Clinical Characteristics and Prognosis of Infective Endocarditis in Women

Juan C. Castillo, Manuel P. Anguita, Mónica Delgado, Martín Ruiz, Dolores Mesa, Elías Romo, Manuel Crespín, Daniel García, José M. Arizón, and José Suárez de Lezo

Servicio de Cardiología, Hospital Universitario Reina Sofía, Cordoba, Spain

Introduction and objectives. Little is known about the prognosis of infective endocarditis in women. The objective of this study was to determine the clinical characteristics and prognosis of infective endocarditis in women diagnosed with the condition at our center during the last 20 years.

Methods. Comparative analysis of 288 patients diagnosed with infective endocarditis between 1987 and 2006. Of these, 104 (36%) were women.

Results. Mean age was similar in the 2 sexes, at 50 (18) years for men and 52 (21) years for women, as was the incidence of early and late prosthetic valve endocarditis: the incidence of early prosthetic endocarditis was 42% in men and 49% in women. Infection occurred more frequently in the mitral valve in women (54% vs 39%) and more frequently in the aortic valve in men (50% vs 29%; *P*<.01). The severe complication rate during the active disease phase was similar in the 2 sexes (76% for women and 73% for men). Fewer women underwent surgery during the active disease phase (44% vs 58%; *P*<.03), and there was a trend to higher mortality in women (24% vs 20.7%; *P*<.1). The 5-year survival rate was similar in the 2 sexes, at 85% in men and 83% in women.

Conclusions. The clinical characteristics of infective endocarditis were similar in men and women. However, women underwent surgery less frequently despite a similar rate of severe complications during the active disease phase.

Key words: *Infective endocarditis. Sex. Prognosis.*

Características clínicas y pronóstico de la endocarditis infecciosa en la mujer

Introducción y objetivos. El pronóstico de la endocarditis infecciosa en la mujer ha sido poco estudiado. El objetivo del presente estudio es analizar las características clínicas y el pronóstico de las mujeres con endocarditis infecciosa atendidas en nuestra institución en los últimos 20 años.

Métodos. Análisis comparativo de 288 pacientes con endocarditis infecciosa desde 1987 hasta 2006. De ellos, 104 (36%) eran mujeres.

Resultados. La media de edad fue similar en ambos grupos (50 ± 18 años los varones y 52 ± 21 las mujeres), así como la incidencia de endocarditis sobre prótesis precoz y tardía (endocarditis protésica precoz: varones, 42%; mujeres, 49%). La infección se localizó con mayor frecuencia en la válvula mitral en las mujeres (el 54 frente al 39%) y en la válvula aórtica en los varones (el 50 frente al 29%; p < 0,01). La tasa de complicaciones severas durante la fase activa fue similar en ambos grupos (el 73% en varones y el 76% en mujeres). Se intervino a mujeres con menor frecuencia durante la fase activa de la enfermedad (el 44 frente al 58%; p < 0,03) y hubo una tendencia a una mayor mortalidad precoz en las mujeres que en los varones (el 24 frente al 20,7%; p < 0,1). La supervivencia a los 5 años fue similar en ambos grupos (el 85% en los varones y el 83% en las mujeres).

Conclusiones. Las características clínicas de la endocarditis infecciosa son similares en varones y mujeres; sin embargo, las mujeres se operan con menor frecuencia a pesar de una tasa similar de complicaciones severas durante la fase activa.

Palabras clave: *Endocarditis infecciosa. Sexo. Pronóstico.*

INTRODUCTION

Cardiovascular disease is the leading cause of death in women from developed countries. In Europe, cardiovascular disease accounts for about 55% of all deaths in women.[1] The clinical manifestations of cardiovascular disease in women are different from those

ABBREVIATIONS

IE: infective endocarditis

seen in men, and this factor may result in a lack of sufficient recognition of cardiovascular disease.[2] Additionally, the prognosis for women with cardiovascular disease is worse than that for men because, among other things, women less often receive invasive treatment, such as thrombolysis, angioplasty, or revascularization surgery.[3,4]

Few studies have specifically examined valvular heart disease in women. The influence of sex on the prevalence of certain forms of valvular heart disease is known. Rheumatic mitral stenosis is more common in women, whereas degenerative valvular diseases seem to affect men and women equally.[5] Although the clinical characteristics and prognosis of infective endocarditis (IE) have been widely studied, little information is available concerning the possible differences between men and women. The aim of this study was to determine possible differences between men and women concerning the treatment and prognosis of IE. We examined the clinical characteristics and the prognosis in women with IE seen at our center over the last 20 years.

METHODS

A total of 288 consecutive cases of IE in patients who were not parenteral drug users were diagnosed at our center from January 1987 to December 2006. Up to 1994, the diagnosis of IE was made according to the criteria of von Reyn et al[6] and with effect from that year with the criteria of Durack et al.[7] Retrospective study showed that all the cases met the new criteria of the European Society of Cardiology.[8] Of the patients with prosthetic valve endocarditis, early prosthetic valve endocarditis was considered to be that in which the episode of IE occurred during the 12 months following the implantation of the prosthetic valve and late prosthetic valve endocarditis was considered to be that diagnosed with effect from these first 12 months after surgery. The indications for surgery during the active phase of the disease (early surgery) were: development of severe heart failure due to valve or prosthesis dysfunction, persistence of sepsis despite correct antibiotic therapy, development of local complications such as abscesses, pseudoaneurysms and fistulas, repeated emboli, and cases caused by aggressive pathogens that usually failed to respond to antibiotics, such as fungi, *Coxiella* spp, and *Brucella* spp. Emergency surgery was defined as that which could not be postponed more than 24 h without risk to the life of the patient, whereas elective surgery

was considered to be that which could be delayed a few days with no increase in risk to life.

The study included all those patients who survived the active phase of IE in a long-term follow-up protocol at our cardiology office. In the event that the patient failed to attend the office for a programmed visit, telephone contact was established with the patient's home. No loss to follow-up occurred. Early death was defined as that which took place during the hospital phase of the disease, before discharge. Deaths after discharge were considered to be late deaths.

Statistical Analysis

The continuous variables are expressed as the mean (standard deviation) and the qualitative variables as percentages. The differences between the different groups of patients studied were evaluated by the χ^2 test or Fisher's exact test for qualitative variables and the Student t test for unpaired data for the quantitative variables. A multivariate analysis was done to determine the influence of sex on mortality, with mortality as the dependent variable and sex as an independent variable, adjusted for the variables that showed differences ($P<.1$) between the 2 sexes in the univariate analysis. The survival curves were determined by the Cox proportional hazards regression model. A P value less than .05 was consideree significant. The statistical analyses were done with the statistical program SPSS®, version 10.0.

RESULTS

A total of 288 non-parenteral drug user patients were diagnosed with IE at our center during the study period. Of these, 104 (36%) were women and 184 (64%) men, with a male to female ratio of 1.8:1. The main clinical characteristics are shown in Table 1. The mean age was similar in both groups (50 [18] years in the men and 52 [21] years in the women). No differences were found concerning the number of prior episodes of IE (12 cases in the men and 7 cases in the women). The portal of entry for the infection was identified in 38% of the cases of IE in the men and 39% in the women. The most usual portal of entry was dental, with 9% in both subgroups. The number of cases of IE on a native valve was similar: 133 (72%) cases in the men and 67 (64%) in the women. The incidence of early and late IE on a prosthesis was similar in both groups: early IE on a prosthesis, 42% in the men, and 49% in the women; late IE on a prosthesis, 58% in the men, and 51% in the women. Concerning the predisposing lesion, rheumatic disease was more common in the women (38% vs 25%) and degenerative valve disease was more common in the men (29% vs 17%; $P<.05$). The infection was most commonly situated on the mitral valve in the women (54% vs 39%) and the aortic valve in the men (50% vs 29%; $P<.01$). The echocardiogram (transthoracic and/or transesophageal)

TABLE 1. General Characteristics of Infective Endocarditis According to Sex

	Women (n=104)	Men (n=184)
Age, mean (SD), y	52 (21)	50 (18)
Previous infective endocarditis	7 (6.7%)	12 (6.5%)
Site of infection[a]		
Mitral	56 (54%)	73 (40%)
Aortic	30 (29%)	92 (50%)
Other	17 (17%)	19 (11%)
Type of predisposing heart disease[b]		
Rheumatic	39 (37%)	45 (25%)
Degenerative	15 (14%)	32 (18%)
Congenital	18 (17%)	52 (29%)
None	32 (31%)	53 (29%)
Type of infectiove endocarditis		
On native valve	67 (64%)	133 (72%)
On prosthesis	37 (36%)	51 (28%)
Vegetations on TT-echo	67 (65%)	121 (66%)
Vegetations on TE-echo	73 (96%)	134 (93%)
Size of the vegetation	11.9 (5)	11.2 (4)

TT-echo indicates transthoracic echocardiogram; TE-echo, tansesophageal echocardiogram.
[a]P<.01.
[b]P<.05.

TABLE 2. Pathogens Causing the Infective Endocarditis

Pathogen	Women (n=104)	Men (n=184)
Staphylococcus aureus	27 (26%)	37 (20%)
*S epidermidi*s	14 (14%)	25 (14%)
Streptococcus viridans	23 (22%)	39 (22%)
Enterococcus	13 (13%)	27 (15%)
Diphtheroid	1 (1%)	11 (6%)
Brucella	—	3 (2%)
Coxiella burnetii	3 (3%)	10 (5%)
Fungus	2 (2%)	3 (2%)
Other	4 (4%)	8 (4%)
Unknown	16 (15%)	18 (11%)

TABLE 3. Cardiac and Non-cardiac Complications in Patients With Infective Endocarditis

	Women (n=104)	Men (n=184)
Heart failure	44 (42%)	87 (47%)
Neurologic complications[a]	19 (18%)	32 (17%)
Persistent sepsis	26 (25%)	42 (23%)
Embolisms	22 (21%)	40 (22%)
Abscesses	12 (11%)	22 (12%)
Renal dysfunction (creatinine >2 mg/dL)	8 (8%)	12 (6%)

[a]Ictus due to embolisms, cerebral hemorrhage, encephalitis, meningitis, and mycotic aneurysms.

detected a similar proportion of vegetations (90% in the men and 92% in the women). The rate of negative blood cultures was similar in both groups of patients (11% in the men and 15% in the women) and no significant differences were found regarding the causative pathogen (Table 2). The rate of severe complications during the active phase of the disease was high, though similar in both groups (73% in the men and 76% in the women). The rates of heart failure, peripheral emboli, abscesses and neurologic complications were all similar in the 2 groups (Table 3).

Concerning the treatment received during hospitalization, women were less often operated on during the active phase of the disease (47 women [44%] vs 107 men [58%]; P<.03), whereas the proportion of emergency surgery was similar between men and women (21 women [20%] and 33 men [18%]). The indications for surgery during the acute phase of the disease were also similar, mainly the development of heart failure (33% in the women and 30% in the men) and the persistence of sepsis (11% in the women and 15% in the men).

Deaths during the hospital phase were similar: 25 women (24%) and 38 men (21%) (P<.1). No differences were found in mortality depending on the type of treatment (medical or surgical) received during the active phase: 12 women died in the surgical subgroup and 13 in the medical subgroup. Of the 12 women who underwent surgery and who died during the active phase, 9 had undergone emergency surgery, and 3 elective surgery (P<.01). After a similar mean follow-up in both groups (69 [70] months in the men and 63 [71] months in the women), 1-year and 5-year survival in the patients who

survived the active phase of the disease was similar in both groups. The distributions of the survival in the men and the women were compared with univariate and multivariate regression models (Figure 1).

Multivariate analysis, adjusted for the variables with significant differences between the men and the women, ie, the type of predisposing heart disease, the site of the infection, and the need for surgery during the active phase, showed that sex was not an independent predictor of death (hazard ratio [HR]=1.15; 95% confidence interval [CI], 0.75-1.77; P=.53).

DISCUSSION

The findings of this study suggest that infective endocarditis in women seems to have a very similar behavior to that in men. In our series, as in those of others,[9] the infection was more usual in men than in women, with a ratio of 2:1. No plausible explanation exists for this possible lower susceptibility of women to develop the valve infection, although hormone differences have been suggested.

Concerning the management of cardiovascular diseases depending on the sex of the patient, we know that female sex is associated with a lower use of diagnostic procedures and aggressive procedures, which thus confers a worse
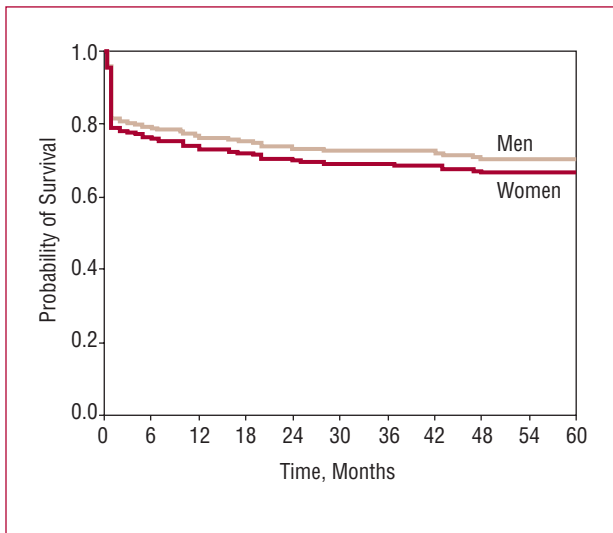
Figure 1. Long-term survival in men and women with infective endocarditis.

prognosis. Likewise, women currently tend to have a greater mortality during cardiac valve surgery. In fact, prognostic scales like EuroSCORE consider female sex to be a risk factor.[10] A registry of surgical procedures in patients with valve disorders has recently been published,[11] and in the analysis of the predictive factors for death, female sex is an independent predictive factor of death, with an odds ratio of 1.37.

Our data illustrate that sex itself does not appear to be a prognostic factor, in spite of the different management in the women with infective endocarditis during the active phase of the disease. Although fewer women at our center underwent surgery during the active phase than men, the women who only received medical treatment during the active phase and who did not require surgery (56% of the 104 women) had comparable results to those who did undergo surgery (early mortality, 23% vs 26%). Nevertheless, this group included 2 very different subgroups: low-risk women with a good prognosis, who recovered with no complications, and the subgroup of women with an indication for surgery but who did not undergo surgery because of the high risk involved (and thus with a very poor prognosis). The results of these 2 groups are consequently very difficult to compare. Although the rate of severe complications during the active phase was similar in both sexes, the men more often underwent surgery, probably because the infection in the men was more often located in the aortic position and, as most publications recognize, aortic infective endocarditis is associated with a higher rate of complications (such as abscesses, conduction defects or fistulas) and it is more likely to require surgery during the active phase.[12,13]

Only 1 study, from Duke University, has been published recently regarding the prognosis and management of infective endocarditis in women.[14] The univariate analysis in this study showed interesting significant results concerning the use of surgery during the active phase of the disease. One third of the male patients with infective endocarditis underwent surgery during the active phase, as compared with just one fifth of the women (a much lower proportion than that in our series). Mortality during the hospital phase was also remarkable, as short-term mortality in the women was double that of the men. These differences, however, disappeared in the multivariate analysis, such that in the different models used, sex was never an independent prognostic factor. Although both hospitals are tertiary referral centers, with the corresponding selection bias, our data are not comparable, as they derive from different populations and also include different study periods.

CONCLUSIONS

The clinical characteristics of infectious endocarditis are similar in both men and women. However, the women underwent surgery less often despite a similar rate of severe complications during the active phase of the disease. This probably explains why mortality in women during the active phase of infective endocarditis tends to be greater than that of men. Once the active phase of the infection has passed, however, the long-term prognosis is similar for both sexes.

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