

Higher Mortality in Women Undergoing Primary Angioplasty. Another Gender Enigma?

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It is well established that acute myocardial infarction (AMI) is more prevalent in men than women, at a ratio of 3:1. This predominance is most apparent in patients aged less than 60 years and is accompanied by differences in the incidence of risk factors, with an increased incidence of smoking in young men, and of diabetes and hypertension in women aged more than 60 years. This association is especially true for infarction with ST-segment elevation and slightly less for coronary syndromes without ST-segment elevation. In women, ischemic heart disease is manifested from age 50 to 60 years, in other words, around 10 to 20 years later than in men,¹ and unlike in men, the initial presentation is usually angina and not AMI.² This observation is an expression of a larger variety of causes of angina in women, especially those causes related to functional abnormalities of the coronary arteries.

Mortality and Risk Factors

In recent years, there has been increasing interest in studying sex differences in the prevalence, morbidity, and mortality of acute coronary syndromes. It has been consistently demonstrated that among patients with AMI, women present higher mortality,^{3,4} and that this seems to be largely attributable to a greater accumulation of risk factors than in men, namely more advanced age and a higher incidence of hypertension and diabetes mellitus.^{5,6} Vaccarino et al,⁵ in a review of 27 studies performed between 1966 and 1994, were able to associate increased mortality with a greater incidence of diabetes, hypertension, and heart failure, and with increased age, both prior to and after the introduction of fibrinolysis.⁵ This greater potential arteriosclerotic load appears to be translated into more extensive coronary disease than in men of a comparable age.

Nevertheless, other researchers maintain that the higher mortality in women would remain following correction for age and incidence of diabetes and hypertension.⁷⁻¹⁰ In a recent analysis, mortality in women remained higher than in men in 14 out of 19 AMI registries following correction for age.¹¹

In this issue of *REVISTA ESPAÑOLA DE CARDIOLOGÍA*, Hurtado-Martínez et al¹² describe the results of a registry in Murcia, Spain, in which they analyzed possible sex differences related to treatment by primary percutaneous transluminal coronary angioplasty (PTCA) in 838 patients with ST-segment elevation AMI. The interest in that study lies in the analysis of whether increased mortality in women with AMI is affected by the use of primary PTCA. To date, there have been few studies addressing that point and the results have been inconclusive.^{10,13,14} In the study by Hurtado-Martínez et al, women treated by primary PTCA once again show higher mortality than men. However, multivariate analysis did not reveal risk factors as determinants, with the exception of the protective factor of smoking among men. This protective factor should not be considered as such, however, given that the reduced mortality is directly related to the lower age of the patients and not to smoking, the prothrombotic and vasoconstrictive effects of which on the coronary arteries have been clearly demonstrated. The study also reveals that women are older and have a higher incidence of hypertension and diabetes than men, as well as a tendency towards a larger number of affected vessels. Nevertheless, following correction for those variables, the odds ratio continues to indicate increased mortality associated with female sex, although the causes are not clear. However, the more advanced age of the women would partly explain the increased mortality and would also lead to a reduced success of primary PTCA, especially in individuals aged more than 65 years. The fact that hypertension and diabetes did not appear in the multivariate analysis as elements associated with increased mortality could perhaps be due to the relatively low number of women included in the study. The same would be true of the extent of coronary disease, which tended to be greater in women but did not reach statistical significance. Hence, the authors indicated the presence of factors intrinsically related to sex to explain the increased mortality in women.

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Delayed Hospitalization and Cardiogenic Shock

The mortality associated with primary PTCA in the registry of Hurtado-Martínez et al¹² is relatively high for the group of patients, despite the fact that the time to treatment and the mean age of the patients were comparable with those of previous studies.^{15,16} In general, the mortality associated with primary PTCA is around 6% to 7%, and if patients with cardiogenic shock are excluded it can be less than 5%.^{15,16} In a multicenter registry of 2291 cases, the mortality in patients aged at least 70 years was 12% and in women it was 9%, compared with 4.4% in men.¹⁵ It is likely, however, that the higher proportion of patients with cardiogenic shock included in the registry of Hurtado-Martínez et al, especially among women, partly explains the increased mortality. Another possible explanation could be the reduced diameter of the revascularized vessels in women.

Another important factor relating to the increased mortality observed in women could be the greater delay in hospitalization and PTCA, a finding that had been made previously in other studies.^{5,8,10,13,14} It is likely that the main consequence of that delay is a reduced effectiveness of reperfusion, leading to a larger infarct and greater impairment of systolic function.¹⁷ Recently, in an analysis of 1791 patients, de Luca et al¹⁸ demonstrated that for every 30 minutes of delay in primary PTCA, there was a 1.08-fold increase in 1-year mortality. The greater delay is partially reflected in the higher incidence of cardiogenic shock in women prior to PTCA. The higher mortality among those patients with cardiogenic shock is consistent with the findings of previous studies^{7-10,13} and is associated with reduced success of recanalization (TIMI III flow) of the responsible artery, since this is achieved in only half of all cases.¹⁷

To better understand the differences in mortality, it would have been of interest to know the extent of the infarct and the ventricular function, as well as the cause of in-hospital mortality, given that it is possible that the incidence of septal or free wall rupture was greater in women,¹³ especially those who had a longer delay in recanalization treatment.

Additional Differential Elements

It has been suggested that the lower incidence of AMI in women is associated with a reduced tendency to present arterial thrombosis.^{19,20} In fact, some anatomic and pathophysiologic peculiarities may in part explain those differences. For instance, among those patients of the Coronary Artery Surgery Survey (CASS) registry who received medical treatment and presented 1 or 2 vessel disease, the 12-year mortality was lower in women, a finding that was attributed to less progression of the coronary disease.²¹ Consistent with this, atherosclerotic plaques in the carotid artery²² and also the coronary

arteries²³ of women have been described as “younger” than in men and contain a lower proportion of fibrous tissue, which is a component of later stages in the development of the plaque.²³

In addition to these “intravascular” factors, other elements that affect the vessel wall could contribute to differences in presentation of angina between men and women. The lower incidence of AMI in women occurs despite a higher incidence of angina, which is associated with a higher prevalence of nonsignificant coronary lesions or the absence of lesions.^{9,21,24} In fact, the incidence of significant coronary stenosis is lower in women, in those patients with unstable angina (31% vs 14% in the GUSTO IIB trial)⁹ or with stable angina.²⁴ In the CASS study, for instance, the incidence of nonsignificant coronary lesions in 23 467 patients with angina or previous infarctions was 29%.²⁴ Nevertheless, in the subset of patients with stable angina, 73% of the 2810 women did not present significant stenosis and 55% presented stenosis of less than 30%, while in men that occurred in only 38% and 23%, respectively.²⁴ However, there is little variation in the incidence of risk factors between these different presentations of angina. In a recent series of 176 patients with syndrome X, only 19% did not have any risk factors, while 40% had 2 or more.²⁵

Likewise, women also present a lower incidence of variant angina—partly due to the lower incidence of smoking—and its progression is accompanied by a lower incidence of AMI than in men.²⁶ In contrast, the phenomenon of transient apical ballooning (tako-tsubo syndrome), which also appears to be attributable to coronary vasoconstriction, although in this case more associated with emotional stress, is presented more often in women.²⁷

These peculiarities certainly suggest that coronary disease adopts both common and distinct presentations in women and men. However, the causes and mechanisms that explain the differences remain largely unknown. While the study by Hurtado-Martínez et al¹² favors the existence of these differences, the lack of information on the extent of the infarction, ventricular function, and cause of death represent methodologic limitations in the interpretation of their results.

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