Introduction and objectives. Clinical trials have shown that combining beta-blockers and angiotensin-converting enzyme (ACE) inhibitors has an additive effect in reducing mortality in patients with left ventricular dysfunction following acute myocardial infarction. Whether this additive effect also occurs in unselected post-myocardial infarction patients is unknown.

Methods. In total, 5397 patients who were discharged from hospital after suffering an acute myocardial infarction were followed for 1 year. The primary endpoint was all-cause mortality. The effects of the medications on 1-year survival were analyzed using a Cox regression model, which included propensity scores for beta-blocker and ACE inhibitor use to take account of any potential imbalance in drug prescription rates.

Results. At hospital discharge, 55.9% of patients were receiving beta-blockers and 45.1%, ACE inhibitors. The 1-year mortality rate was 5.5%. Overall, combination of the two medications significantly reduced the 1-year mortality rate (hazard ratio [HR]=0.51; 95% confidence interval [CI], 0.32-0.82; P < 0.005) to a greater extent than ACE inhibitors alone (HR=0.78; 95% CI, 0.54-1.12; P = 0.2) or beta-blockers alone (HR=0.67; 95% CI, 0.43-1.05; P = 0.08). The same trend was also observed in low-risk patients without acute heart failure who had an ejection fraction ≥40%.

Conclusions. In unselected post-myocardial infarction patients, combined prescription of beta-blockers and ACE inhibitors had an additive effect on the 1-year survival rate.

Key words: Beta-blockers, Angiotensin-converting enzyme inhibitors, Survival, Myocardial infarction.

Efecto de la asociación de bloqueadores beta e inhibidores de la enzima de conversión en la supervivencia al año tras un infarto agudo de miocardio. Resultados del registro PRIAMHO II

Introducción y objetivos. La combinación de bloqueadores beta e inhibidores de la enzima de conversión de la angiotensina (IECA) ha demostrado reducir la mortalidad en pacientes con infarto de miocardio y disfunción sistólica. Sin embargo, no sabemos si esta asociación presenta efectos aditivos sobre la supervivencia al año en una población no seleccionada de pacientes con infarto agudo de miocardio con y sin elevación del segmento ST.

Métodos. Se realizó un seguimiento durante un año a 5.397 pacientes dados de alta tras un infarto agudo de miocardio. El criterio de valoración fue la mortalidad por cualquier causa. Para analizar el efecto de la medicación se utilizó el modelo de regresión logística de Cox, en el que se incluyó el propensity score para compensar las posibles desviaciones en la prescripción de los 2 grupos de fármacos.

Resultados. En el momento del alta, el 55,9% de los pacientes recibió bloqueadores beta y el 46,1%, IECA. La mortalidad al año fue del 5,5%. En el grupo total, la combinación se asoció con una reducción significativa de la mortalidad (hazard ratio [HR] = 0,51; intervalo de confianza [IC] del 95%, 0,32-0,82; p < 0,005) superior a la de los IECA solos (HR = 0,78; IC del 95%, 0,54-1,12; p = 0,2) y los bloqueadores beta solos (HR = 0,67; IC del 95%, 0,43-1,05; p = 0,08). Esta misma tendencia se observó en los
The aim of this study was to investigate whether BB combined with ACE inhibitors improves survival compared to each drug alone in an unselected patient population, with or without ST-segment elevation AMI 1 year after the acute episode and who had been discharged to their homes.

METHODS

The PRIAMHO II study (Proyecto de Registro de Infarto Agudo de Miocardio HOspitalario) was designed by the Ischemic Heart Disease and Coronary Care Units Section of the Spanish Society of Cardiology with the collaboration of the SEMICYUC Cardiology Intensive Care Working Group. This consists of a registry of patients with AMI admitted to coronary care units. The methodology has been previously published. In brief, 81 of the 165 public hospitals with coronary units were randomly selected and invited to participate. All centers had to meet the following requirements: a) register at least 70% of AMI patients admitted to the hospital (ascertainment rate); b) register more than 75% of the AMI patients admitted to coronary intensive care unit (CICU) (ascertainment rate); c) have a kappa index of 70% between the registered data and that obtained by an external auditor in a random sample of 20% of the patients included in each center (concordance rate); and d) >90% follow-up rate in registered patients at 1 year.

The study was developed between 15 May and 16 December 2000. At the end of this period, 58 of the 81 invited hospitals met all the requirements.

The diagnosis of infarction was based on the presence of at least 2 of the following criteria: ischemic symptoms of over 20 min duration, presence of pathological Q-waves, and an increase in serial enzyme markers of myocardial necrosis more than double the normal value and showing an enzyme kinetics curve. Demographic data, clinical background, and complications during hospitalization were recorded, as well as the diagnostic and therapeutic procedures used during hospital stay. All the variables had been previously defined and their collection standardized.

Patients were followed up for a minimum of 1 year. All deaths that occurred within the first 28 days after the AMI were considered to be related to this event. After this period, the assessment criterion was mortality from any cause.

Statistical Analysis

Continuous variables are presented as mean±SD. Discrete variables appear as percentages. Univariate analysis was carried out with the Student t test for continuous variables with normal distribution and the Fisher test for dichotomous variables, or the $\chi^2$ test.

In order to control for the differences in baseline clinical characteristics between the treated and untreated
patients, a logistic regression analysis was done for each treatment (ACE inhibitors and BB) and, thus, the propensity score of receiving a given treatment could be calculated. All the clinical variables were included in these analyses. Between-factor interactions were also evaluated. The capacity of the model to discriminate between patients discharged under treatment was measured through the C-statistic.

Cox regression was used to determine the variables associated with 1-year survival and to estimate the hazard ratio (HR) with a 95% confidence interval (CI) of dying between hospital discharge and 1-year follow-up. The clinical variables that showed significant differences in the univariate analysis were included in the different models, as well as the propensity score of receiving ACE inhibitors and/or BB. The interactions were also assessed between treatment at the time of discharge (none, ACE inhibitors only, BB only, or both) and the remaining factors. A statistically significant interaction was found between treatment and the variable “high risk” (Killip class I or ejection [EF] <0.40%). For this reason, the results are presented separately depending on whether high-risk was present or not. Statistical significance was set at P<0.05.

RESULTS

Baseline Characteristics

Between 15 May and 15 December 2000, 6221 patients were enrolled with a 93% 1-year follow-up rate. Table 1 shows the patients’ baseline data, as well as mortality in different phases of the study. Initial ST-segment elevation was found in 66.3% of the patients, whereas Q-wave AMI was much more frequent than non-Q-wave AMI (65.6 vs 34.4%). Post-hospital discharge mortality was 5.5%, 28-day mortality, 11.4%, and 1-year mortality, 16.5%.

Treatment at of Discharge and 1-Year Mortality

Some 5397 patients survived the acute phase. At the time of hospital discharge, 91% received antiplatelet agents; 55.9%, BB; 45%, ACE inhibitors; and 45%, statins. Table 2 shows the distribution of BB and ACE inhibitors by group. Angiotensin-converting enzyme inhibitors were most frequently prescribed in women and in patients with diabetes, hypertension, previous infarction, and heart failure during hospitalization, and with EF<40%. Patients treated with BB at the time of discharge were younger, smoked more, and had received reperfusion treatment more often.

One-year mortality was 9.6% in patients treated with ACE inhibitors vs 2.5% and 3.6% in those treated with BB only or in combination, respectively (P<0.001) (Table 2). Table 3 shows the factors related to 1-year survival from the time of hospital discharge. Independent predictors of mortality after discharge were: age, female sex, non-Q-wave infarction, the presence of CHF during the acute phase (Killip class I), or significant systolic dysfunction (EF<40%). On the other hand, primary reperfusion led to an important reduction in mortality.

The patients who received BB only or BB with ACE inhibitors at discharge had a higher probability of being alive at 1 year, as well as those treated with aspirin or hypolipidemic agents. However, the opposite was the case with ACE inhibitors, nitrates, and calcium antagonists (Table 3).

The C-statistic (area under the receiver operating characteristic curve) was 0.81 for ACE inhibitors and 0.85 for BB in the analysis that included all the variables listed in Table 2, together with CICU treatment, demonstrating that the models have a good level of discrimination between patients receiving each treatment.

A significant interaction (P=0.044) was found between treatment and high-risk (Killip class I or EF<0.40%). Thus, different analyses are shown in Table 4: for all patients (no interaction), low-risk patients (Killip class I and EF>40%), and high-risk patients (Killip class I or EF<40%, 3.1% 1-year mortality rate following discharge) and high-risk patients (Killip class I or EF<40%, 12.8% 1-year mortality rate following discharge).

If we adjust the model for possible confounding variables detected in the univariate analysis, the data presented in Table 4 show an additional positive effect of ACE inhibitors combined with BB. Thus, in the

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**TABLE 1. Clinical Characteristics and Background of Patients Included in PRIAMHO II. Mortality at Different Times During the Study**

<table>
<thead>
<tr>
<th>Total Group (n=6221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Background</strong></td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Previous infarction</td>
</tr>
<tr>
<td>Previous revascularization</td>
</tr>
<tr>
<td><strong>ECG at admission</strong></td>
</tr>
<tr>
<td>ST-segment elevation/LBBB</td>
</tr>
<tr>
<td>ECG at discharge</td>
</tr>
<tr>
<td>Q-wave infarction</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
</tr>
<tr>
<td>CICU mortality</td>
</tr>
<tr>
<td>Mortality following discharge</td>
</tr>
<tr>
<td>28-day mortality</td>
</tr>
<tr>
<td>1-year mortality</td>
</tr>
</tbody>
</table>

*LBBB indicates left bundle branch block; SD, standard deviation; ECG, electrocardiogram; CICU, cardiac intensive care unit, coronary unit.*
group that includes all the patients, treatment with ACE inhibitors and BB was independently related to a significant reduction in mortality (HR=0.51; 95% CI, 0.32-0.82; \(P=.005\)), whereas the reduction found with ACE inhibitors only or BB only did not reach statistical significance. The same trend was observed in the low-risk group, since the lower probability of dying was obtained with the combination of drugs (HR=0.49 with ACE inhibitors-BB; HR=1.39 with ACE inhibitors only; HR=1.00 with BB only). The 3 treatments analyzed significantly reduced mortality in the high-risk group (Table 4).

**DISCUSSION**

The results of our study demonstrate that ACE inhibitors combined with BB yield a greater reduction in mortality than each drug group separately after 1-year follow-up in an unselected group of patients with AMI, with or without ST-segment elevation, who survive the acute phase. This finding accquires importance given the scarcity of data on the additive effect of combined ACE inhibitors and BB begun during hospitalization, although the results of a registry cannot be considered definitive.

In recent years various drugs and therapies have demonstrated their efficacy in treating acute coronary syndrome. ACE inhibitors form one of the groups for which indications have possibly increased. In the 1996 treatment guidelines for AMI the prescription of ACE inhibitors was a class I recommendation in patients with previous AMI or with clinical acute CHF, as well as in patients with EF<40%. There was no clear recommendation regarding the use of long-term ACE inhibitors. In the guidelines for ST-segment elevation AMI published in 2004, the type I indications during hospitalization were not changed, although prescribing ACE inhibitors is accepted for all patients with AMI in the first 24 h, in the absence of contraindications (a class
and 23 patients found a significant difference in their studies, although these are non-clinical studies. This was confirmed in the CAPRICORN study, 12,218 patients diagnosed myocardial infarction, and only 8.1% presented another risk factor. Of these, 52.6% had an old vascular disease or diabetes associated with it.

According to Vital Status per Year Among the Survivors

<table>
<thead>
<tr>
<th>Complications</th>
<th>Alive per Year</th>
<th>Death per Year</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killip class II-IV at the time of admission, %</td>
<td>5.0</td>
<td>18.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Killip class II during admission, %</td>
<td>22.6</td>
<td>57.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Repeat-AMI, %</td>
<td>2.0%</td>
<td>3.4</td>
<td>.112</td>
</tr>
<tr>
<td>Post-AMI angina, %</td>
<td>14.6</td>
<td>17.1</td>
<td>.235</td>
</tr>
<tr>
<td>VF/VT, %</td>
<td>5.6</td>
<td>5.5</td>
<td>.905</td>
</tr>
<tr>
<td>Advanced AV block, %</td>
<td>4.6</td>
<td>5.8</td>
<td>.355</td>
</tr>
<tr>
<td>Flutter/AF, %</td>
<td>6.6</td>
<td>17.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mechanical complication, %</td>
<td>0.2</td>
<td>1.7</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Treatment in ICU

Primary reperfusion, % | 47.8 | 26.4 | <.001 |

Fibrinolysis, % | 42.5 | 21.9 | <.001 |

PTCA balloon/other, % | 5.3 | 4.5 | .546 |

EF<40%, % | 12.3 | 27.4 |

Killip class ≥II or EF<40%, % | 22.7 | 57.4 | <.001 |

Treatmen at time of discharge

Nitrates, % | 37.1 | 49.7 | <.001 |

Calcium antagonists, % | 15.7 | 20.2 | .042 |

Aspirin, % | 84.6 | 78.4 | .005 |

Lipid-lowering agents, % | 47.1 | 30.5 | <.001 |

BB, % | 58.1 | 30.8 | <.001 |

ACE inhibitors, % | 43.3 | 52.7 | .002 |

BB and ACE inhibitors, % | 23.0 | 15.1 | .002 |

*PTCA indicates percutaneous transluminal coronary angioplasty; AV, atrioventricular; BB, beta-blockers; LBBB, left branch bundle block; SD, standard deviation; AF, atrial fibrillation; EF, ejection fraction; VF, ventricular fibrillation; AMI, acute myocardial infarction; CICU, cardiac intensive care unit, coronary unit.

The new indication for the long-term administration of ACE inhibitors in patients without heart failure is EF<40% in an echocardiographic substudy (patients with CHF were excluded from the study). Treatment with 10 mg/day ramipril over a mean follow-up of 5 years reduced cardiovascular mortality from 17.8 to 6.1% (P<.001). ACE inhibitors achieved a beneficial effect in these studies. However, a recent metaanalysis of the HOPE, EUROPA, and PEACE studies found a significant reduction in mortality. This outcome was only achieved in the high-risk subgroup in our registry, although our patients began treatment in the acute phase rather than in the chronic, as in the trials cited. Furthermore, follow-up was only for 1 year, which was insufficient time to show a beneficial effect in these studies.

The combination of ACE inhibitors plus BB yielded the greatest reduction in mortality in the low-risk subgroup, but without reaching statistical significance. On the other hand, in the high-risk subgroup, BB only, ACE inhibitors only, and their combination significantly reduced mortality. The additive effect of the combination on high-risk patients has been reported in a post-infarction registry of patients >65 years old with systolic dysfunction. This was confirmed in the CAPRICORN study.

Arós F et al. Reduction in Postinfarction Mortality With Beta-Blocker and Angiotensin-Converting Enzyme Inhibitor
clinical trial with carvedilol in patients with AMI, with or without CHF, and EF \( \leq 40\% \) treated with ACE inhibitors and aspirin.

14 The reduced effect in our study can be attributed to the difference between the populations analyzed. In the study by Shilapak et al mortality due to acute events from the time of discharge to 1 year was 30\% versus 12.8\% in our high-risk patients. It cannot be ruled out that the BB used may not be the most effective means for treating patients with CHF or depressed EF, now that we know that there are differences between them.

15 Study Limitations

Our results are based on the PRIAMHO II registry which included patients with AMI admitted to the CICU. Thus, the patients were not randomly distributed. The different treatments prescribed were based on the criteria of the acting physician and we do not have data on contraindications or adverse drug effects. Neither do we know the specific active ingredients or dose. Furthermore, we lack information on whether changes were introduced regarding treatment during the follow-up year.

The new definition of AMI was published in September 2000 and coincided with the final part of our study. Thus, it could not be included in patient selection criteria.

**CONCLUSIONS**

In an unslected patient population with AMI, with or without ST-segment elevation, the prescription of BB and ACE inhibitors at the time of hospital discharge demonstrates additive effects on 1-year survival, which supports their prescription to all the post-infarction patients without contraindications, although their effect is more pronounced in the high-risk subgroup.

**APPENDIX. RESEARCHERS PARTICIPATING IN PRIAMHO II (PROYECTO DE REGISTRO DE INFARTO AGUDO DE MIOCARDIO HOSPITALARIO)**

Hospital General de Albacete, Albacete: J. Enero; Hospital Punta Europa, Algeciras (Cádiz): P. Cobo; Hospital Universitario Sant Joan d’Alacant, Alicante: V. Boronuca, P. J. Moriles, A. Frutos, F. Comunia; Hospital General Universitario...
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