

In-Hospital Mortality and Early Preinfarction Angina: a Meta-Analysis of Published Studies

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Introduction and objectives. The occurrence of preinfarction angina (PA) reduces the extent of myocardial necrosis, increases the volume of viable myocardium, and improves left ventricular function. However, there is no agreement about the effect of PA on mortality. The objective of this study was to determine whether PA is associated with in-hospital mortality.

Method. A meta-analysis (fixed effects model) of all published reports evaluating in-hospital mortality in patients with acute myocardial infarction according to the presence or absence of PA was performed. PA was defined as the occurrence of angina in the 24 hours before onset of the infarction. We searched the Medline and Embase databases in June 2004 using "preinfarction angina or prodromal angina and mortality" as search terms. Six studies involving a total of 3497 patients were finally identified.

Results. Only one study reported that PA had a statistically significant beneficial effect on in-hospital mortality. However, combining the data showed that the presence of PA was associated with a significant decrease in the probability of in-hospital death (odds ratio=0.61; 95% CI, 0.48-0.78; $P<.0001$). We did not detect any significant heterogeneity between the studies ($\chi^2=5.92$; $P=.31$).

Conclusions. The occurrence of preinfarction angina in the 24 hours before the onset of myocardial infarction was associated with a significant reduction in in-hospital mortality of 39%.

Key words: *Unstable angina. Myocardial infarction. Prognosis. Meta-analysis.*

Mortalidad intrahospitalaria y angina preinfarto temprana: metaanálisis de los estudios publicados

Introducción y objetivos. La presencia de angina preinfarto (AP) reduce el tamaño de la necrosis miocárdica e induce más cantidad de miocardio viable y una mejor función ventricular izquierda. Sin embargo, la asociación entre mortalidad y AP es controvertida. El objetivo de este estudio fue determinar si la AP se asocia con la mortalidad intrahospitalaria.

Método. Se realizó un metaanálisis (modelo de efectos fijos) de los estudios publicados hasta el momento en los que se analiza la mortalidad intrahospitalaria de pacientes con infarto agudo de miocardio según presenten o no AP, definida como la que acontece en las 24 h previas al comienzo del infarto. A partir de las bases de datos MEDLINE y EMBASE se realizó una búsqueda en junio de 2004 con los términos «preinfarction angina or prodromal angina and mortality» y se incluyeron finalmente 6 trabajos, con un total de 3.497 pacientes.

Resultados. En sólo uno de los estudios se encuentra una asociación beneficiosa estadísticamente significativa entre AP y mortalidad intrahospitalaria. Tras agrupar los datos se encontró una reducción significativa en la probabilidad de muerte intrahospitalaria en pacientes con AP (odds ratio = 0,61; intervalo de confianza del 95%, 0,48-0,78; $p < 0,0001$). No se encontró heterogeneidad significativa entre los estudios ($\chi^2 = 5,92$; $p = 0,31$).

Conclusiones. La presencia de angina en las 24 h previas al inicio del infarto de miocardio se asocia con una reducción significativa de la mortalidad intrahospitalaria del 39%.

Palabras clave: *Angina inestable. Infarto de miocardio. Pronóstico. Metaanálisis.*

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INTRODUCTION

Episodes of angina prior to the onset of acute myocardial infarction can slow the process of cell death.¹ Because of this fact, more cells survive in the myocardial risk area when coronary flow is restored in patients with angina prior to infarction than in those without. Several mechanisms explain this phenomenon: ischemic preconditioning,¹ development of collateral cir-

ABBREVIATIONS

PA: preinfarction angina.
OR: odds ratio.

culation,² and earlier and more effective reperfusion after administration of fibrinolytic treatment or primary angioplasty.³⁻⁵ The most important consequences of preinfarction angina (PA) are a larger volume of viable myocardium⁶ and greater recovery of ventricular function at mid-term following infarction.⁷⁻⁹

There are no conclusive data regarding the association between PA and mortality. Some studies have shown a beneficial association regarding hospital mortality in patients presenting PA,^{4,10-13} at least in the youngest patients,¹³ whereas other studies have demonstrated no benefits¹⁴ or have reported a detrimental effect.¹⁵ Similar results have been found in analyses of middle- and long-term mortality.^{10,14-19} Several factors can explain these differences: a small sample size in most of the series with insufficient statistical power to detect differences, different definitions used for PA, variations in the reperfusion treatment applied in the acute phase, and dissimilar control of confounding variables between the 2 groups.

It is difficult to conduct a large-scale study assessing the association between PA and mortality. It would require a large sample size, which would need coordination among several centers, and a considerable economic investment, which many organizations (e.g., research-funding agencies and the pharmaceutical industry) are not willing to provide. For these reasons, this meta-analysis was designed to assess the influence of PA on in-hospital mortality and evaluate the clinical repercussions derived from the results obtained.

METHOD

Inclusion and Exclusion Criteria

The meta-analysis included published studies that analyzed the relationship between mortality and PA (although this was not their primary objective of analysis). The following studies were excluded: *a*) those that provided duplicate information (the study offering the most up-to-date information or the largest number of patients was chosen); *b*) those that did not analyze or did not specifically report total in-hospital mortality; and *c*) those that did not define PA as an event occurring in the 24 hours before the onset of infarction. If these data were not available in the study and could not be obtained from the principal author, the study was excluded. Acceptance or exclusion of an

original study for the analysis was carried out independently by three investigators. In the case of disagreement, the choice was resolved by consensus.

Literature Search

The studies were obtained by searching MEDLINE and EMBASE using the following terms: *preinfarction angina* or *prodromal angina* and *mortality* in the month of June 2004. Initial selection of the studies was made according to title and abstract, and all those apparently not reporting on the research objective were excluded. Three reviewers read the remaining studies independently and analyzed the literature references they contained. The following data were extracted from each of the original studies: design, mean age and number of patients included, percentage of patients treated with fibrinolysis, primary angioplasty or surgery in the acute phase of infarction, percentage of patients who had PA, percentage of patients with a non-Q-wave infarction, and percentage of patients with infarction in an anterior location.

Data Analysis

The main measure of the association was the odds ratio (OR) and 95% confidence interval (CI). The ORs of the individual studies were combined using the fixed effects model according to the method of Mantel-Haenszel.^{20,21} The DerSimonian and Laird²² test was used as the random effects model. Heterogeneity between the studies was assessed with the χ^2 test and the Galbraith plot.²³ Briefly, the Z-statistic (mortality in each study divided by the square root of its variance) was plotted on the y-axis against the inverse of the standard error of each study on the x-axis. An unweighted regression line constrained through the origin was constructed. The studies farthest from this line, which have a standard deviation (SD) of 1, i.e., the outliers, are those that contribute the most to the heterogeneity between the studies. Sensitivity was analyzed to assess the importance of the different statistical models used, the effect of the number of patients treated by reperfusion during the acute phase of infarction, the effect of the study designs, and the influence of each of the original studies. RevMan, version 4.2 (Cochrane Collaboration Oxford, United Kingdom) was used for the statistical analyses. Statistical significance for the effects of treatment and heterogeneity was established at $P < .05$ and $P < .1$, respectively.

RESULTS

Results of the Search

The search results are summarized in Figure 1. A total of 55 studies were initially identified as potential

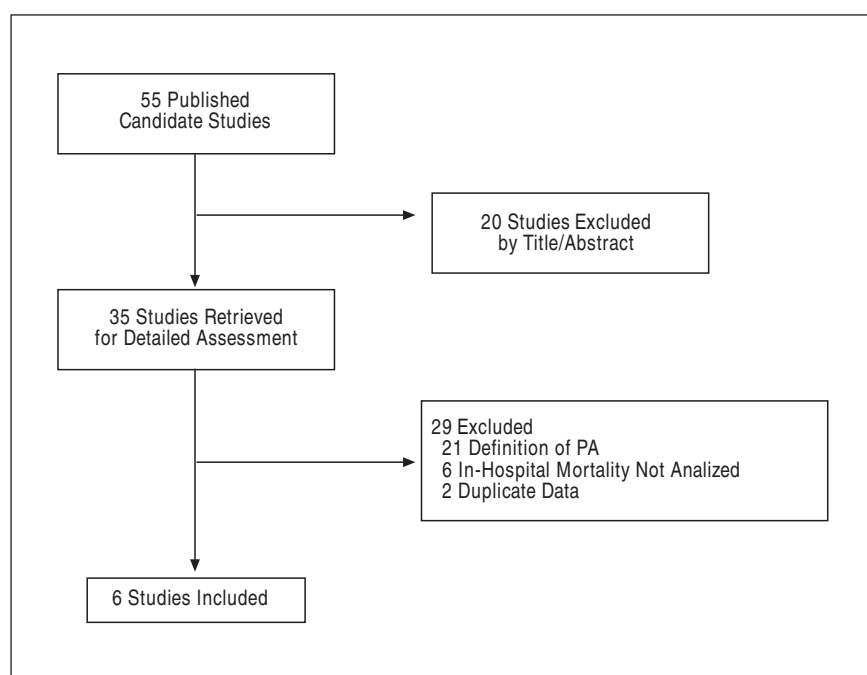


Figure 1. Number of studies assessed for inclusion in the meta-analysis. See more information in the text. PA indicates preinfarction angina.

candidates for inclusion in the meta-analysis. On the basis of the title and abstract, 20 studies were excluded because they did not report on in-hospital mortality and PA. Among the 35 remaining studies, 21 were excluded because of the definition used for PA,^{5,9-15,17,24-35} 6 because they did not analyze in-hospital mortality,^{16,36-40} and 2 because they presented duplicate data.^{4,41} The 6 studies that remained analyzed the influence of PA on in-hospital mortality.^{19,42-46}

Qualitative Findings

Three of the 6 studies ultimately included in the analysis were retrospective^{42,43,46} and the other 3 prospective^{19,44,45} (Table 1). Mean age in the study by Abete et al,⁴⁶ which included patients older than 65 years, was higher than that of patients in the remaining studies. Despite the fact that a uniform definition of PA was used, the study by Abete et al⁴⁶ presented a higher percentage of patients with this symptom (63%) than the remaining studies. In addition, the per-

centage of patients in this study who received reperfusion treatment in the acute phase of infarction was lower (35%) as compared to the others. Two original studies included patients with chronic angina and 5 incorporated patients with a prior history of acute myocardial infarction.^{42-44,46} Two studies contained patients with a diagnosis of non-Q-wave myocardial infarction.^{43,46}

Quantitative Findings

Only 1 of the studies⁴⁴ reported a significantly reduced OR for in-hospital mortality in the group with PA, although the study by Kosuge et al⁴³ showed a clear tendency toward this same association.

When the data were grouped (a total of 3497 patients, 1217 of whom had PA, with 125 deaths in the PA group and 293 in the group without PA), the presence of angina within 24 h before infarction was associated with a significant reduction in the OR for total deaths during in-hospital monitoring (OR=0.61;

TABLE 1. Characteristics of the Studies Included in the Meta-Analysis*

	Design	Mean Age, Years	N	Percentage of Reperfusion and Method	Percentage of Prior Infarction	Percentage of Preinfarction Angina	Percentage of Non-Q-Wave Infarction
Tamura et al ⁴⁵	P	61	140	59%, FNL, PCI	51	24	0
Gorecki et al ⁴⁴	P	66	331	100%, FNL	43	24	0
Kosuge et al ⁴³	R	66	913	100%, PCI	49	39	12
Tomoda et al ⁴²	R	63	613	69%, FNL, PCI	49	27	0
Ishihara et al ¹⁹	P	61	990	100%, FNL, PCI, CS	51	26	0
Abete et al ⁴⁶	R	73	510	35%, FNL, PCI	—	63	17

*CS indicates coronary surgery; FNL, fibrinolysis; PCI, percutaneous coronary intervention; P, prospective; R, retrospective.

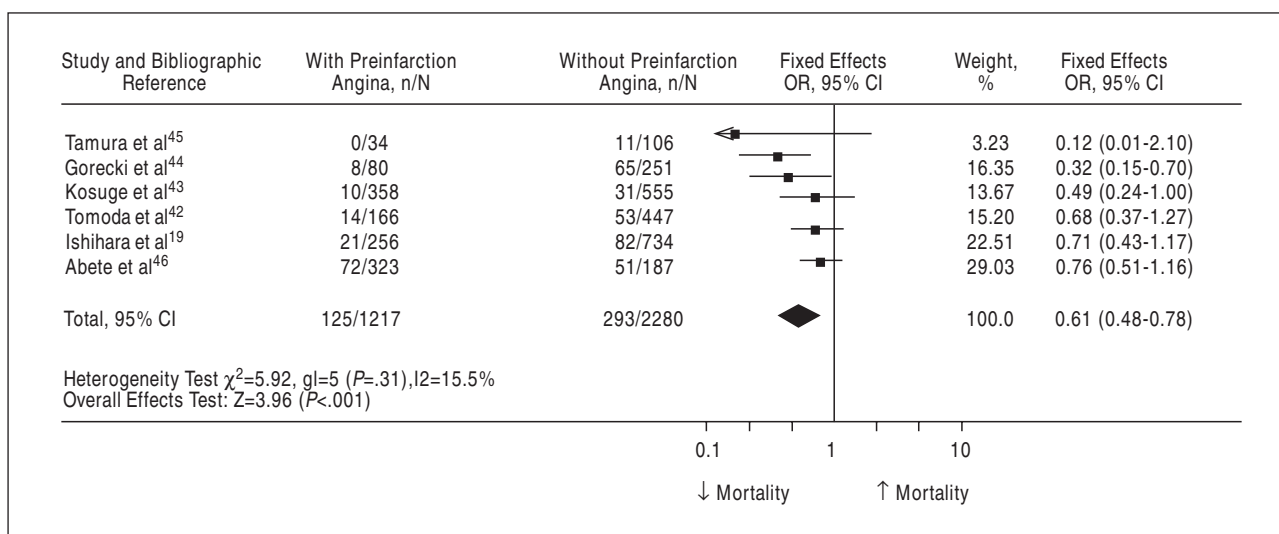


Figure 2. Estimation of the association between preinfarction angina and mortality in the individual studies and after their combination.

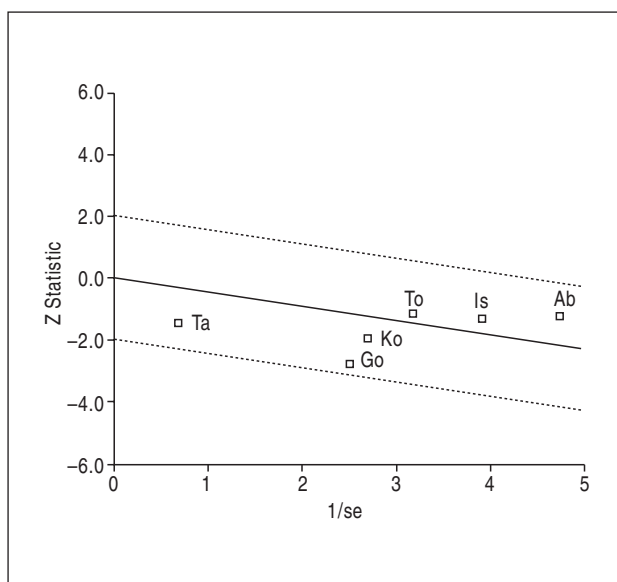


Figure 3. Galbraith plot.

Ab indicates Abete; Go, Gorecki; Is, Ishihara; Ko, Kosuge; Ta, Tamura; To, Tomoda.

95% CI, 0.48-0.78; $P<.0001$) (Figure 2). No significant differences were found in the heterogeneity test ($\chi^2=5.92$; $P=.31$). In addition, significant heterogeneity was not seen in the Galbraith plot (Figure 3), which showed no outliers far from the regression line (more than 2 SD).

Sensitivity Analysis

A sensitivity analysis was performed to determine whether the results were consistent (Table 2). First, the analyses performed with the fixed effects method and the random effects method were compared. The 2

models provided a similar estimation of the OR. Second, the studies in which the percentage of patients revascularized in the acute phase was 100% or <100% were analyzed separately. A more beneficial association between PA and mortality in the OR estimation was found when the total of patients was reperfused in the acute phase (0.3 vs 0.0), with both analyses being statistically significant. The influence of the study design (prospective or retrospective) was investigated and in both cases the association was significant, although it was more pronounced for the prospective

TABLE 2. Sensitivity Analysis of the Association Between Preinfarction Angina and In-Hospital Mortality*

	Number of Studies	Number OR of Patients	for Mortality (95% CI)
<i>Statistical model</i>			
Fixed effects	6	3497	0.61 (0.48-0.78)
Random effects	6	3497	0.62 (0.46-0.82)
<i>Revascularization treatment</i>			
All patients	3	2234	0.53 (0.37-0.76)
Not all patients	3	1263	0.70 (0.50-0.97)
<i>Study design</i>			
Prospective	3	1461	0.51 (0.34-0.78)
Retrospective	3	2036	0.68 (0.50-0.92)
<i>Analysis when excluding</i>			
Tamura et al ⁴⁵	5	3357	0.62 (0.49-0.80)
Gorecki et al ⁴⁴	5	3166	0.67 (0.51-0.86)
Kosuge et al ⁴³	5	2584	0.63 (0.48-0.82)
Tomoda et al ⁴²	5	2884	0.59 (0.45-0.78)
Ishihara et al ¹⁹	5	2507	0.58 (0.44-0.77)
Abete et al ⁴⁶	5	2987	0.54 (0.40-0.74)

*OR indicates odds ratio.

studies (0.51 vs 0.68). Lastly, to assess the influence of the individual studies, each study was excluded from the analysis one by one. The OR values varied from 0.54 to 0.67 after exclusion of the original studies in this manner. None of the studies showed a decisive impact on the overall OR estimation.

DISCUSSION

The results of this study showed a significant reduction in in-hospital mortality in patients with acute myocardial infarction, the majority reperfused in the acute phase, if they had presented episodes of angina within the 24 hours prior to the onset of infarction.

Previous studies have reported that PA has a beneficial clinical effect, including preservation of left ventricular function, a lower probability of heart failure,^{11,26} and a reduction in the susceptibility to present ventricular arrhythmia.^{36,45} There are several mechanisms by which PA exerts these marked benefits. Probably the most important is a biphasic biochemical phenomenon known as ischemic preconditioning. Recent studies on this phenomenon have implicated transient mitochondrial permeability transition pore (mPTP) opening, which could have the ATPase-dependent potassium channel as a component.⁴⁷ Another mechanism is the development of collateral circulation from the non-ischemic areas. In 2 of the studies included in the meta-analysis,^{9,42} the presence of collateral circulation was assessed by the method of Rentrop et al,⁴⁸ with no significant differences observed between the 2 groups. It is likely that the short evolution time for angina prior to infarction defined in the present study as an inclusion criterion did not allow the development of macroscopic collateral circulation. Only 2 of the studies analyzed included cases of chronic angina,^{44,46} with a total of 284 patients (8% of all patients in the meta-analysis); thus, considerable development of collateral circulation may not be the definitive explanation for the results of the meta-analysis. Another proposed mechanism for the benefits of PA is better and more stable reperfusion with fibrinolytic treatment³ or primary angioplasty.^{4,5} In the meta-analysis, the majority of patients received revascularization treatment in the acute stage of infarction (overall, 82% of the patients included); hence this could be an important factor to explain the results found. This mechanism seems even more relevant considering the sensitivity analysis, in which the association with mortality was more pronounced when only the studies with 100% reperfusion were included. Another benefit of PA has been attributed to reductions in microvascular injury⁵ and reperfusion injury,⁴⁹ although these factors have not been investigated in depth. Moreover, an association has been described between PA and spontaneous recanalization of the artery causing the infarction, a fact that can contribute to the clinical benefits observed by facilitating

earlier perfusion.⁵⁰ Lastly, the beneficial association between PA and mortality may be related to differing pharmacological treatment between the 2 groups before the onset of infarction. This hypothesis also requires further investigation.

The meta-analysis included patients with diabetes, patients treated with percutaneous revascularization in the acute phase, and elderly patients; in one study only patients 65 years and older participated.⁴⁶ There are some doubts as to the benefits of PA in these 3 groups.^{25,41,42,51,52} It is unknown whether the decrease in mortality might be even higher in patient populations outside of these groups, and further specific analyses investigating this hypothesis would be desirable. This consideration is important when interpreting the results of the present study, since 26% of the patients analyzed had diabetes and 54% (1884 patients) underwent percutaneous revascularization in the acute phase (65% of all patients with acute-phase reperfusion). It is possible that the association between PA and mortality might be stronger in the group of non-diabetic patients treated with intravenous fibrinolysis. The clinical benefits of PA in patients with primary angioplasty is under discussion,^{9,25} although an association has been described between the presence of PA and the probability of complete epicardial recanalization of the culprit artery during the procedure⁴ (this fact is important considering that 5 of the 6 studies included in the meta-analysis used this revascularization method in the acute phase). Nevertheless, the design of the studies and the number of patients included raise doubts as to the validity of the results. One prospective study by our group done in patients with elevated ST segment myocardial infarction undergoing primary angioplasty in the acute phase showed a significant reduction in the size of the infarct measured by ^{99m}Tc-sestamibi scintigraphy in those presenting PA (data accepted for publication). Therefore, it cannot be ruled out that the benefits of PA are also maintained in patients treated with primary angioplasty.

The results of this study raise the question as to whether a prospective study including a large number of patients is necessary to analyze the influence of PA in the prognosis. It is known that agreement for the direction of the effect between the results of a meta-analysis and those of large-scale studies analyzing a similar effect and performed after the meta-analysis is approximately 80%.⁵³ Therefore, it is very probable that the direction of the association of PA is toward a reduction in mortality, even though only one original study suggested a significant association in this regard.

Limitations of the Study

Potential publication bias should be taken into account when interpreting the results of this study. Attempts were made to avoid publication bias by per-

forming a comprehensive review of the subject and analyzing the funnel plot, in which asymmetry in the distribution of the studies was found. Nevertheless, the usefulness of the funnel plot is likely to be limited by the small number of studies included in the meta-analysis. The fact that only published studies were included may have induced bias in the selection of candidate studies to be incorporated. Relevant information that has not been published in scientific journals may have been excluded from the study.

The compiling of individual studies with differing designs and criteria for exclusion and inclusion gives the sample an appearance of heterogeneity. Nonetheless, significant heterogeneity was not detected and the sensitivity analysis showed a relationship between PA and mortality that was similar and in the same direction in all cases. However, the dissimilar characteristics of the patients included in the individual studies should be taken into account in the interpretation of the results; in two studies^{43,46} patients with non-ST segment elevation myocardial infarction were incorporated and there was considerable variation in the use of reperfusion treatment in the acute phase. These 2 factors are important if we take into account that the benefit of PA should be limited to the group of patients in whom prolonged ischemia is interrupted by acute-phase revascularization treatment. Although it would have been desirable to estimate the quality of the studies for their subsequent analysis, this was not done because of the small number of studies ultimately included.

CONCLUSIONS

The presence of PA was associated with a significant reduction in in-hospital mortality. Several mechanisms could be responsible for this beneficial association. It would be desirable to conduct a large-scale study to determine the precise magnitude of this benefit as well as its pathophysiological mechanisms, particularly in patients with fibrinolytic treatment or primary percutaneous revascularization, since these seem to be the ones that obtain the greatest benefits.

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