Reinfarction as a Complication of Acute Myocardial Infarction. PRIMVAC Registry Data

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Introduction and objectives. The clinical profile of patients with acute myocardial infarction (AMI) who have reinfarction (REAMI) during their stay in the intensive cardiologic care unit (ICCU) is not well known. The aim of this study was to identify factors predictive of REAMI, as well as its global incidence and mortality.

Patients and method. All patients with AMI admitted to the ICCU of 17 hospitals in the Comunidad de Valencia (Spain) in the period 1995-2000 (PRIMVAC Registry) were included. Differential characteristics between patients with or without REAMI were determined, and odds ratios (OR) for possible predictive factors were estimated with their 95% confidence intervals by logistic regression.

Results. A total of 12 071 patients were included. Mean age of the patients was of 65.5 years, the percentage of women was 23.8%, and the incidence of REAMI was 2.8%. The REAMI group was significantly older than the non-REAMI group. Female sex was significantly more common in the REAMI group. More diagnostic and therapeutic procedures were carried out, more drugs were used and there were more complications in the REAMI group. Mortality was significantly higher in the REAMI group (37.8% vs 12.6%). Only age, diabetes mellitus, previous myocardial infarction, and the appearance of Q waves in the electrocardiogram were independently associated with the presence of REAMI.

Conclusions. REAMI in the ICCU was associated with high mortality. Some clinical factors present during the first few hours after AMI were associated independently with the appearance of REAMI.

Key words: Risk factors. Myocardial infarction. Registry. Reinfarction.

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El reinfarto como complicación del infarto agudo de miocardio. Datos del registro PRIMVAC

Introducción y objetivos. El perfil clínico de los pacientes con infarto agudo de miocardio (IAM) que presentan un reinfarto (REIAM) durante su estancia en la unidad de cuidados intensivos cardiológicos (UCIC) es poco conocido. El objetivo de este trabajo es determinar los factores predictores de REIAM, su incidencia global y su mortalidad.

Pacientes y método. Se incluyó a todos los pacientes con IAM ingresados en las UCIC de 17 hospitales de la Comunidad Valenciana en el período 1995-2000. Se determinaron las características diferenciales de los pacientes con y sin REIAM, y se calcularon las odds ratio y sus intervalos de confianza del 95% mediante un análisis de regresión logística para los posibles factores predictores.

Resultados. Se incluyó a 12.071 pacientes con IAM. La edad media fue de 65,5 años, la proporción de mujeres del 23,8% y la incidencia de REIAM del 2,8%. La edad fue significativamente mayor en el grupo con REIAM que en el grupo sin REIAM, al igual que el porcentaje de mujeres. Se realizaron más procedimientos, se utilizaron más fármacos y hubo más complicaciones en el grupo con REIAM. La mortalidad fue significativamente mayor en el grupo con REIAM (37,8 frente a 12,6%). La edad, la diabetes mellitus, el infarto de miocardio previo y el desarrollo de onda Q en el electrocardiograma se asociaron de forma independiente con la presencia de REIAM.

Conclusiones. El REIAM en la UCIC conlleva una alta mortalidad. Algunos factores presentes en las primeras horas del IAM se asocian con la aparición de REIAM.

Palabras clave: Factores de riesgo. Infarto de miocardio. Registro. Reinfarto.

ABBREVIATIONS

AMI: acute myocardial infarction.
ACE inhibitor: angiotensin-converting enzyme inhibitor.
PRIMVAC: Acute Myocardial Infarction Registry Project of Valencia, Alicante, and Castellón.
REAMI: reinfarction.
ICCU: intensive cardiologic care unit.

INTRODUCTION

Reinfarction (REAMI) is a serious complication that can present after acute myocardial infarction (AMI) in patients in the intensive cardiologic care unit (ICCU). It is a heterogeneous entity with a complex pathophysiology that extends the damage produced by the AMI that led to the hospitalization of the patient (index AMI), worsening the course.[1] There is still little information concerning its incidence, the clinical profile of the patients in whom it occurs and the factors that cause it during the hospital stay. Most of the studies on the variables predictive of the onset of REAMI refer to that occurring during the months after hospital discharge.[2-4]

The PRIMVAC (Acute Myocardial Infarction Registry Project of Valencia, Alicante, and Castellón) is a registry of cases of AMI resulting in ICCU admission in the hospitals of the Community of Valencia. Since its establishment in 1995, it has collected comprehensive data on the clinical characteristics of a large number of AMI patients.

The objective of this study was to determine the incidence, mortality rate, clinical features and factors predictive of REAMI occurring in the ICCU on the basis of the analysis of the PRIMVAC Registry data.

PATIENTS AND METHODS

All the patients enrolled in the PRIMVAC Registry between 1 January 1995 and 31 December 2000 were included. This registry consists of the patients admitted to the ICCU of 17 hospitals in the Community of Valencia with a diagnosis of AMI. The participating hospitals serve approximately 72% of the total population of this autonomous community (4 162 780 inhabitants according to the 2001 census). The design of the PRIMVAC Registry and the characteristics of the participating centers were described in a previous report.[5]

Two groups were established: patients who had a REAMI during their ICCU stay and those who did not. We adopted the definition of REAMI used for the PRIMVAC Registry: clear evidence, more than 24 hours after the index AMI, of a renewed increase in cardiac enzymes (more than twice the laboratory reference values if they had decreased to below that level), with or without chest pain and/or electrocardiographic changes (ST segment elevation or depression), which can occur in the same leads as the index AMI or in others. For the diagnosis, cardiac enzymes were measured at least once every 24 hours. We analyzed the demographic characteristics, coronary history, coronary risk factors, electrocardiographic data from the index AMI, diagnostic and therapeutic procedures carried out during the ICCU stay, medication administered during the ICCU stay and the complications presenting in the ICCU. These variables have been defined elsewhere.[5]

Statistical Analysis

The quantitative (continuous) variables are expressed as the mean and standard deviation and the proportions as percentages. The differences between the categorical variables were analyzed using the Pearson χ^2 test with Yates' correction and Fisher's exact test, when necessary. For the continuous variables, Student's *t* test was employed. All statistical tests were two-sided and considered significant at $P<.05$.

A logistic regression model was used to predict the onset of REAMI. The following variables were assessed during the first 24 hours after the index AMI: age, sex, smoking habits, hypercholesterolemia, hypertension, diabetes mellitus, previous myocardial infarction, Q wave index infarction (or undetermined), and thrombolysis. The variables were included according to their relevance, not on the basis of the results of univariate analysis. All the variables were made to remain within the model. Risk was estimated using odds ratio (OR), and 95% confidence intervals (CI) were calculated.

RESULTS

The PRIMVAC registry included a total of 12 071 patients with AMI. The overall mean age was 65.5±12.05 years and 23.8% were women. Thrombolysis was performed in 5 139 patients (42.6%). There were 344 REAMI, for an overall incidence of 2.8%. Age was significantly greater in the REAMI group (69.5±10.4 years) than in the non-REAMI group (65.4±12.1 years) ($P<.001$). The proportion of women was also higher in the REAMI group (34.3% vs 23.5%; $P<.001$).

Patient History and Risk Factors

The patient histories and risk factors of the REAMI and non-REAMI groups are shown in Table 1. In the REAMI group, the incidences of diabetes melli-

TABLE 1. **Patient Histories and Risk Factors of REAMI and Non-REAMI Patients: PRIMVAC Registry**

	REAMI (n=344)	Non-REAMI (n=11 727)	*P*
Smoking	25.3% (87)	37.5% (4398)	<.001
Hypercholesterolemia	30.5% (105)	29.8% (3496)	.780
HT	50.0% (172)	45.9% (5378)	.130
Diabetes	40.4% (139)	27.4% (3218)	<.001
Intermittent claudication	7.0% (24)	5.6% (652)	.260
Previous AMI	23.5% (81)	17.4% (2041)	.003
Previous angina	31.4% (108)	20.9% (2455)	<.001
Previous PTCA	3.5% (12)	1.6% (193)	.009

AMI indicates acute myocardial infarction; HT, hypertension; PTCA, percutaneous transluminal coronary angioplasty; REAMI, reinfarction.
The absolute number of cases is shown in parentheses.

tus (40.4% vs 27.4%; *P*<.001), previous myocardial infarction (23.5% vs 17.4%; *P*=.003), previous angina pectoris (31.4% vs 20.9%; *P*<.001), and prior angioplasty (3.5% vs 1.6%; *P*=.009) were significantly greater than in the non-REAMI group. There were significantly fewer smokers among the REAMI patients (25.3% vs 37.5%; *P*<.001). The differences in the remaining variables did not reach statistical significance.

Characteristics of the Index AMI

As shown in Table 2, the 2 groups did not differ significantly in terms of the electrocardiographic features of the index AMI except for right ventricular involvement, which was more frequent in the REAMI group (10.5% vs 6.7%; *P*=.007).

Diagnostic and Therapeutic Procedures

In general, these procedures were performed more frequently in REAMI patients (Table 3). The differences were statistically significant for echocardiography (41.9% vs 22.4%; *P*<.001), Swan-Ganz catheter insertion (13.4% vs 3.4%; *P*<.001), temporary pacemaker insertion (10.9% vs 5.2%; *P*<.001), electrical cardioversion (5.8% vs 3.4%; *P*=.020), cardiopulmonary resuscitation (21.3% vs 7.5%; *P*<.001), coronary angiography (17.7% vs 6.8%; *P*<.001), cardiac surgery (1.2% vs 0.4%; *P*=.047) and mechanical ventilation (21.6% vs 7.2%; *P*<.001).

Pharmacological Treatment

During the first 24 hours after admission for treatment of the index AMI, thrombolytics were administered more frequently in the non-REAMI patients (44.8% vs 39.0%; *P*=.040). The use of other drugs during the ICCU stay in the 2 groups of patients is shown in Table 4.

TABLE 2. **Characteristics of AMI in REAMI and Non-REAMI Patients: PRIMVAC Registry***

	REAMI (n=344)	Non-REAMI (n=11 716)	*P*
Q wave	78.8% (271)	75.2% (8809)	.300
RV involvement	10.5% (36)	6.7% (790)	.007
Site			
Anterior	43.6% (150)	42.2% (4950)	.090
Inferior	39.8% (137)	44.5% (5209)	.090
Mixed	4.1% (14)	2.4% (279)	.090
Undeterminable	12.5% (43)	10.9% (1278)	.090

*AMI indicates acute myocardial infarction; Q wave, development of Q wave in the electrocardiogram after index myocardial infarction; REAMI, reinfarction; RV, right ventricle.
The absolute number of cases is shown in parentheses.

TABLE 3. **Diagnostic and Therapeutic Procedures Employed in REAMI and Non-REAMI Patients: PRIMVAC Registry***

	REAMI (n=344)	Non-REAMI (n=11 727)	*P*
Echocardiography	41.9% (144)	22.4% (2623)	<.001
Swan-Ganz	13.4% (46)	3.4% (402)	<.001
Temporary pacemaker	10.9% (37)	5.2% (604)	<.001
Cardioversion	5.8% (20)	3.4% (401)	.020
CPR	21.3% (73)	7.5% (884)	<.001
Coronary angiography	17.7% (61)	6.8% (796)	<.001
PTCA	5.3% (18)	4.2% (496)	.350
Cardiac surgery	1.2% (4)	0.4% (44)	.047
Mechanical ventilation	21.6% (72)	7.2% (835)	<.001

*CPR indicates cardiopulmonary resuscitation; PTCA, percutaneous transluminal coronary angioplasty; REAMI, reinfarction.
The absolute number of cases is shown in parentheses.

TABLE 4. **Drugs Administered to REAMI and Non-REAMI Patients During the Acute Phase of Myocardial Infarction: PRIMVAC Registry***

	REAMI (n=344)	Non-REAMI (n=11 727)	*P*
Thrombolysis	39.0% (127)	44.8% (5012)	.040
ASA	86.3% (297)	88.4% (10 363)	.250
Heparin	68.6% (236)	61.4% (7196)	.007
i.v. NTG	76.5% (263)	67.0% (7858)	.002
Oral nitrates	31.1% (107)	31.9% (3745)	.750
Beta-blockers	24.1% (83)	22.1% (2596)	.380
ACE-inhibitors	46.5% (160)	37.6% (4407)	.008
Lidocaine	15.1% (52)	9.9% (1162)	.002
Diuretics	49.7% (171)	24.4% (2856)	<.001
Dopamine/dobutamine	47.4% (163)	17.6% (2063)	<.001
Amiodarone	16.9% (58)	8.3% (979)	<.001
Digitalis	15.1% (62)	9.9% (1162)	<.001
Diltiazem	3.5% (12)	3.1% (368)	.710
Verapamil	0.6% (2)	0.5% (57)	.690
Nifedipine	2.3% (8)	1.7% (201)	.390
Insulin	27.6% (95)	16.3% (1910)	<.001

*ACE indicates angiotensin-converting enzyme; ASA, acetylsalicylic acid; i.v. NTG, intravenous nitroglycerin; REAMI, reinfarction.
The absolute number of cases is shown in parentheses.

TABLE 5. **Complications Occurring in REAMI and Non-REAMI Patients: PRIMVAC Registry***

	REAMI (n=344)	Non-REAMI (n=11 727)	*P*
VT	9.6% (33)	6.4% (755)	.020
VF	9.3% (32)	5.1% (601)	<.001
AF	19.8% (68)	9.4% (1106)	<.001
AVB 3	10.8% (37)	5.4% (637)	<.001
IV conduction defect	5.2% (18)	3.1% (358)	.020
Postinfarction angina	20.6% (71)	9.1% (1066)	<.001
VSD	1.5% (5)	0.6% (69)	.060
LV free wall rupture	4.1% (14)	1.4% (161)	<.001
Papillary muscle rupture	0.6% (2)	0.2% (21)	.140
Papillary muscle dysfunction	2.6% (9)	0.6% (69)	<.001
Peripheral embolism	0.6% (2)	0.1% (12)	.060
Heart failure (Killip>I)	73.8% (254)	36.3% (4255)	<.001

*AF indicates atrial fibrillation; AVB 3, third-degree atrioventricular block; IV, intraventricular; LV, left ventricle; VF, ventricular fibrillation; VSD, ventricular septal defect; VT, ventricular tachycardia.
The absolute number of cases is shown in parentheses.

Complications

The REAMI patients experienced more arrhythmic complications (Table 5), with more episodes of ventricular tachycardia (9.6% vs 6.4%; *P*=.020), ventricular fibrillation (9.3% vs 5.1%; *P*<.001), atrial fibrillation (19.8% vs 9.4%; *P*<.001), high degree atrioventricular block (10.8% vs 5.4%; *P*<.001), and acute intraventricular conduction defects (5.2% vs 3.1%; *P*=.020). They also developed more ischemic and mechanical complications such as postinfarction angina (20.6% vs 9.1%; *P*<.001), left ventricular free wall rupture (4.1% vs 1.4%; *P*<.001) and papillary muscle dysfunction (2.6% vs 0.6%; *P*<.001). Heart failure (Killip-Kimball classes II-IV) occurred significantly more frequently in the REAMI group (73.8% vs 36.3%; *P*<.001). The mortality in the REAMI group was 37.8% (n=130), a rate three-fold higher than that of the non-REAMI group (12.6%; n=1478); this difference was statistically significant (*P*<.001).

Multivariate Analysis

In the multivariate analysis (Table 6), only age (OR=1.02; 95% CI, 1.01-1.04), diabetes mellitus (OR=1.50; 95% CI, 1.19-1.89), previous myocardial infarction (OR=1.38; 95% CI, 1.06-1.81), and Q wave on electrocardiogram (OR=1.36; 95% CI, 1.01-1.83) were independently associated with REAMI.

Other factors that had been found to be predictive of REAMI in the univariate analysis, such as smoking and female sex, lost their statistical significance after multivariate adjustment.

TABLE 6. **Factors Predictive of REAMI: Multivariate Analysis***

	OR	95% CI
Age	1.02	1.01-1.04
Sex	1.27	0.98-1.64
HT	0.98	0.78-1.23
Previous AMI	1.38	1.06-1.81
Cholesterol	1.09	0.85-1.34
Smoking	0.84	0.63-1.13
DM	1.50	1.19-1.89
Q wave	1.36	1.01-1.83
Thrombolysis	0.91	0.72-1.16

*AMI indicates acute myocardial infarction; CI, confidence interval; DM, diabetes mellitus; HT, hypertension; OR, odds ratio; REAMI, reinfarction.

DISCUSSION

In-hospital REAMI is a serious complication of AMI. It can occur within days of AMI and is a major prognostic factor.[1] In our study, we found an incidence of REAMI in ICCU of 2.8%, very similar to that obtained in other registries. In the Acute Myocardial Infarction Registry of the City of Valencia (RICVAL),[6] based on criteria similar to those of the PRIMVAC Registry, the overall incidence of REAMI in the ICCU was 4%. Likewise, in the Acute Myocardial Infarction Hospital Registry Project (PRIAMHO study),[7] the incidence of REAMI in the ICCU was 3.2%. In a study designed to evaluate the utility of intermediate care units,[8] the incidence of REAMI among patients in the ICCU was 1%. In the Acute Coronary Ischemia Investigation, Specific Search and Registry (IBERICA study),[9] which described the variability of AMI management in Spain in 1997, the overall incidence of REAMI within 28 days of the onset of the symptoms was 2.8%, although this value ranged between 1.4% and 4.2%, depending on the region. In another study of 22 613 patients with AMI presenting an elevated ST segment, included in 2 German registries (Maximal Individual Therapy in Acute Myocardial Infarction [MITRA] and the Myocardial Infarction Registry [MIR]), the in-hospital incidence of REAMI was 4.7%,[10] a rate somewhat higher than ours, possibly owing to the longer follow-up period.

Although other studies involving different diagnostic criteria for REAMI reported much higher incidences,[1,11-13] ranging between 10% and 80%, in general, the findings in registries similar to the PRIMVAC fall between 1% and 4.7%.

In our registry, a series of variables determined at the time of admission or within the first 24 hours after the index AMI are independently associated with REAMI. In some studies, patient age is considered a predictive clinical factor for REAMI; in the PRIMVAC Registry, it was found to be independently associated with the occurrence of REAMI in the ICCU.

This independent association between age and REAMI was also observed in the MITRA-MIR Registry.[10] In the Primary Angioplasty in Myocardial Infarction (PAMI) Trial,[14] Stone et al observed this association in a population of AMI patients with in-hospital ST segment elevation. In contrast, in a study involving only patients who had undergone thrombolysis, Birnbaum et al[15] observed no differences in the ages of patients who experienced REAMI during admission and those who did not. In a previous report in which PRIMVAC data were employed,[16] the incidence of REAMI was 0.3% in patients under 45 years of age, versus 3.2% among older patients, a finding that agrees with the association we observed in this study. Although we recorded a higher proportion of women among REAMI patients, this difference lost statistical significance after multivariate analysis. In the RICVAL Registry,[6] there were no statistically significant differences between men and women in terms of the incidence of REAMI. In contrast, the MITRA-MIR Registry reflected a greater proportion of women among REAMI patients, an association that remained statistically significant after multivariate analysis.

According to the PRIMVAC Registry, diabetes mellitus is also an independent variable in REAMI. These results coincide with those reported by Birnbaum et al.[15] In contrast, according to the MITRA-MIR Registry,[10] although the incidence of diabetes mellitus was greater among REAMI patients in the univariate analysis, it was not statistically significant according to the multivariate model.

In our study, a history of myocardial infarction was an independent predictive factor for REAMI. This relationship was also observed in the MITRA-MIR Registry[10] and in other studies,[3,4,17] although not all of them focus on the period spent in the ICCU or hospital. While the work of Birnbaum et al[15] did not corroborate this association, there appears to be a certain consistency in the different studies with respect to the predictive role of this variable; in any case, it seems logical to consider that patients with previous cardiovascular events would be at greater risk for REAMI given that they frequently present multivessel coronary disease. We observed no significant differences between REAMI and non-REAMI patients with respect to the site of the index myocardial infarction. Kornowski et al[2] found that REAMI during the first year was more common among survivors of myocardial infarction involving anterior wall. In contrast, Dönges et al[10] observed no association between a history of anterior wall index infarction and REAMI.

The results in the literature differ with respect to the relationship between the presence or absence of Q wave in the index infarction and the incidence of REAMI. Some studies report that REAMI occurs more frequently following non-Q wave index infarction.[1,3] In contrast, other authors have not observed this relationship.[2,14,18-20] In our study, multivariate analysis demonstrated a statistically significant association between the presence of Q wave on electrocardiogram following index AMI and the occurrence of REAMI.

In the early stages of the use of thrombolytic therapy, it was associated with a higher incidence of REAMI when compared with placebo; however, the combination of thrombolytic agents with acetylsalicylic acid reduced the number of REAMI.[21] When univariate analysis was employed, the data recorded in the PRIMVAC Registry showed that the administration of thrombolytics during the first 24 hours after hospital admission was less common among the REAMI patients, although the differences disappeared after multivariate analysis. On the basis of these findings, we can not establish a causal relationship.

On the other hand, the PRIMVAC Registry revealed that the patients with REAMI underwent more diagnostic and therapeutic procedures during their stay in the ICCU than non-REAMI patients, a finding that agrees with the higher morbidity rate in the former group. In particular, they required coronary angiography or cardiac surgery more frequently. Birnbaum et al[15] observed that angioplasty had to be repeated more frequently during the hospital stay in REAMI patients, who were also more likely to require emergency aortocoronary bypass. With respect to angioplasty, although the incidence was slightly greater among REAMI patients than non-REAMI patients, the differences were not statistically significant. These data probably reflect the presence of coronary lesions for which angioplasty was unsuitable and a greater proportion of individuals who were liable to require surgery among the REAMI patients.

With respect to treatment, univariate analysis demonstrated statistically significant differences between the 2 groups in terms of the use of heparin sodium, intravenous nitrates, angiotensin converting enzyme (ACE) inhibitors, lidocaine, diuretics, dopamine/dobutamine, amiodarone, digitalis, and insulin. In another study,[15] no association was found between REAMI and the use of heparin, beta-blockers or lidocaine, In contrast, the authors did observe an association with the use of nitrates and ACE inhibitors. Although one study[22] suggested the possibility that nitrates might be associated with a greater frequency of REAMI, this association was not supported by the multivariate analysis. This finding probably only reflects a greater utilization of these substances to treat recurrent ischemia. Given the characteristics of the registry, it was not possible to draw definite conclusions concerning the relationship between the onset of REAMI and the number of procedures performed or the use of medication as we were unable to determine whether they were utilized before or after the

event. The different use of procedures and treatment probably only reflects the higher morbidity in these patients, although this finding is of descriptive value.

As shown in Table 5, complications were more common in the REAMI patients. In particular, the PRIMVAC Registry revealed a very high mortality among these patients during their ICCU stay. The rate we observed of 37.8% is slightly lower than the 41.2% found in the MITRA-MIR Registry,[10] which included the in-hospital mortality, and the 47% of the RICVAL,[6] a registry that is similar to the PRIMVAC. The lower in-hospital mortality observed in other publications,[1,15] which ranged between 12.9% and 21%, could be due to selection biases, given that these studies correspond to clinical trials. Thus, despite the low incidence of REAMI, given the high mortality with which it is associated, its importance should be stressed.

Limitations

Although our results show that certain simple clinical variables can help identify groups at highest risk for REAMI, this work analyzes the data of a registry that was not designed specifically for the study of REAMI. Thus, the findings have lower statistical power than those of randomized studies. To add weight to the conclusions, studies adopting standardized diagnostic criteria and designed specifically for the study of REAMI need to be performed. The data in this registry were collected between 1995 and 2000, and certain aspects of the management of AMI may have changed since then, although this would not affect the validity of the results in their temporal context. The characteristics of the registry impede the establishment of strong causal relationships between the onset of REAMI and the use of certain treatments or procedures. However, the results provide valuable information for routine medical practice within the context of the definitions applied to the variables considered.

CONCLUSIONS

Although REAMI is an uncommon complication in the ICCU, it is associated with high mortality. The early detection of those patients at greatest risk for REAMI could lead to a more aggressive therapeutic approach in the attempt to reduce its incidence. Our report shows that certain variables that can be assessed during the first 24 hours after admission, such as patient age, diabetes mellitus, a history of previous myocardial infarction and the presence of Q wave in the electrocardiogram following the index AMI, are associated with a greater risk of REAMI during the ICCU stay.

APPENDIX

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