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Cardiac surgery during the acute phase of infective endocarditis: discrepancies between European Society of Cardiology guidelines and practices

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Aims Indications for surgery in acute infective endocarditis (IE) are detailed in guidelines, but their application is not well known. We analysed the agreement between the patient's attending physicians and European Society of Cardiology guidelines regarding indications for surgery. We also assessed whether surgery was performed in patients who had an indication.

Methods and results From the 2008 prospective population-based French survey on IE, 303 patients with definite left-sided native IE were identified. For each case, we prospectively recorded (i) indication for surgery according to the attending physicians and (ii) indication for surgery according to guidelines. Surgery was indicated in 194 (65%) patients according to attending physicians and in 221 (73%) according to guidelines, while 139 (46%) underwent surgery. Agreement was moderate between attending physicians and guidelines (kappa 0.41–0.59) and between indication according to guidelines and the performance of surgery (kappa 0.38). Of the 90 (30%) patients not operated despite indication, contraindication to surgery was reported by the attending physicians in 42 (47%), and indication was not identified in 48 (53%). One-year survival was 76% in patients with indication and surgery performed ($n = 131$), 69% in patients without indication and no surgery ($n = 74$), 56% in patients with identified indication and contraindication to surgery ($n = 42$), and 60% in patients with no identified indication ($n = 48$; $P = 0.059$).

Conclusion Cardiac surgery during acute IE was recommended in almost three out of four patients, although fewer than half were actually operated. Indication was not acknowledged by the attending physicians in one out of six patients.

Keywords Endocarditis • Guidelines • Valvular surgery

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Introduction

Despite medical and surgical treatment, infective endocarditis (IE) remains associated with a poor prognosis, with intra-hospital mortality around 20%, and a high burden of long-term sequelae.[1] The most severe complications of IE are heart failure, embolic events, and persistent infection, which are indications for valve surgery during the acute phase of IE in guidelines.[2,3] Observational studies have compared patient characteristics and outcome in operated vs. non-operated patients to assess the impact of early surgery,[4] and several studies suggested that cardiac surgery for acute IE improves the prognosis of high-risk patients.[5–7] However, non-operated patients are a heterogeneous group that includes patients without indication for surgery and patients with indication(s) for but also contraindications to surgery. Only two studies analysed the outcome of patients with IE who did not undergo valve surgery although they had an indication.[8,9] However, no study analysed the agreement between the decision of the patient's attending physicians and guidelines. Discrepancies between guidelines and practices have previously been reported in elective valvular surgery.[10,11] Analysing the application of guidelines is an essential complement of their elaboration and is of particular importance in severe disease such as IE.

The objectives of this study were to analyse in a prospective population-based survey on IE the agreement between: (i) indication for surgery during the acute phase of IE according to the attending physicians and to European Society of Cardiology (ESC) guidelines and (ii) indication for cardiac surgery according to guidelines and the actual performance of surgery. We also analysed patients' outcomes according to indication for surgery and whether or not surgery was actually performed.

Methods

Population

The survey was conducted in 8 French administrative areas representing 15.3 million adult inhabitants, i.e. 32% of the French population. All patients aged $\geq$18 years living in the study area were prospectively included if they were hospitalized with a first diagnosis of IE between 1 January and 31 December 2008. Survey organization, data collection, and variables analysed were previously detailed.[12] All cases were validated according to the case report forms by an expert team in each administrative area. Only definite IE cases according to the modified Duke classification were included.

Cardiac surgery during the acute phase of IE was defined by surgery performed during antibiotic treatment or $\leq$30 days after the completion of antibiotic therapy.

The study was approved by an institutional review committee (Comité de Protection des Personnes, Besançon). Patients were informed of the study but did not have to provide individual consent, in accordance with French regulations.

Indication for surgery as reported by the patients' attending physicians

The patient's attending physicians prospectively reported indication(s) for surgery following a two-step process. First, if the attending physicians considered cardiac surgery during acute IE, they have to specify the reasons(s), i.e. heart failure, uncontrolled infection, or prevention of embolism, regardless of potential contraindication to surgery. Secondly, when surgery was indicated but not performed, the attending physicians had to mention the reason why it was not performed using a predefined list.

Indications for surgery according to European Society of Cardiology guidelines

From the data collected in the case report form, not taking into account the opinion of the attending physicians, we retrospectively analysed, for each patient, whether there was or not an indication for valve surgery during acute IE according to the 2009 ESC guidelines. An indication for surgery was defined as the presence of at least one criterion corresponding to a class I or IIa recommendation, regardless of any consideration on operative risk.[2]

Agreement between guidelines and practice

The agreement between the attending physicians and the ESC guidelines regarding indications for valve surgery was determined in each individual patient. The agreement was also analysed within each type of indication (heart failure, uncontrolled infection, and prevention of embolism). When there was an indication for surgery according to guidelines but not according to the attending physicians, the indication was considered as 'no identified indication'.

Follow-up

One-year follow-up was part of the survey protocol and prospectively recorded by telephone contact with the patient and/or his/her family physician.

Statistical analysis

Continuous variables were expressed as mean value $\pm$ standard deviation (SD). Cumulative survival curves were determined by the Kaplan–Meier method. Comparisons of patient characteristics between subgroups used a *t*-test for continuous variables and a χ^2 test for categorical variables. Agreements were analysed using the percentage of concordant pairs and kappa coefficient.

The analysis of the factors associated with 1-year survival was performed using a log-rank test and a multivariate Cox proportional hazards model adjusting for age and Charlson comorbidity index. Analysis was performed with SAS statistical software (release 9.2, SAS Institute Inc. SAS Institute, Cary, NC, USA).

Results

Population

During the year 2008, 497 cases with validated definite IE were included. Of these, 391 had left-sided IE: 303 native valve IE, 71 prosthetic IE, 10 native and prosthetic IE, and 7 IE on a repaired valve. The 303 patients with native aortic and/or mitral IE were considered for the present study. Patient characteristics are detailed in *Table 1*. Nine patients had previous pacemaker implantation but no evidence of infection in the foreign material.

Indication for surgery according to the patient's attending physicians

According to the attending physicians, there was at least one indication for surgery in 194 patients (64%) which was due to heart failure in 143 patients (47%), uncontrolled infection in 63 (21%), and prevention of embolism in 103 (34%) (74, 32, and 53% of patients with an indication, respectively).

Table 1 Characteristics of the 303 patients with native valve left-sided infective endocarditis

	Mean ± SD or *n* (%)
Patient characteristics	
Age (years)	62 ± 15
Sex (men)	228 (75.2)
Diabetes mellitus	66 (21.8)
Hypertension	140 (46.2)
Cancer	58 (19.1)
Dialysis	9 (3.0)
Charlson comorbidity index	1.9 ± 2.3
euroSCORE	8.5 ± 3.3
Previous IE	13 (4.3)
Pacemaker or ICD	9 (3.0)
Known valve disease	109 (35.9)
Mode of IE acquisition	
Community-acquired	230 (78.2)
Healthcare-associated	51 (17.4)
Drug use-associated	13 (4.4)
Clinical and biological features	
Fever ≥38°C	267 (88.4)
Congestive heart failure	107 (35.3)
Vascular phenomena	
Cerebral embolism	72 (23.8)
Cerebral haemorrhage	22 (7.3)
Other embolism	104 (34.3)
Serum creatinin ≥180 μmol/L	88 (29.5)
C-reactive protein >120 mg/L	136 (46.3)
Location of IE	
Aortic	98 (32.3)
Mitral	149 (49.2)
Aortic and mitral	45 (14.9)
Left- + right-sided	11 (3.6)
Echocardiographic findings	
Vegetation	294 (97.0)
Vegetation length (mm)	14 ± 11
Abscess	42 (13.9)
Regurgitation ≥grade 3/4	153 (51.0)
Microorganisms	
Streptococci	179 (59.1)
Staphylococci	88 (29.0)
Other microorganisms	23 (7.6)
No microorganism identified	13 (4.3)

ICD, implantable cardioverter defibrillator.

Indication for surgery according to the 2009 European Society of Cardiology guidelines

According to ESC guidelines, there was an indication for surgery in 221 patients (73%) due to heart failure in 166 patients (55%), uncontrolled infection in 63 (21%), and prevention of embolism in 98 (32%) (75, 29, and 44% of patients with an indication, respectively).

Surgery during the acute phase of infective endocarditis

Surgery was performed during acute IE in 139 patients (46%), 131 of whom had indication(s) for surgery according to ESC guidelines. Median time between the initiation of antibiotic therapy and surgery was 11 days [interquartile range 3–22]. Surgery was not performed in 164 patients (54%), of whom 90 had indication(s) according to ESC guidelines (*Figure 1*).

Agreement between the attending physicians and European Society of Cardiology guidelines

Table 2 presents the agreement between the attending physicians and ESC guidelines. Although the indication according to the attending physicians was consistent with guidelines in more than 70% of cases, the kappa coefficients only ranged between 0.41 and 0.59.

Agreement between the guidelines and the actual performance of surgery

There was an agreement between guidelines and practices in 205 patients (68%), and a disagreement in 98 (32%). The corresponding kappa coefficient was 0.38 (95% CI 0.29–0.46) (*Table 3*).

Agreement

Among the 205 patients with an agreement between practice and guidelines, there were 131 patients with a class I or IIa indication for surgery who underwent surgery (indication and surgery performed), and 74 with no indication according to ESC guidelines and no surgery performed.

Disagreement

Among the 98 cases with a disagreement between practices and guidelines, only 8 cases were due to the performance of surgery in patients with no class I or IIa indication. The reason for surgery reported by the attending physicians was the prevention of embolism in seven patients who had vegetations without prior embolic event and heart failure in three, although no heart failure was mentioned in the case report form.

In most cases (90 out of 98 patients), disagreement was due to the absence of surgery despite a class I or IIa recommendation. In these 90 patients, indication(s) for surgery were identified by the attending physicians in 42 patients (47%) but not in 48 (53%), hereafter referred to as 'no identified indication'. The distribution of patients according to the indication for surgery according to ESC guidelines and surgical treatment actually performed is summarized in *Figure 1*.

Comparison of patient characteristics according to agreement between guidelines and practices

The 131 patients who had an indication for surgery according to ESC guidelines and surgery performed were compared with the

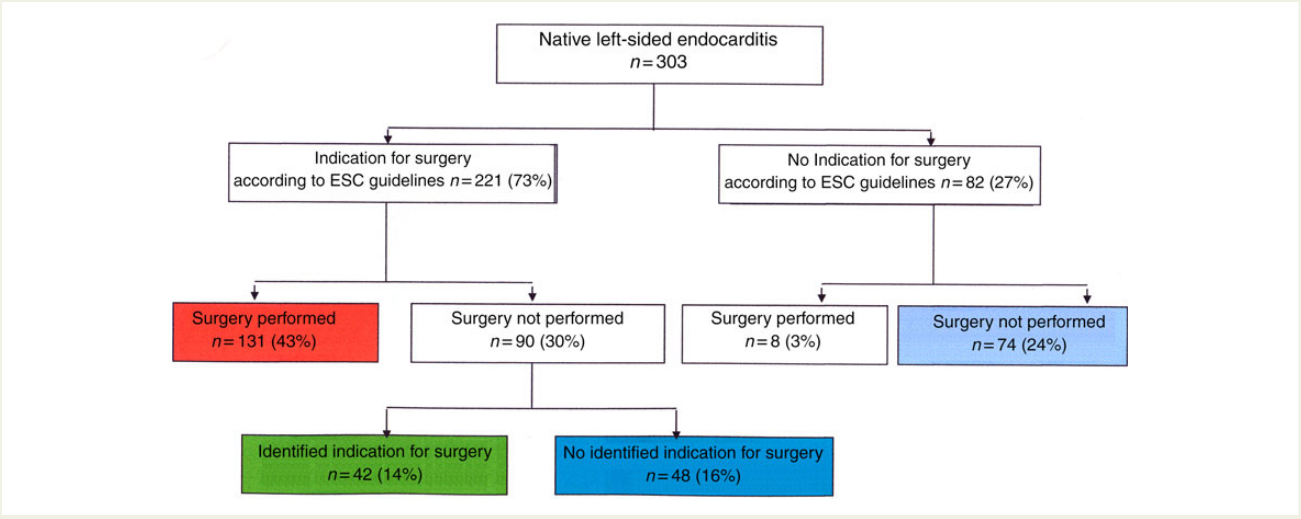

Figure 1 Distribution of indications for surgery according to European Society of Cardiology guidelines and practices.

Table 2 Agreement on indications for surgery between the attending physicians and European Society of Cardiology guidelines

Guidelines indication	Attending physicians		Agreement (%)	Kappa coefficient [95% CI]
	Indication	No indication		
Heart failure			79	0.59 [0.50–0.68]
Indication	123	43		
No indication	20	117		
Uncontrolled infection			80	0.40 [0.27–0.52]
Indication	33	30		
No indication	30	210		
Prevention of embolism			74	0.41 [0.30–0.52]
Indication	61	37		
No indication	42	163		
≥1 indication for surgery			77	0.48 [0.37–0.58]
Indication	173	48		
No indication	21	61		

CI, confidence interval.

48 patients with no identified indications (*Table 4*). Patients with no identified indications had a higher risk profile: they were significantly older, had higher Charlson comorbidity index, and more frequent healthcare-associated IE than patients with an indication and surgery performed. Conversely, operated patients presented with significantly more frequent severe regurgitations, multivalve IE, and a trend towards more frequent congestive heart failure and embolic events.

The 48 patients with no identified indication were compared with the 42 patients who had an identified indication for surgery according to the guidelines, and according to the attending physicians, but in whom cardiac surgery was considered contraindicated (*Table 5*). Apart from the frequency of severe regurgitation, there were no differences in patient characteristics between the two subgroups.

Reasons advocated for the absence of surgery in patients with identified indication by the attending physicians were either singly or in combination, prohibitive operative risk due to general status in 62% of patients, death before surgery in 21%, improvement of heart failure in 21%, severe neurological impairment in 17%, patient

Table 3 Agreement between indications for surgery according to European Society of Cardiology guidelines, and the actual performance of surgery

	Surgery performed	Surgery not performed
ESC guidelines		
Indication	131	90
No indication	8	74

Table 4 Comparison between the 131 patients with an indication for surgery according to European Society of Cardiology guidelines and surgery performed, and the 48 patients with an indication for surgery according to guidelines but not identified by the attending physicians

	Indication and surgery performed ($n = 131$)	No identified indication ($n = 48$)	*P*
Patient characteristics			
Age (years)	57 ± 15	67 ± 15	**0.0002**
Sex (men)	107 (81.7)	34 (70.8)	0.12
Diabetes mellitus	29 (22.1)	10 (20.8)	0.85
Hypertension	47 (35.9)	28 (58.3)	**0.007**
Cancer	20 (15.3)	14 (29.2)	**0.04**
Dialysis	1 (0.8)	1 (2.1)	0.47
Charlson comorbidity index	1.5 ± 1.9	2.7 ± 2.7	**0.001**
euroSCORE	8.6 ± 3.1	8.9 ± 3.2	0.57
Previous IE	3 (2.3)	3 (6.3)	0.34
Pacemaker or ICD	1 (0.8)	4 (8.3)	**0.02**
Known native valve disease	41 (31.3)	24 (50.0)	**0.02**
Mode of IE acquisition			**0.001**
Community acquired	110 (84.6)	32 (68.1)	
Heathcare associated	10 (7.7)	14 (29.8)	
Drug use associated	10 (7.7)	1 (2.1)	
Clinical and biological features			
Fever ≥38°C	117 (89.3)	41 (85.4)	0.47
Congestive heart failure	64 (48.9)	16 (33.3)	0.06
Vascular phenomena			
Cerebral embolism	40 (30.5)	9 (18.8)	0.12
Cerebral haemorrhage	13 (9.9)	4 (8.3)	1.0
Other embolism	55 (42.0)	13 (27.1)	0.07
Serum creatinine ≥180 μmol/L	39 (30.0)	12 (26.1)	0.61
C-reactive protein >120 mg/L	58 (46.0)	18 (38.3)	0.36
Location of IE			**0.015**
Aortic	50 (38.2)	14 (29.2)	
Mitral	46 (35.1)	28 (58.3)	
Aortic and mitral	31 (23.7)	4 (8.3)	
Left- + right-sided	4 (3.1)	2 (4.2)	
Echocardiographic findings			
Vegetation	126 (96.2)	47 (97.9)	1.0
Vegetation length (mm)	17.6 ± 14.8	13.5 ± 8.1	0.11
Abscess	30 (22.9)	7 (14.6)	0.22
Regurgitation ≥grade 3/4	103 (79.2)	20 (41.7)	**<0.0001**
Microorganisms			0.91
Streptococci	81 (61.8)	28 (58.3)	
Staphylococci	34 (26.0)	13 (27.1)	
Other	12 (9.2)	6 (12.5)	
None identified	4 (3.1)	1 (2.1)	
Indication for surgery according to ESC guidelines			
Heart failure	107 (81.7)	28 (58.3)	**0.001**
Uncontrolled infection	37 (28.2)	18 (37.5)	0.23
Prevention of embolism	61 (46.6)	20 (41.7)	0.56

ICD, implantable cardioverter defibrillator.
Bold values indicate $P < 0.05$.

Table 5 Comparison between the 48 patients who had an indication for surgery according to ESC guidelines but which was not identified by the attending physicians, with the 42 patients who had an indication for surgery according to guidelines which was identified by the attending physicians, but who were considered contraindicated for surgery

	Identified indication but contraindication ($n = 42$)	No identified indication ($n = 48$)	*P*
Patient characteristics			
Age (years)	66 ± 16	67 ± 15	0.76
Sex (men)	32 (76.2)	34 (70.8)	0.57
Diabetes mellitus	7 (16.7)	10 (20.8)	0.61
Hypertension	22 (52.4)	28 (58.3)	0.57
Cancer	10 (23.8)	14 (29.2)	0.57
Dialysis	2 (4.8)	1 (2.1)	0.60
Charlson comorbidity index	2.0 ± 2.6	2.7 ± 2.7	0.12
euroSCORE	7.9 ± 3.7	8.9 ± 3.2	0.15
Previous IE	3 (7.1)	3 (6.3)	1.0
Pacemaker or ICD	2 (4.8)	4 (8.3)	0.68
Known native valve disease	18 (42.9)	24 (50.0)	0.67
Mode of IE acquisition			0.10
Community-acquired	36 (87.8)	32 (68.1)	
Healthcare-associated	5 (12.2)	14 (29.8)	
Drug use-associated	0 (0)	1 (2.1)	
Clinical and biological features			
Fever ≥38°C	39 (95.1)	41 (85.4)	0.17
Congestive heart failure	16 (38.1)	16 (33.3)	0.64
Vascular phenomena			
Cerebral embolism	6 (14.3)	9 (18.8)	0.57
Cerebral haemorrhage	3 (7.1)	4 (8.3)	1.0
Other embolism	17 (40.5)	13 (27.1)	0.18
Serum creatinine ≥180 μmol/L	15 (35.7)	12 (26.1)	0.33
C-reactive protein >120 mg/L			
Location of IE			0.93
Aortic	10 (23.8)	14 (29.2)	
Mitral	25 (59.5)	28 (58.3)	
Aortic and mitral	5 (11.9)	4 (8.3)	
Left- and right-sided	2 (4.8)	2 (4.2)	
Echocardiographic findings			
Vegetation	39 (92.9)	47 (97.9)	0.34
Vegetation length (mm)	15.4 ± 6.5	13.5 ± 8.1	0.30
Abscess	5 (11.9)	7 (14.6)	0.71
Regurgitation ≥grade 3/4	30 (71.4)	20 (41.7)	**0.005**
Microorganisms			0.11
Streptococci	21 (50.0)	28 (58.3)	
Staphylococci	13 (31.0)	13 (27.1)	
Other	2 (4.8)	6 (12.5)	
None identified	6 (14.3)	1 (2.1)	
Indication for surgery according to ESC guidelines			
Heart failure	31 (73.8)	28 (58.3)	0.12
Uncontrolled infection	8 (19.0)	18 (37.5)	**0.05**
Prevention of embolism	17 (40.5)	20 (41.7)	0.91

ICD, implantable cardioverter defibrillator.
Bold values indicate $P < 0.05$.

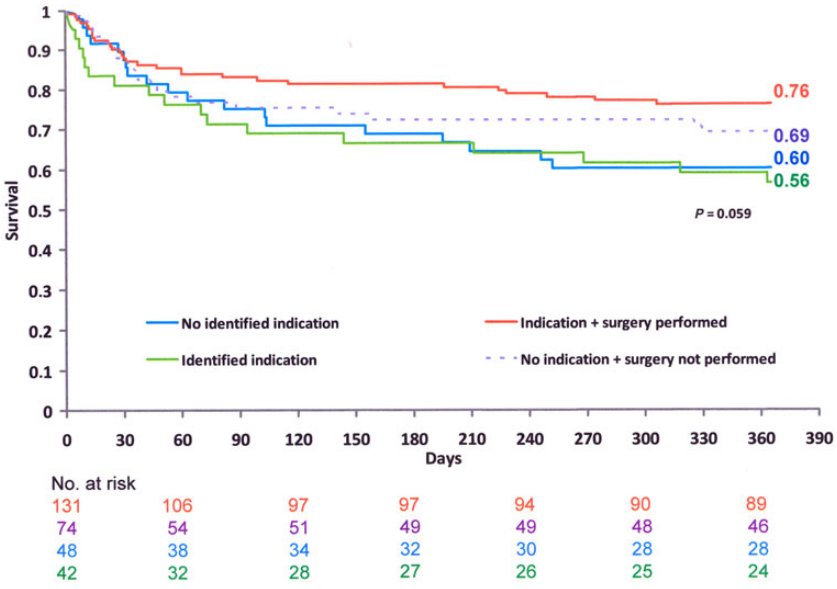

Figure 2 One-year survival according to the concordance between European Society of Cardiology guidelines and practices.

refusal in 17%, cardiac status in 13%, septic status in 8%, and unavailability of surgery in 4%.

One-year survival

One-year survival is represented in *Figure 2* according to indications for surgery and surgery actually performed. Hazard ratios adjusted for age and Charlson comorbidity index, when compared with patients with an indication and surgery performed were:

1.66 (95% CI 0.91–3.05, $P = 0.10$) for patients with identified indication (but contraindication to surgery),

1.24 (95% CI 0.69–2.24, $P = 0.48$) for patients with no identified indication,

1.03 (95% CI 0.59–1.81, $P = 0.91$) for patients with no indication and surgery not performed.

Discussion

In the present study, up to 73% of patients had at least one class I or IIa indication for cardiac surgery during the acute phase of IE according to ESC guidelines. Disagreement was observed between guidelines and the attending physicians, and between guidelines and the actual performance of surgery. The 16% of patients we classified as 'no identified indication' were not significantly different from patients with identified indications and contraindications to surgery.

Population

A strength of this study is its population-based design, which limits referral biases observed in series from tertiary care centres. Mean age over 60 years, male predominance, and the predominance of staphylococci are consistent with other recent population-based studies.[13,14] These characteristics differ from earlier population-based studies which enrolled younger patients, and identified streptococci as the most frequent microorganism.[15,16] These changes were illustrated in the 3 French population-based studies on IE performed in 1991, 1999, and 2008.[17]

We restricted the analysis to left-sided native IE because (i) indications for cardiac surgery are more limited in right-sided than in left-sided IE and (ii) indications for surgery in prosthetic IE were addressed separately in guidelines. As prosthetic IE accounted for only 21% of all cases of IE in the 2008 French survey,[12] the analysis of decision-making for surgery was restricted to left-sided native valve IE. Cardiac surgery was performed during acute IE in 46% of patients, which is consistent with other contemporary series in Europe and the USA.[18–21]

Guidelines

Although this survey was conducted in 2008, we based our analysis on the 2009 ESC guidelines. The 2004 ESC guidelines did not grade recommendations for surgery and presented discrepancies with the 2009 issue. On the other hand, the 2005 guidelines from the French Society of Cardiology on the management of valvular disease were very close to the 2009 ESC guidelines regarding their recommendations for cardiac surgery during the acute phase of IE, and can be considered as the 'reference document' during the study period.[22]

Agreement between guidelines and the attending physicians

The present study is, to our knowledge, the first to specifically analyse the agreement between guidelines and the opinion of the attending physicians. Indications for surgery were in agreement in 77% of cases, with a kappa coefficient of 0.48 indicating a moderate concordance. When considering the type of indication, the best agreement was observed for indications related to heart failure (kappa 0.59), while the kappa coefficient was only around 0.40 for uncontrolled infection and prevention of

embolism. Whether guidelines or the opinion of the attending physicians are considered, heart failure was the most frequent complication of IE, and the most frequent indication for surgery, followed by uncontrolled infection and prevention of embolism. This is consistent with previous series.[18,20] With regards to heart failure, disagreements were most frequently due to an indication according to guidelines which was not identified by the attending physicians, rather than the opposite. Disagreements were more balanced for indications due to uncontrolled infection or prevention of embolism.

Agreement between guidelines and the actual performance of surgery

Although 46% of patients were operated during acute IE, 73% had at least one class I or IIa indication for surgery according to ESC guidelines. This is consistent with a recent analysis from the International Collaboration on Endocarditis, in which the corresponding figures were 57, and 74%, respectively.[9]

Disagreement between guidelines and the actual performance of surgery were seldom due to the performance of surgery without a class I or IIa recommendation. This concerned only 8 (3%) of the 303 patients. For seven of them, surgery was indicated for the prevention of embolism. Indications for surgery based on vegetation size alone are a class IIb in ESC guidelines, while we considered only class I and IIa indications in the present analysis. The most frequent disagreement concerned the 90 patients (30%) with a class I or IIa indication who did not undergo surgery. When considering the reasons given by the attending physician, these 90 patients split approximately into the same proportion of patients with identified indications by the attending physicians, but in whom surgery was considered contraindicated, and patients with no identified indications. The latter were characterized by a higher risk profile due to age and comorbidities, when compared with patients with an identified indication and surgery performed. This is consistent with series comparing operated and non-operated patients regardless of the reasons behind the decision.[5,21,23] However, the present analysis shows that a significant proportion of non-operated patients had indications for surgery according to ESC guidelines, but were considered by the attending physicians as having no indication. The similarity in patient characteristics between patients with identified indication associated with contraindication to surgery, and those with no identified indication, strongly suggests confusion by the attending physician between indication for surgery and the risk of intervention. Of the 48 patients with no identified indication, as many as 58% had heart failure, which highlights the need for implementing guidelines.

The present survey was prospectively designed to collect the opinion of the attending physicians to analyse the relative contributions of indication for cardiac surgery, and contraindications to surgery, to the final decision. However, these two aspects of the decision were not clearly differentiated. Not recognizing an indication for surgery in high-risk patients may hamper decision-making, leading to surgery not being considered instead of analysing competitive risks of complications of IE vs. the risks of surgery. The risk of surgery in IE is difficult to assess given the diversity of patient characteristics. Specific risk scores may be helpful in limiting the subjectivity of risk analysis.[24] The dramatic negative prognostic impact of unstable haemodynamic conditions and emergency surgery highlights the need for timely surgery.[24] The complexity of decision-making strongly supports the management of patients with complicated IE in multidisciplinary endocarditis teams, as recommended in the 2015 ESC guidelines.[25]

Opinion of the attending physician and patient outcome

Among patients with at least one I or IIa indication for surgery according to ESC guidelines, those who were actually operated on for acute IE had a better 1-year survival rate than those who were not. A worse outcome in patients with indication for surgery but who were not operated was shown in other series.[8,9] However, outcome is influenced by confounding factors such as age and comorbidities, which significantly differ between operated and non-operated patients despite an indication for surgery. These confounding factors are attested by the fact that the type of indication was not significantly associated with 1-year survival when adjusted for age and comorbidities, although a trend remained for a worse outcome in patients with identified indication associated with contraindication to surgery.

Study limitations

This study did not allow for assessing the appropriateness of therapeutic decisions for each individual patient. Nevertheless, the overall concordance analysis suggests discrepancies between guidelines and practices, and/or risk assessment.

The relatively small number of patients limits the possibilities of subgroup analyses and of multiple adjustments of survival analyses. However, the strength of this analysis is that it was applied to a population-based prospective survey with systematic case validation and designed to prospectively collect the decision of the attending physicians through a standardized questionnaire.

Conclusion

In this nationwide contemporary study, approximately three out of four patients had at least one I or IIa indication for valve surgery during the acute phase of IE according to ESC guidelines. The fact that only half of the patients underwent surgery was partly related to contraindications to surgery, but indications were not identified in one out of six patients. These findings highlight the need for implementing guidelines and also evaluating their application in these particularly high-risk patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

F.A. performed statistical analysis; X.D., F.A., B.H., F.D., P.T., and C.C. handled funding and supervision; all co-authors contributed to data acquisition; B.I., X.D., F.A., B.H., F.D., P.T., V.L.M., and C.S. conceived and designed the research; B.I., X.D., and T.D.-L. drafted the

manuscript. All co-authors made critical revision of the manuscript for key intellectual content.

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