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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INTRODUCTION: Oral β-blockers improve the prognosis of patients with acute myocardial infarction, while atrial fibrillation worsens the prognosis of this population. The reduction of atrial fibrillation incidence in patients treated with β-blockers could at least in part explain the benefits of this drug.
OBJECTIVE: To investigate the effect of β-blockers on the incidence of atrial fibrillation in patients with acute myocardial infarction.
METHODS: We analyzed 1401 patients with acute myocardial infarction and evaluated the occurrence or absence of atrial fibrillation, the use of oral β-blockers and mortality during the first 24 hours.
RESULTS: a) The use of β-blockers was inversely correlated with the presence of atrial fibrillation ($\rho = 0.004$; OR = 0.54). b) Correlations with mortality were as follows: 31.5% in patients with atrial fibrillation, 9.2% in those without atrial fibrillation ($\rho < 0.001$; Odds Ratio = 4.52), and 17.5% in patients not treated with β-blockers and 6.7% in those who received the drug ($\rho < 0.001$; OR = 0.34). c) Adjusted Models: The presence of atrial fibrillation was independently correlated with mortality (OR = 2.48, $\rho = 0.002$). The use of β-blockers was inversely and independently correlated with mortality (OR = 0.53; $\rho = 0.002$). The patients who used β-blockers showed a lower risk of atrial fibrillation (OR = 0.59; $\rho = 0.029$) in the adjusted model.
CONCLUSION: The presence of atrial fibrillation and the absence of oral β-blockers increased in-hospital mortality in patients with acute myocardial infarction. Oral β-blockers reduced the incidence of atrial fibrillation, which might be at least partially responsible for the drug's benefit.

KEYWORDS: Acute myocardial infarction; β-blockers; Atrial fibrillation; Mortality; Arrhythmias.

INTRODUCTION

In the United States, more than one million people suffer an acute myocardial infarction (AMI) each year. Even with recent advances in diagnosis and treatment, global mortality rates are still around 30%.[1] Several studies have shown that the early use of β-blockers in patients with AMI is able to limit the extent of myocardial injury and improve the short- and long-term prognosis.[1-9] Thus, routine use of β-blockers is recommended in patients with AMI, provided there are no contraindications.

It has classically been accepted that the main mechanisms responsible for the beneficial effects of β-blockers involve blocking myocardial sympathetic stimulation, a decrease in heart rate and blood pressure and a benefit for heart remodeling.[1] However, some recent publications have suggested that the reduction in the incidence of arrhythmias after AMI, seen after β-blocker treatment, could also have a leading role in explaining the benefits obtained with the use of these drugs.[2,11-17] It is also well demonstrated that atrial fibrillation (AF) is considered a factor of poor prognosis in myocardial infarction, even in adjusted models.[14,18-25]

In this context, we analyzed data from 1401 patients with AMI in a single institution in order to investigate the effect of β-blockers on the incidence of AF and to analyze the relationships between mortality in 24 hours and 1) the use of β-blockers and 2) the incidence of AF.

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METHODS

This study was a retrospective unicentric study. All included patients with AMI (n = 1401; median age = 63 years) were hospitalized in a single coronary intensive care unit and were prospectively included in a specific database. The patients were analyzed during the first 24 hours after hospitalization. The definitions and medical procedures followed the institutional routines, in accordance with recent guidelines. During this period, AF was treated with synchronized electrical cardioversion and the use of amiodarone in all patients.

A diagnosis of AMI was established when patients had chest pain at rest with concomitant ischemic ST-T changes and positive serum troponin.[26] The left ventricular ejection fraction (LVEF) was calculated by Doppler echocardiography (Simpson). Only the period when patients were hospitalized was analyzed, taking into account the presence of AF, the use of oral β-blockers and all-cause mortality. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as indicated. The Student's t test was used to compare continuous variables.

In adjusted models, the analyses were performed by stepwise logistic regression. In the first model, AF was included as a dependent variable. The adjusted R^2 was 0.114. The following variables were considered independent: LVEF, age, gender, previous diabetes mellitus, previous myocardial infarction, current myocardial infarction location, ST elevation, admission creatinine, coronary surgery and angioplasty during hospitalization, use of aspirin, angiotensin-converting enzyme inhibitor and use of β-blockers. In the second model, death was the dependent variable. AF was added to the other independent variables included in the first model. The adjusted R^2 of this model was 0.226.

In all models, statistical significance was set at 5% ($\rho < 0.05$).

RESULTS

a. Population studied

As stated above, 1401 patients were examined. The average age of the population was 63.19 + 12.7 years and 1021 patients (72.9%) were men. The left ventricular ejection fraction was, on average, 51.1% + 15.5. During the hospitalization, 150 patients (10.7%) died.

b. Univariate analysis

b.1. Occurrence of AF

The baseline characters and univariate analysis of their association with AF is shown in Table 1. The use of β-blockers was inversely correlated with the presence of AF. As shown in Table 1, age, diabetes mellitus, previous AMI, coronary surgery, angioplasty, creatinine clearance and LVEF also had a significant correlation with the presence of AF. Excluding patients who used intravenous β-blockers followed by oral β-blockers did not change the results; the ρ value was 0.009 for the correlation between oral β-blockers and AF.

Table 1 - Baseline characters in patients with AF and without AF

Variables	AF (n = 92)	Without AF (n = 1309)	Odds Ratio	ρ value *
Age (years)	70 +/- 10.3	63 +/- 12.8		< 0.001
Male gender (%)	65.2	73.4	2.92	NS
Diabetes mellitus (%)	38	27.3	1.64	0.026
Previous AMI (%)	41.3	27	1.91	0.003
CABG (%)	34.8	17.1	2.58	< 0.0001
PTCA (%)	26.1	36.8	0.61	0.038
LVEF (%)	0.43 +/- 16.4	0.51 +/- 15.3		< 0.001
Creatinine clearance	38.3 +/- 20.4	55.7 +/- 41.5		< 0.001
STEMI (%)	55.4	57.2	0.93	NS
Anterior AMI (%)	43.5	42.8	1.03	NS
β-Blocker (%)	48.9	63.8	0.54	0.004
ACE inhibitors (%)	54.3	50	1.19	NS
Aspirin (%)	94.6	94.3	1.06	NS

AF = atrial fibrillation; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; PTCA = percutaneous coronary angioplasty; LVEF = left ventricular ejection fraction; STEMI = ST elevation myocardial infarction; ACE = angiotensin-converting enzyme inhibitor; NS = not significant. * = $\rho < 0.05$.

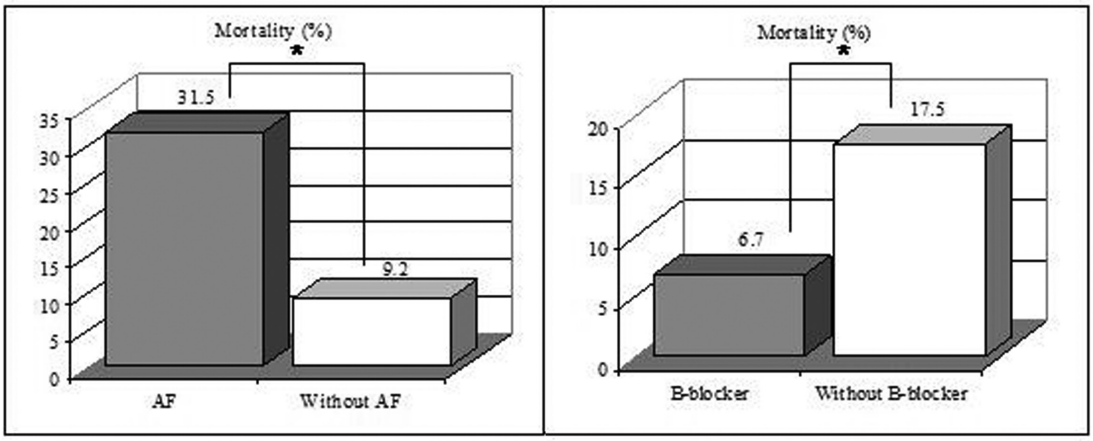

Figure 1 - The relationship between use of β-Blocker and AF with mortality. Legend: AF = atrial fibrilation. * = ρ < 0.001.

b.2. Mortality

As noted in Figure 1, 31.5% of the patients in the group that presented with AF died, compared to 9.2% in the group without arrhythmia (ρ < 0.001; Odds Ratio = 4.52). Figure 1 clearly shows an inverse correlation between the use of β-blockers and mortality (17.5% mortality in patients who did not use β-blockers and 6.7% mortality in those that did; ρ < 0.001; OR = 0.34). LVEF and age also showed a correlation with mortality (Table 2). The incidence of death among women was 13.2% (50/380), while in males it was 9.8% (100/1021, OR = 0.72, ρ = 0.07). Two hundred and forty patients used both oral and intravenous β-blockers. The results did not change when these patients were excluded. Values of ρ <0.001 were found for the correlations between mortality and the use of oral β-blockers, AF, and also found between use of oral β-blockers or presence of AF and mortality.

Table 2 - The relationship between age, ejection fraction and mortality LVEF = left ventricle ejection fraction

	Age (years)*	Ejection fraction of LVEF*
Deaths	72 +/- 11.9#	0.41 +/- 15.0#
Live	62 +/- 12.4#	0.52 +/- 15.1#

* = average; +/- standard deviation; # = ρ value <0.001.

c. Adjusted Models

c.1. Occurrence of AF

The patients who used β-blockers showed a lower risk of AF (OR = 0.59; ρ = 0.029) in the adjusted model. Age, coronary surgery and LVEF also had a significant correlation with the presence of AF, as shown in Table 3.

c.2. Mortality

The multivariate analysis of the association between different clinical variables and mortality is shown in Table 4. The presence of AF was independently correlated with mortality (OR = 2.48, ρ = 0.002). The use of β-blockers was inversely and independently correlated with mortality (OR = 0.52; ρ = 0.002). Table 4 also shows the correlation between mortality and age, LVEF, creatinine clearance and use of angiotensin-converting enzyme inhibitors.

Table 3 - Multivariate analysis of the association between different clinical variables and the occurrence of AF

Variables	Odds Ratio	CI 95%	ρ value*
Age	1.045	1.024 – 1.067	< 0.0001
Diabetes mellitus	1.164	0.711 – 1.907	NS
Previous AMI	1.297	0.792 – 2.124	NS
CABG	3.085	1.886 – 5.057	< 0.0001
PTCA	0.925	0.531 – 1.611	NS
LVEF	0.968	0.952 – 0.983	< 0.001
Creatinine clearance	1.248	0.960 – 1.621	NS
STEMI	1.144	0.703 – 1.861	NS
Anterior AMI	1.008	0.621 – 1.634	NS
β-Blocker	0.59	0.367 – 0.948	0.029
ACE inhibitors	1.492	0.925 – 2.408	NS
Aspirin	0.9	0.328 – 2.471	NS

AF = atrial fibrillation; CI = confidence interval; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; PTCA = percutaneous coronary angioplasty; LVEF = left ventricular ejection fraction; STEMI = ST elevation myocardial infarction; ACE = angiotensin-converting enzyme inhibitor; NS = not significant. * = ρ < 0.05.

Limitations

This study was a retrospective study based on a databank. However, the fact that the data were included prospectively decreases the chance of any bias related to the results. Due to retrospective design of the study,

Table 4 - Multivariate analysis of the association between different clinical variables and mortality

Variables	Odds Ratio	CI 95%	ρ value*
Age	1.061	1.042 – 1.081	< 0.0001
Diabetes mellitus	1.097	0.703 – 1.712	NS
AF	2.476	1.399 – 4.382	0.002
Previous AMI	0.781	0.495 – 1.233	NS
CABG	1.222	0.720 – 2.075	NS
PTCA	0.703	0.436 – 1.133	NS
LVEF	0.955	0.940 – 0.969	< 0.001
Creatinine clearance	1.694	1.297 – 2.214	< 0.001
STEMI	1.127	0.732 – 1.737	NS
Anterior AMI	1.089	0.709 – 1.671	NS
β-Blocker	0.521	0.342 – 0.794	0.002
ACE inhibitors	0.481	0.312 – 0.740	0.001
Aspirin	1.027	0.451 – 2.337	NS

AF = atrial fibrillation; CI = confidence interval; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; PTCA = percutaneous coronary angioplasty; LVEF = left ventricular ejection fraction; STEMI = ST elevation myocardial infarction; ACE = angiotensin-converting enzyme inhibitor; NS = not significant. * = ρ < 0.05.

some important data, including echocardiography parameters (ejection fraction, left atrial size, left ventricular hypertrophy, diastolic function), electrolyte levels and oxygen status are missing.

DISCUSSION

In accordance with previous evidence, this sample showed a significant association between the use of β-blockers and reduction in mortality during the hospitalization of patients with AMI. In these results, the lack of β-blocker use was related to increased mortality and AF. This correlation remained significant even in adjusted models. Most studies that evaluated the effect of β-blockers after AMI reported a short-term reduction of up to 50% in the risk of death, similar to our results.[1,3,5,6,8] However, there are no studies that clearly associated β-blockers, AF and in-hospital mortality after an AMI.

Dargie et al. conducted a randomized, multicenter, placebo-controlled study (CAPRICORN) examining the use of carvedilol in 1959 infarcted patients with left ventricular dysfunction (EF < 40%) over a period of 1.3 years. As expected, the observed mortality was lower in the group that received carvedilol than in the control group (12% vs. 15%, respectively, ρ = 0.03).[9] Recently, the COMMIT/CCS-2 study[10,27] assessed the in-hospital use of intravenous metoprolol followed by oral treatment in 45,852 patients with ST-segment elevation AMI. Despite the reduction in ventricular arrhythmias in the β-blocker group, the drug was related to an increased risk of cardiogenic shock, especially in patients in Killip 3 and 4. These results raised some issues: should β-blockers be used orally or intravenously? Which mechanisms are responsible for the drug's benefit? In what group of patients should we use the drug after AMI? In fact, a previous study, based on the GUSTO-1 trial, showed a larger benefit in patients who used oral β-blockers than in those who used intravenous followed by oral treatment.[12] In our study, intravenous β-blockers was not better than oral treatment. In any case, all of the available evidence has led the most recent guidelines to suggest caution when using intravenous β-blockers after AMI.[26]

The analysis of AF after AMI showed that, as in previous publications, patients who had had an arrhythmia during hospitalization had an increased mortality rate (31% vs. 9.2%, ρ < 0.001).[14,15,18-25] Laurent et al. conducted a retrospective study in patients with non-ST elevation AMI. The study showed that the occurrence of AF in the first 24 hours after AMI significantly increased in-hospital mortality compared to patients who did not have the arrhythmia (21% vs. 6%, respectively, ρ = 0.03).[21] In another retrospective study, Pedersen et al. observed that patients with left ventricular dysfunction who had AF after AMI also showed increased in-hospital mortality (OR = 1.8, ρ <0.05).[20] In a sub-analysis of the GUSTO-III trial, 13,858 patients were assessed after AMI. Investigators correlated the occurrence of AF and prognosis. The mortality in patients with AF was greater than in the group without the arrhythmia [OR = 1.63 (1.31-2.02)].[28] Additionally, Asanin et al. demonstrated that the recurrence of AF during hospitalization for AMI further increases the risk of death compared to those with a single episode of arrhythmia (36.1% vs. 12.9%, respectively).[14]

Regarding the anti-arrhythmic effects of β-blockers, previous studies have shown controversial results regarding the ability of the drug to reduce the risk of AF after AMI.[13,14,18,28,29] A study conducted by McCullough et al. prospectively examined the benefits of the use of β-blockers in 1724 patients after AMI with chronic renal failure. The authors reported a significant reduction in the incidence of AF in patients using β-blockers compared to patients who had not used the drug (9.5% vs. 16.4%, respectively, p < 0.0001).[13] On the other hand, other major studies have found different results. The retrospective analysis of the AIRE study, which assessed the use of β-blockers in patients with AMI and ventricular dysfunction, showed reduced mortality but no differences in the incidence of arrhythmia in patients who used the drug.[18] Similarly, Yilmaz et al. reported an AF incidence of 23.8% after AMI, without any reduction in the risk of

arrhythmia in the group treated with β-blockers.[29] On the other hand, our study found a significant increase in the incidence of AF in patients who had not used β-blockers compared to those who used the drug. Even after multivariate analysis, the risk of AF in patients who had not used β-blockers remained high and significant.

CONCLUSION

The presence of AF and the absence of oral β-blocker use increased in-hospital mortality in patients with AMI. Oral β-blockers reduced the incidence of AF, a mechanism that might be at least partially responsible for the drug's benefit.

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