Prognostic Role of Systemic Hypertension and Diabetes Mellitus in Patients With Unstable Angina Undergoing Coronary Stenting

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Background and objectives. The adverse effects of systemic hypertension and diabetes mellitus in coronary patients are well known, although their long-term prognostic influence on patients with unstable angina (UA) undergoing percutaneous coronary intervention (PCI) with coronary stenting is uncertain. The aim of this study was to determine the influence of these pathologies in this population at 3-year follow-up.

Patients and method. We studied 279 consecutive patients with UA who underwent coronary stenting. 129 (46.2%) of them had hypertension and 60 (24.7%) had diabetes. Clinical follow-up was obtained in 92.14% after 3 years.

Results. Although the need for new PCI at the target lesion was higher for patients with hypertension and diabetes (12.1 vs 8.4%; p = 0.31, and 14.5 vs 8.6%; p = 0.16, respectively), the differences were not significant with respect to the control groups. Multivariate analysis showed hypertension (OR = 4.71; CI 95%, 1.01-42.2; p = 0.04) and ejection fraction (OR = 0.95; CI 95%, 0.91-0.99; p = 0.03) to be predictors of mortality, and diabetes to be a predictor of myocardial infarction and infarction resulting in death (OR = 3.01; CI 95%, 1.13-8.02; p = 0.02, and OR = 2.68; CI 95%, 1.03-6.95; p = 0.04, respectively).

Conclusions. Hypertension was the only independent long-term predictor of mortality in our series of patients with UA who underwent coronary stenting. Diabetes was the only predictor of myocardial infarction or for the combined event of infarction and death. Risk of myocardial infarction was threefold as high in this diabetic patient population, and was the main cause of mortality.

Key words: Unstable angina. Diabetes Mellitus. Hypertension. Prognosis. Stent.

Papel pronóstico de la hipertensión arterial y de la diabetes mellitus en los pacientes con angina inestable tratados con stents coronarios

Introducción y objetivos. Aunque se conocen bien los efectos desfavorables de la hipertensión arterial y la diabetes mellitus en la enfermedad coronaria, su influencia en pacientes con angina inestable (AI) a los que se ha realizado intervencionismo coronario percutáneo (ICP) con stent (ICPS) es menos conocida. El objetivo de este trabajo es conocer su influencia en esta población en un seguimiento de tres años.

Pacientes y método. Para ello, estudiamos a 279 pacientes consecutivos con AI e ICPS. De éstos, 129 (46.2%) eran hipertensos y 69 (24.7%), diabéticos. Se realizó seguimiento clínico en el 92,14% a los 3 años.

Resultados. La necesidad de nuevo ICP en la lesión diana era mayor en los grupos con hipertensión y diabéticos (12,1 frente a 8,4%; p = 0,31, y 14,5 frente a 8,6%; p = 0,16, respectivamente), pero no alcanzaba significación estadística con respecto a sus controles. En el análisis multivariable, la hipertensión fue una variable predictora de mortalidad (OR = 4,71; IC del 95%, 1,01-42,2; p = 0,04) junto con la fracción de ejección (OR = 0,95; IC del 95%, 0,91-0,99; p = 0,03). La diabetes era la única variable predictora de infarto de miocardio e infarto-muerte (OR = 3,01; IC del 95%, 1,13-8,02; p = 0,02, y OR = 2,68; IC del 95%; 1,03-6,95; p = 0,04, respectivamente).

Conclusiones. En nuestra serie de pacientes con AI a los que se realiza ICPS, la hipertensión es el único factor independiente de mortalidad a los 3 años. La diabetes es el único factor predictivo de infarto o del evento combinado infarto-muerte. El riesgo de sufrir infarto se triplica en los pacientes diabéticos y es su principal causa de mortalidad.

Coronary Stent in Unstable Angina. Relevance of Arterial Hypertension and Diabetes


Coronary intervention (PCI) in recent years which have greatly limited the number of perioperative complications.\textsuperscript{1,2} Stenting has reduced the need for further revascularizations and the use of coated stents should come close to eliminating this need.\textsuperscript{3} In contrast, long-term events such as myocardial infarction (MI) or mortality after PCI do not appear to have been influenced by these recent advances.\textsuperscript{4,5} although debate persists on this point.\textsuperscript{6} Because of this lack of agreement, clinical characteristics of the patient rather than factors related to the procedure have become more important for providing a prognosis for these patients. Conditions such as unstable angina (UA), arterial hypertension (HT) and diabetes mellitus (DM) have been shown to negatively affect patients with coronary heart disease\textsuperscript{7-12} and may be particularly important in the long term. Diabetes mellitus is an unfavorable condition for a patient undergoing PCI mainly because a patient with DM is more likely to need further revascularizations, particularly at 6-month to one-year follow-up.\textsuperscript{13-14} In the longer term (3 years), the effects of HT and DM in patients with acute coronary syndrome (excluding the acute phase of infarctions) who undergo PCI with stenting (PCIS) are less well known, and there is lack of agreement among different studies. The objective of this study was to evaluate the long-term influence of these conditions on such patients after PCI.

**PATIENTS AND METHOD**

**Study population**

We retrospectively studied 279 consecutive patients (311 lesions) who had undergone PCIS during acute coronary syndrome (ACS) between August 1997 and 1999. Patients over 80 years old were excluded. Other exclusion criteria were shock, poor prognosis due to systemic disease (limiting clinical follow-up), coronary bypass surgery, PCI in acute myocardial infarction (primary or rescue PTCA) and procedural complications or failure that might influence the prognosis. Hypertension was diagnosed in 129 of these patients. Patients were classified as having HT if diagnosed in their clinical history or if their blood pressure exceeded 140/90 mm Hg on hospitalization for the intervention. A further 69 patients had DM. Similarly, patients were considered diabetic if they had been diagnosed with DM in their clinical history or if their fasting blood sugar levels exceeded 140 mg in 2 or more analyses after admission to hospital. Of these diabetic patients, 23 (33.3%) had type 1 DM and 46 (66.6%) had type 2 DM. The presence of coronary thrombus was determined if a filling defect and/or a lesion that caused a flow grade <3 according to the Thrombolysis In Myocardial Infarction (TIMI) classification were observed.

**Procedure**

Direct stenting was performed in 20% of the operations. The inflation pressure was set at the surgeon’s discretion. Mean pressure was 11.75±2.27 atmospheres. Patients received between 10 000 and 12 500 U heparin at the start of the procedure unless abciximab was used. Abciximab (70 U/kg) (bolus of 0.25 mg/kg) for 12 h at 0.125 µg/kg/min) was used in 113 patients (40.5%). Abciximab was used in 47.8% of patients with DM compared to 38.6% in those without DM. In the group with DM, abciximab was used more often in patients with type 1 DM (65.2%) than in those with type 2 DM (41.3%). On the same day, patients received a 500 mg loading dose of ticlopidine and then 250 mg/12 h for one month.

**Follow-up and clinical events**

After 6 months, 96.78% of the patients had undergone clinical follow-up and 63% angiographic examination. The angiographic examinations of these 176 patients were performed by an independent laboratory using quantified coronary angiography (QCA). Proximal and distal reference diameters, minimum lumen diameter and percentage of stenosis before and after the operation and at follow-up were determined.

After 3 years, clinical follow-up information was available for 92.14% of the patients. Follow-up was by personal or telephone interview. If patients had received care for the event in a different hospital in the region, the information was obtained from the treating physician. Events comprised death, MI and need for further revascularization.

**Statistical analysis**

The baseline characteristics of the groups were compared with Student’s t test for continuous variables and...
the χ² test for discrete variables. Survival time was measured from the time of stenting until the endpoint or censor time. The endpoints were death due to any cause, infarction, need for further revascularization and a combined endpoint of death or infarction. A censor time was recorded if the patient was lost to follow-up or did not have any events at the end of study. Long-term survival was estimated with a life table model. The log-rank test was used to compare the difference in cumulative survival among groups. The Cox proportional hazards model (univariate or multivariate) was used to assess the impact of independent predictive factors on survival. All analyses were performed with the SPSS package for Windows 9.0.

RESULTS

Table 1 shows the overall characteristics of the patients. We see that 44.4% of patients had prior MI and 29% (n=81) had an intracoronary thrombus. In Table

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>HT</td>
</tr>
<tr>
<td>DM</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Smokers</td>
</tr>
<tr>
<td>Dilution of ARI</td>
</tr>
<tr>
<td>Prior MI</td>
</tr>
<tr>
<td>Single vessel disease</td>
</tr>
<tr>
<td>Angiographic thrombus</td>
</tr>
<tr>
<td>Use of abciximab</td>
</tr>
<tr>
<td>EF, %</td>
</tr>
<tr>
<td>Stents per patient</td>
</tr>
<tr>
<td>Stents per lesion</td>
</tr>
<tr>
<td>Stent diameter, mm</td>
</tr>
<tr>
<td>Stent length, mm</td>
</tr>
<tr>
<td>Inflation atmospheres</td>
</tr>
</tbody>
</table>

HT indicates arterial hypertension; ARI, artery related to infarction; EF, ejection fraction; DM, diabetes mellitus; MI, myocardial infarction.

2, the baseline characteristics are stratified by whether or not the patients had HT. Patients with HT were older and a higher proportion were woman. After 3 years, mortality in patients with HT was higher than in those without HT. No significant differences were found in the remaining events in the univariate analysis (on including the main baseline, clinical, anatomical and procedural variables) (Table 3).

Multivariate analysis performed with variables including age, sex, and other coronary risk factors (diabetes, smoking, hyperlipemia), use of abciximab, prior MI and ejection fraction showed that the factors predictive of long-term mortality were HT (OR=4.71; 95% CI, 1.01-42.2; P=.04) and ejection fraction (OR=0.95; 95% CI, 0.91-0.99; P=.03). The survival

<table>
<thead>
<tr>
<th>TABLE 3. Single and combined events after 3 years in patients with and without hypertension</th>
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</thead>
<tbody>
<tr>
<td>Events after 3 years</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Nonfatal IM</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Same vessel PTCA</td>
</tr>
<tr>
<td>Different vessel PTCA</td>
</tr>
<tr>
<td>Cardiovascular death</td>
</tr>
<tr>
<td>Death (total)</td>
</tr>
<tr>
<td>IM+death</td>
</tr>
<tr>
<td>IM+death+RVAV</td>
</tr>
</tbody>
</table>

RVAV indicates revascularization of any vessel. The number of partial events does not add up to the total number of events because some patients had more than one event, in which case only the most serious one was counted. There was one death due to cancer during follow-up in the group with hypertension.
The causes of death in patients with HT were MI in 4 patients, heart failure in 2 patients, and hospital admission related to the postoperative procedure for further revascularization and cancer in one patient each. The analysis based on cardiovascular death only is shown in Table 3 (RR=4.07; \(P=0.08\)).

Table 4 shows the characteristics of patients according to whether they had DI or not. A greater proportion of patients with DI had restenosis (32.7% with DI vs 12.4% without DI), but the difference was not significant (\(P=0.27\)). After 3 years there was a greater incidence of MI, combined event of MI and death, mortality and revascularization in patients with DI, all differences being statistically significant (Table 5). Multivariate analysis was performed with the variables age, sex, and other coronary risk factors (diabetes, smoking, hyperlipemia), use of abciximab, prior MI and ejection fraction. Diabetes emerged as a predictive factor for nonfatal infarction (OR=4.03; 95% CI, 0.90-18.04; \(P=0.06\)), infarction and death (OR=2.68; 95% CI, 1.03-6.95; \(P=0.04\)) and overall infarction (OR=3.01; 95% CI, 1.13-8.02; \(P=0.02\)). Figure 2 shows the survival curve without MI up to 3 years for patients with and without DI. We investigated the combined effect of HT and diabetes but found no interaction between the two.

There were 22 patients (7.8%) lost to follow-up. These patients showed no differences in baseline characteristics, except for greater use of Reopro (\(P=0.014\)). More than half of them (14, 63.6%) were lost at the
TABLE 5. Single and combined events after 3 years in patients according to whether or not they have diabetes mellitus (DM)

<table>
<thead>
<tr>
<th>Events after 3 years</th>
<th>DM</th>
<th>No DM</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total MI</td>
<td>8 (11.6%)</td>
<td>8 (4.1%)</td>
<td>3.09 (1.1-8.6)</td>
<td>.03</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>4 (5.8%)</td>
<td>3 (1.5%)</td>
<td>3.97 (0.86-18.2)</td>
<td>.07</td>
</tr>
<tr>
<td>Surgery</td>
<td>1 (1.4%)</td>
<td>4 (2%)</td>
<td>0.71 (0.07-6.49)</td>
<td>.76</td>
</tr>
<tr>
<td>Same vessel PTCA</td>
<td>10 (14.5%)</td>
<td>17 (8.6%)</td>
<td>1.80 (0.78-4.15)</td>
<td>.16</td>
</tr>
<tr>
<td>Different vessel PTCA</td>
<td>6 (8.7%)</td>
<td>9 (4.6%)</td>
<td>1.98 (0.68-5.81)</td>
<td>.2</td>
</tr>
<tr>
<td>Any RV</td>
<td>14 (20.3%)</td>
<td>26 (13.2%)</td>
<td>1.67 (0.81-3.43)</td>
<td>.156</td>
</tr>
<tr>
<td>Death</td>
<td>4 (5.8%)</td>
<td>6 (3%)</td>
<td>1.9 (0.54-7.19)</td>
<td>.28</td>
</tr>
<tr>
<td>MI+death</td>
<td>8 (11.6%)</td>
<td>9 (4.6%)</td>
<td>2.73 (1.01-7.41)</td>
<td>.047</td>
</tr>
<tr>
<td>IM+death+RV</td>
<td>18 (26.1%)</td>
<td>31 (15.8%)</td>
<td>1.87 (0.97-3.63)</td>
<td>.059</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; RV, revascularization. The number of partial events does not add up to the total number of events because some patients have more than one event, in which case only the most serious one was counted.

**DISCUSSION**

**Homogeneity of risk in our population**

Currently, patients with unstable angina account for between 50% and 60% of interventional procedures performed in routine work in electrophysiological laboratories. All our population had undergone PCI. The improvements in stent design and current anticoagulant regimens have reduced the number of postoperative events, particularly in patients with complex lesions or thrombus, thus reducing the importance of UA for short-term prognosis after PCIS. Some studies with long-term follow-up have, however, emphasized the importance of UA for the prognosis in patients who had received an intracoronary stent.

**Prognostic influence of diabetes mellitus in long-term follow-up**

The unfavorable effect of DM on the prognosis of ischemic heart disease is well known, with the mortality rate increasing 2-4 fold. In patients who have undergone PCIS, the effect of DM on prognosis for restenosis/revascularization and for MI, mortality or combined events is more controversial.

Although stenting is preferable to conventional balloon angioplasty because it reduces the rate of restenosis and the need for further intervention on the target lesion, intrastent restenosis in these patients remains a problem. There is general agreement that patients with DM develop restenosis more often than those without, as illustrated in the study by Elezi et al (37.5% for patients with DM vs 28.3% for those without; P=.001). But the need for revascularization of the target vessel varies greatly in different study populations. Results range from no differences to differences observed only in patients with type I DM or in patients with incomplete revascularization or in vessels less than 3 mm. Comparison of patients with and without DM in our population showed differences in the proportions of restenosis (32.7% for patients with DM vs 24.2% for those without) and need of revascularization of the target vessel (14.5% for patients with DM vs 8.5% for those without). However, these differences were not statistically significant, perhaps because of the small sample size. A meta-analysis of 3 randomized studies of PCIS has been performed in which patients with DM represented 20% of the overall population. The authors found that 31% of the patients with DM had intrastent restenosis compared to 24% of patients without DM (P=.074) and 15% of the patients with DM had revascularization of the target lesion compared to 10% of those without DM (P=.001). These findings are similar to those from our study.

Researchers also fail to agree on the influence of DM on Q-wave myocardial infarction in patients with PCIS. Some studies show no differences after follow-up for 1 or 2 years, in contrast to others such as a study performed by Elezi et al (10.1% for patients with DM vs 5.6% for patients without; P<.01). Our findings are similar to those of this latter study (11.6% for patients with DM vs 4.1% for patients without; P=.03). Various factors could have influenced our findings. For example, our study selected only patients with acute coronary syndrome, had a greater percentage of patients with type 1 diabetes, and followed the patients for longer.
Earlier publications that examined different populations also fail to agree on the influence of DM on mortality. In our study, mortality was not significantly higher in patients with DM (5.8% vs 3%; OR=1.9), but significant differences were observed for patients with type 1 DM (P=.03). The main cause of death in patients with DM was myocardial infarction over the stented area (50% of deaths). This is in agreement with the BARI study, which found that the rate of infarctions after 5 years in patients with PTCA was 8% and the death rate was 80%. Our findings also agree with those from a study by Van Belle, in which diabetic patients with occlusive restenosis after PTCA had a higher mortality rate after 10 years than patients with nonocclusive restenosis or without restenosis, with an OR for heart mortality of 2.38.

Most studies do agree on the influence of DM on combined events (death, infarction or revascularization). Very similar results for survival were obtained in a study by Pascual Figal et al (73.1% for patients with DM vs 84.7% for those without; P=.09) and in our study (73.9% for patients with DM vs 84.2% for those without; P=.059). In both studies, event free survival was worse in patients with DM, but the difference was significant only for patients with type 1 DM (P<.001). For combinations of events such as death and myocardial infarction, we did find differences between patients with DM and those without (11.6 vs 4.6%; P=.047).

We also investigated a possible influence due to abciximab. This was used more often in patients with type 1 DM because events occur more often in these patients. Nevertheless, the number of infarctions after 5 years in the group of patients with DM who received abciximab was about one-third that in other patients with diabetes who did not receive this drug (6.1 vs 16.7%), although the result was not statistically significant because of the small number of patients. Results from other studies seem to justify the use of this drug for patients with DM, and this use may have prevented DM from being predictive of mortality in our population.

**Prognostic influence of hypertension**

Hypertension is the most important risk factor for premature vascular disease, with a high prevalence in most populations of persons treated with myocardial revascularization. Reductions of 5-6 mm Hg in diastolic blood pressure correspond to a 25% decrease in coronary mortality. In patients who suffer an infarction, a history of HT increases mortality. Despite these data, there is little agreement on the prognostic importance of HT in patients who have had ACS, particularly in the group of patients who need coronary revascularization. Amar et al recently reported that 32.4% of the patients with ACS were discharged from French hospitals without appropriate control of blood pressure, and in the Euroaspir study this figure was as high as 50%. In our patients with ACS and PCIS, HT appeared as the main and only factor predictive of overall mortality after 3 years, with an OR of 4.7 (P=.04; OR=4.07 for cardiovascular mortality; P=.08). We think that this finding is of great interest; in this context, relatively recent studies have documented the importance of HT as a long-term prognostic factor in patients with PCI, and findings from these studies fully support our results.

For example, Odell et al studied a European population of unselected patients, 33% of whom had unstable angina. The researchers investigated the factors that influenced prognosis after one year, and whether performing PCI with balloon angioplasty instead of stenting changed the prognosis for percentage of events such as MI and mortality. As expected, use of a stent reduced the need for further revascularization, but the death rate (2.0% for stenting vs 1.4% for balloon angioplasty) and the combined endpoint of death and MI (6.6% for stenting vs 6.1% for balloon angioplasty) were not influenced by the use of a stent. After one year, only the presence of UA as an indication for the procedure and HT were predictive of the combined event of death and infarction (RR=1.53 and 1.5, respectively). Hypertension was the only factor that predicted long-term mortality, with a RR of 2.48.

Other recent studies also show the influence of HT on the incidence of long-term events in patients with a coronary stent. Dannenberg et al reported that MI as a long-term event after PCIS (0.8% of patients) was predicted only by HT.

At least 2 other papers highlight the role of HT as a key predictive factor in long-term follow-up, in this case in patients with intrastent restenosis. The prognostic role of HT after surgical revascularization was also investigated recently in work by Voors et al. These researchers found that high systolic blood pressure one year and 5 years after surgery predicted heart mortality during long-term follow-up, almost certainly because of an unfavorable effect of high blood pressure on the bypass.

The effect of HT on both supply (endothelial dysfunction and acceleration of arteriosclerosis) and demand (increase in oxygen consumption, left ventricular hypertrophy) may explain the unfavorable long-term prognosis in such patients. Moreover, the contribution of hemodynamic forces to plaque disruption and generation of secondary acute coronary syndrome had been shown by some researchers. An increase in left ventricular mass (>270 g), mean heart rate >80 beats/min and an increase in pulse pressure are factors associated with plaque disruption, whereas the use of beta-blockers shows a negative association, and so is favorable.
Limitations of the study

Our study is observational, but we believe that it accurately reflects operations being performed in our interventional cardiology unit, and possibly in most similar units in Spain. Most patients in our population had an ejection fraction >45%, and although 47.3% had disease in more than one vessel, the number of stents per patient was 1.13. This small number partly reflects the tendency to perform PCI in patients who do not have three—vessel disease, or to aim for so-called functionally appropriate revascularization even if it is incomplete, particularly in patients with ACS. Angiographic follow-up was only performed in 63% of the patients. Finally, we are aware that there were not many patients in our population, which inevitably limits the prognostic analysis.

CONCLUSIONS

Arterial hypertension and DM were important prognostic factors during a 3-year follow-up of patients with acute coronary syndrome who underwent PCIS (excluding primary and rescue PTCA). Hypertension was the most important independent risk factor and the only predictor of long-term mortality. Diabetes was the only predictive factor of MI or the combined event of death and infarction, tripling the risk of MI (the main cause of mortality in these patients). Despite a greater need for revascularization and a higher rate of combined events at 3 years in the diabetic group, the differences in our population were not statistically significant (possibly because of the small number of patients). The differences, however, were significant for patients with type 1 DM.

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