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Predictors of Sterile Aortic Valve Following Aortic Infective Endocarditis. Preliminary Analysis of Potential Candidates for TAVI

Predictores de esterilidad de la válvula aórtica tras endocarditis infecciosa aórtica. Análisis preliminar de potenciales candidatos para TAVI

To the Editor,

There are only a few anecdotic reports of aortic infective endocarditis (IE) treated with transcatheter aortic valve replacement (TAVR).[1,2] Although dysfunction of a damaged valve can be treated with a TAVR device, persistent local infection requires debridement of the affected tissue and precludes the use of TAVR since reinfection would carry a dreadful prognosis.[2] Thereafter, IE has been an exclusion criterion in most landmark studies and the use of TAVR in this context has been empirically disregarded. In contrast, it is well known that antibiotic treatment in IE is highly effective in some particular etiologies and, often, the only reason for cardiac surgery is the residual symptomatic severe valvular dysfunction.[3] On this basis, TAVR might represent a novel alternative in this particular high operative risk subset if specific markers of healed infection could be determined.

The aim of this study was to identify the main predictors of active local infection at the time of intervention that would preclude TAVR use in IE. Among a total of 732 episodes of left-sided IE consecutively diagnosed in 2 tertiary centers between 1996 and 2015, 432 patients underwent cardiac surgery and 224 of them had involvement of either native or biological prosthetic aortic valves. Only patients with culture of the removed cardiac tissue (n = 182) were included. In addition, patients with discordant positive valve culture (n = 14) were excluded due to the impossibility of ruling out culture contamination.

We defined active local infection at the time of intervention as the presence of either periannular complications or concordant positive cultures (same microorganism in the blood and the cardiac tissue removed during surgery). Biological tissues were grown on brain heart broth and thioglycollate, and on 4 types of agar media (Columbia sheep blood, chocolate supplemented with IsoVitaleX, McKonkey, and Schaedler).

To determine predictors of active local infection at the time of intervention, we built a predictive model using a logistic regression model with the maximum likelihood method and backward stepwise selection, which included the variables that were clinically relevant and statistically significant in the univariable analysis. Only the last step is shown. The goodness-of-fit for each model was determined with the Hosmer–Lemershow test and the area under the receiver operating characteristics curve (AUC-ROC).

The Table summarizes the univariable and multivariable predictors of active local infection at the time of intervention. The main independent predictors of active local infection were diabetes mellitus (odds ratio [OR], 2.8; 95% confidence interval [95%CI], 1.1-7.4), *Staphylococcus aureus* (OR, 4.3; 95%CI, 1.4-13.4) and concomitant mitral involvement (OR, 2.5; 95%CI, 1.1-5.8). In contrast, an interval between diagnosis and intervention $\geq$ 10 days (estimated cut-off value) was a predictive factor of healed infection (OR, 0.25; 95%CI, 0.1-0.5). The model had an AUC-ROC of 0.776 (95%CI, 0.705-0.847) and a Hosmer–Lemershow *P* value of .848. Indeed, after 10 days of appropriate antibiotic treatment and in the absence of diabetes mellitus, *Staphylococcus aureus*, concomitant mitral involvement, or aortic prosthesis, only 1 patient out of 29 (3.5%) had a positive culture at the time of intervention.

Recommendations against the use of TAVR in the context of uncomplicated aortic valve IE are based on unfounded but extensively accepted arguments. For the first time, we have evaluated the actual risk of this potential management in a large population of surgical patients whose resected tissue was cultured, demonstrating that most patients have a predictable lack of local infection after antibiotic therapy. This hypothesis-generating finding might support the use of TAVR in selected cases of IE with "healed" infection but residual lesion and high surgical risk. Conversely, periannular complications, the need for extensive

Table 1
Univariable and Multivariable Predictors of Active Local Infection at the Time of Cardiac Surgery in Patients With Aortic Valve Infective Endocarditis

Variables	Nonactive local infection (n = 79)	Active local infection (n = 89)	P[a]	OR	95%CI		P[a]
					Inferior	Superior	
Age, y	61.6 ± 14	63.4 ± 14.7	.434				
Male sex	64 (81)	69 (78)	.579				
Nosocomial origin[b]	10 (13)	21 (24)	.068				
Heart disease	63 (80)	60 (67)	.072				
Degenerative	21 (27)	18 (20)	.330				
Prosthesis	11 (14)	26 (29)	**.017**	2.5	0.99	6.1	.054
Rheumatic	3 (4)	0 (0)	.102				
Comorbidities[c]	36 (46)	47 (53)	.349				
Charlson index	3.3 ± 2.9	3.4 ± 2.3	.886				
Chronic renal failure	5 (6)	11 (12)	.184				
Diabetes mellitus	8 (10)	25 (28)	**.003**	2.8	1.1	7.4	**.032**
Clinical progression							
Heart failure	55 (70)	65 (74)	.543				
Renal failure	24 (30)	23 (26)	.543				
Septic shock	1 (1)	8 (9)	**.036**				
Stroke	11 (14)	9 (10)	.463				
Microbiology							
Streptococci species	34 (43)	22 (25)	**.012**				
S. bovis	7 (9)	4 (5)	.253				
S. viridans	20 (25)	16 (18)	.247				
Enterococci species	12 (15)	12 (14)	.752				
Staphylococci species	15 (19)	40 (45)	< **.001**				
S. aureus	5 (6)	18 (20)	**.009**	4.3	1.4	13.4	**.011**
Coagulase-negative *Staphylococci*	10 (13)	22 (25)	**.047**				
Echocardiographic findings							
Vegetation	77 (98)	77 (87)	**.010**				
Significant valvular dysfunction	70 (89)	77 (87)	.683				
Concomitant mitral disease	14 (18)	30 (34)	**.019**	2.5	1.1	5.8	**.027**
Outcomes							
Urgent surgery[d]	48 (61)	69 (78)	**.018**				
Elective surgery[e]	31 (39)	20 (22)					
Time from diagnosis to surgery, d[f]	13.5 [6.5-27]	6 [2-12]	< **.001**	0.25	0.1	0.5	<**.001**
Time from correct antibiotic beginning to surgery, d	17 [7-31]	8 [3-17]	< **.001**				
In-hospital mortality	12 (15)	22 (25)	.125				
Relapses	0 (0)	2 (2)	.499				

95%CI: 95% confidence interval; OR: odds ratio.
The data are expressed as mean ± standard deviation or median [interquartile range] or No. (%).
[a] Significant *P* values in bold letters.
[b] Nosocomial origin: signs and symptoms of infective endocarditis starting after 48 hours from hospital admission or in the first 3 days after discharge or up to 30 days after a surgical intervention.
[c] Comorbidities: defined by the presence of either diabetes mellitus, chronic renal failure, immunosuppression, chronic pulmonary disease, cancer, collagenopathy requiring steroids, HIV or intravenous drug use.
[d] Urgent surgery: surgery performed during the active phase of infective endocarditis, before the end of the antibiotic treatment.
[e] Elective surgery: surgery performed after the end of the antibiotic treatment.
[f] For the multivariable analysis, we included time between diagnosis and surgery ≥ 10 days.

surgical repair, septic shock, and infection of biological prosthesis might be related to persistent infection, suggesting that TAVR should be also avoided in these scenarios until further data are available.[4,5]

In conclusion, our findings suggest that in poor surgical candidates and under the assessment of a multidisciplinary experienced IE team, TAVR could be considered as an alternative therapeutic option in selected cases of IE with low risk of local infection at the time of the planned intervention.

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Combining Disability and Frailty in an Integrated Scale for Prognostic Assessment After Acute Coronary Syndrome

Combinación de discapacidad y fragilidad en una escala integrada para la valoración pronóstica después de un síndrome coronario agudo

To the Editor,

Disability refers to a decrease in functional status related to activities of daily living. The Barthel index is used to measure disability and has proved to be useful in assessing functional status in elderly patients after stroke.[1] The relationship between disability and prognosis after acute coronary syndromes, however, has been little investigated to date.

The boundaries between frailty and disability are unclear: although both conditions can overlap, some authors argue that frailty should be considered a predisability state.[2] Following this line of thought, we speculated that there is a continuum of progressive vulnerability from frailty to disability and that an index integrating frailty and disability would improve risk stratification after acute coronary syndrome. This hypothesis was tested in the present study.

The study group consisted of 342 hospitalized patients who had survived acute coronary syndrome. Before discharge they underwent a full geriatric assessment, which included frailty, disability (Barthel index) and comorbidities (Charlson index). Likewise, a large number of variables were included from clinical assessment, electrocardiograms, blood tests, and echocardiograms. Further details of the study are provided elsewhere.[3,4] The primary endpoint was all-cause mortality at a median follow-up of 4.7 years.

By Cox regression analysis (backward method), the clinical predictive model included the following independent variables: age, Killip class ≥ 2, left ventricular ejection fraction, hemoglobin and Charlson index. All predictive analyses involving frailty and disability were adjusted for this clinical model. Frailty was evaluated with the Fried and Green scores, the latter being used for statistical adjustment since it was the strongest predictor in a previous study.[3,4] The Barthel index was analyzed as a continuous and dichotomized variable, dividing the patient cohort into nondisabled (Barthel index > 90; n = 279) and disabled (Barthel index ≤ 90; n = 63) subgroups according to the predefined moderate disability cutoff.[1]

Of 342 patients hospitalized for acute coronary syndrome (mean age 77.5 $\pm$ 7.1 years, 21% ST-segment elevation acute myocardial infarction), a total of 156 patients died after discharge. The median Barthel index was 100 points [98.75-100]. Sixty-three (18%) patients showed at least moderate disability (Barthel index $\leq$ 90). The Barthel index was not significantly associated with mortality (per point, $P = .13$; Barthel ≤ 90 points; $P = .09$), after adjustment for the clinical model and the Green score. Frailty, however, was predictive: per point of the Green score, hazard ratio, 1.19; 95% confidence interval, 1.06-1.21; $P = .0001$; Green score ≥ 5 points, hazard ratio, 1.91; 95% confidence interval, 1.28-2.89; $P = .002$). The 5-point cutoff was chosen according to a previous study.[3]

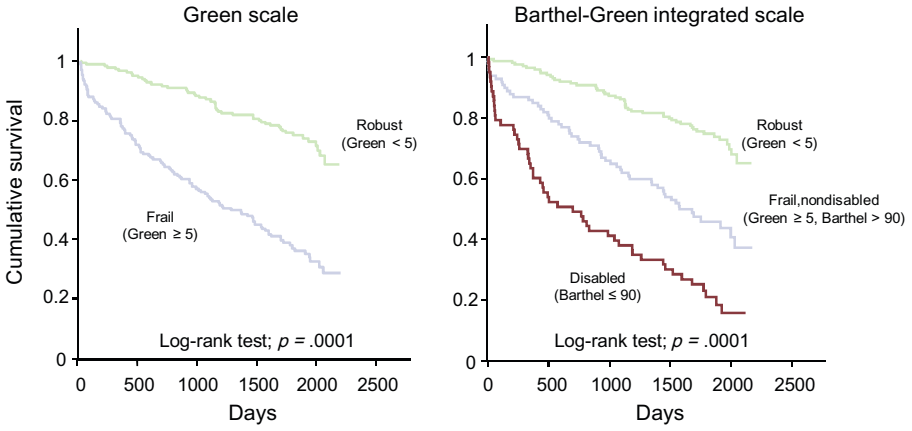

Figure 1. Risk stratification according to frailty using the Green score (left) and according to the Barthel-Green integrated scale (right).