

# Rationale, design, and methods for the early surgery in infective endocarditis study (ENDOVAL 1): A multicenter, prospective, randomized trial comparing the state-of-the-art therapeutic strategy versus early surgery strategy in infective endocarditis

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**Background** The prognosis of infective endocarditis is poor and has remained steady over the last 4 decades. Several nonrandomized studies suggest that early surgery could improve prognosis.

**Methods** ENDOVAL 1 is a multicenter, prospective, randomized study designed to compare the state-of-the-art therapeutic strategy (advised by the international societies in their guidelines) with the early-surgery strategy in high-risk patients with infective endocarditis. Patients with infective endocarditis without indication for surgery will be included if they meet at least one of the following: (1) early-onset prosthetic endocarditis; (2) *Staphylococcus aureus* endocarditis; (3) periannular complications; (4) new-onset conduction abnormalities; (5) new-onset severe valvular dysfunction. A total of 216 patients will be randomized to either of the 2 strategies. Stratification will be done within 3 days of admission. In the early surgery arm, the surgical procedure will be performed within 48 hours of randomization. The only event to be considered will be death within 30 days. The study will be extended to 1 year. In the follow-up substudy, death and a new episode of endocarditis will be regarded as events.

**Conclusion** ENDOVAL 1, the first randomized study on endocarditis, will provide crucial information regarding the putative benefit of early surgery over the state-of-the-art therapeutic approach in high-risk patients with infective endocarditis. (Am Heart J 2008;156:431-6.)

## Background

Whereas mortality has been dramatically reduced in some areas of cardiac diseases thanks to continuous progress in treatment, endocarditis remains a high-

mortality disease with steady percentages of mortality in the last 30 years.<sup>1-3</sup> Several reasons may help to account for this frustrating comparison. The changing pattern of the epidemiology of endocarditis surely has contributed to the still high mortality.<sup>4,5</sup> Patients are older, prosthetic and nosocomial endocarditis are currently more frequent, and *Staphylococcus aureus* has increased as the causative agent. On the other hand, clinical investigators in this field must be aware of our fault in not generating evidence-based investigations. A paucity of comprehensive information exists and high-quality evidence is lacking. In fact, not even a single randomized study is available regarding the most challenging decision in endocarditis which is to decide whether and when surgery has to be undertaken in the active phase of the disease. Therefore, guidelines on treatment of endocarditis endorsed by the most prestigious scientific societies are supported by moderate (level B) or low level of evidence (level C).<sup>6,7</sup> Not even a single

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This study was financed in part by the Cooperative Network for Cardiovascular Research (Red Cooperativa de Enfermedades Cardiovasculares, RECAVA) of the Spanish National Institute of Health (Instituto de Salud Carlos III). ClinicalTrials.gov identifier: NCT 00624091.

Submitted October 13, 2007; accepted April 9, 2008.

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0002-8703/\$ - see front matter

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doi:10.1016/j.ahj.2008.04.006

**Table I.** Inclusion and exclusion criteria

## Inclusion criteria

1. Patients >18 years old.
2. Infective endocarditis diagnosed by modified Duke criteria.
3. At least one of the following risk factors:
  - a. Periannular complications
  - b. New onset auriculo-ventricular block
  - c. New onset severe valvular insufficiency
  - d. Early-onset prosthetic valve endocarditis
  - e. *Staphylococcus aureus* endocarditis

## Exclusion criteria

1. Patients with urgent/emergent indication of surgery when endocarditis is diagnosed:
  - a. Heart failure because of valvular insufficiency.
  - b. Fungal endocarditis.
  - c. Septic shock.
2. Patients referred from other centers to be operated on.
3. Patients without echocardiographic evidence of endocarditis.
4. Pregnant or lactating women.
5. Simultaneous participation in other research study.
6. Incapacity to maintain the conditions of the study.
7. Patients referred from other centers more than 5 days after the diagnosis of infective endocarditis.
8. Patients with prohibitive risk for surgery owing to comorbidities, estimated by previous validated scales. A Euroscore value >40% will be considered a contraindication to enter the protocol.
9. Patients with ischemic or hemorrhagic stroke within 1 m before the diagnosis of endocarditis.
10. Endocarditis in intravenous drug addict patients.

recommendation on medical versus surgical treatment is based on a high level of evidence (level A). Unfortunately, there is still as much art as science in the care of patients with endocarditis.<sup>8</sup> The only way investigators can tip the balance in favor of science is promoting randomized clinical studies with power enough to answer unsettled crucial clinical questions. Some authors encourage taking this track.<sup>9</sup> It has been suggested by others, however, that a randomized study comparing medical versus surgical treatment in endocarditis cannot be undertaken.<sup>1,10</sup>

American<sup>6</sup> and European guidelines<sup>7</sup> state with subtle differences that surgery should be considered in active infective endocarditis in the following situations (level of evidence B or C): heart failure, valve abnormalities (dehiscence, perforation, or rupture), periannular complications, persistent vegetation after systemic embolization, increase in vegetation size despite appropriate antibiotics, persistent infection, and infection by microorganisms known not to be cured by antimicrobial therapy.

All those indications are well-known predictors of poor short-term outcome in infective endocarditis and surgery is presumed to favorably alter that prognosis. However, it is already known that results of surgery are worse if patients have heart failure or persistent infection.<sup>11</sup> Besides, those indications appear frequently several days later after the initial diagnosis.

Finally, early surgery in active endocarditis has shown a lower mortality when compared to the usual medico-surgical approach.<sup>12-15</sup> Based on this background, we hypothesize that if we wait for predictors of poor prognosis to appear, surgery may come too late. If, nonetheless, surgery is performed within the first 3 days after admission in patients with a high-risk profile before the clinical course worsens, prognosis may be improved. To test this hypothesis, factors that define early high-risk profile have to be identified. With this aim, we undertook a prospective, multi-center study in 317 patients with left-sided endocarditis and demonstrated that heart failure, *Staphylococcus aureus*, and periannular complications detected within 72 hours after admission identified patients with poor prognosis.<sup>16</sup>

In summary, predictors of poor prognosis available within 72 hours after admission can accurately identify high-risk patients. The initial clinical profile, the results of the first transesophageal echocardiogram, and the initial blood cultures are accurate enough to stratify patients into high- and low risk. Whether early surgery can improve prognosis when undertaken in the former is an attractive hypothesis never tested so far.

Once we are able to identify early the high-risk profile patients with infective endocarditis, the following step has to be a randomized study in which the state-of-the-art therapeutic strategy for patients with endocarditis (medical treatment and surgery if predictors of poor prognosis appear early or late in the disease process) is compared to an early surgical approach. Of course, surgery and medical treatment cannot be compared and it would be unethical to do so. What we are designing is a study to compare 2 different therapeutic strategies in high-risk patients, the state-of-the-art approach, proposed by the international societies, and the early-surgery strategy which includes 2 consecutive steps: (1) identification of high-risk patients by means of predictors available within 72 hours of admission; (2) surgery within 48 hours of inclusion of a patient in the high-risk group.

## Methods

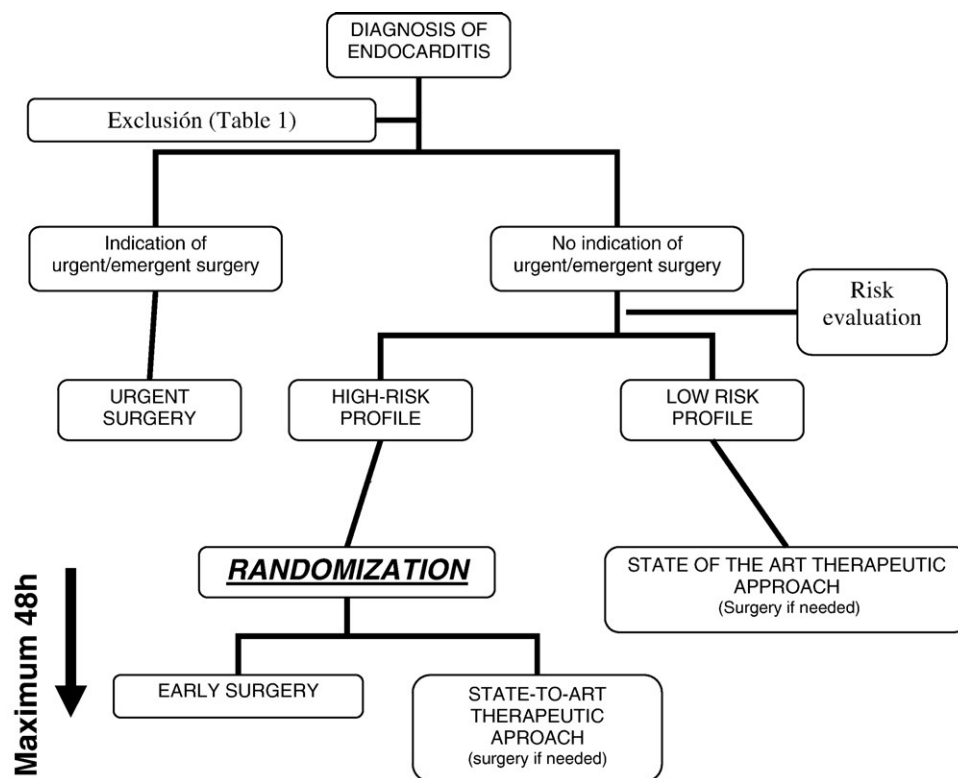
### Study hypothesis

Our hypothesis is that early surgery in high-risk patients with active infective endocarditis decreases mortality and should be considered the treatment of choice in this population.

### Study objectives

Our objective was to compare the 30-day mortality rate in high-risk patients with active infective endocarditis between an early surgical approach (surgery performed within the first 48 hours after inclusion or 5 days after the initial diagnosis) and the state-of-the-art treatment in this disease (medical treatment followed by surgery if predictors of poor prognosis appear early or late).

**Figure 1**



Study flow chart.

### Study population

Our initial study population is made up of patients with active infective endocarditis in the initial phase of the disease (<5 days of the diagnosis) who do not meet the exclusion criteria (Table 1). Diagnosis of infective endocarditis will be performed according to the modified Duke criteria.<sup>17</sup> Patients who require urgent surgery (heart failure, septic shock, or fungal endocarditis) are rapidly sent to surgery. Patients with >5 days between the diagnosis and the first contact with our centers are excluded as the concept of early surgery cannot be applied to them. Patients with a surgical risk of >40% calculated by means of the logistic Euroscore system<sup>18</sup> are also excluded as their pre-operative status is so poor that the surgical risk prohibits a surgical approach. Finally, patients with ischemic or hemorrhagic stroke are also excluded given its very difficult management during the perioperative period which may introduce bias in the results.

### Definition of high-risk profile

A patient is considered to have a high-risk profile and, therefore, will be included in the trial when at least one of the following is met: (1) early-onset prosthetic endocarditis; (2) *S aureus* endocarditis; (3) periannular complications; (4) new-onset conduction abnormalities; (5) new-onset severe valvular dysfunction. When none of these criteria are present, the patient will be considered to bear a low-risk profile.

### Study design

Patients without any exclusion criteria will be divided into 2 groups according to the risk profile. When patients do not fulfill any of the high-risk criteria, they are considered low risk and are managed with the state-of-the-art therapeutic strategy, according to the guidelines accepted by the different international societies: medical management by a multidisciplinary team is accomplished. A complete clinical examination is done every day. Blood and urine analysis, chest x-ray, electrocardiogram, and blood cultures are taken initially and every 7 days. Transthoracic and transesophageal echocardiography are performed initially and will be reviewed by an expert who performs the exam. All the previous tests, including transesophageal echocardiography, are performed whenever the clinical status changes. Computed tomography scan is indicated when stroke or peripheral emboli are clinically suspected. Surgery is considered and decided on an individual basis when any of the following is present: heart failure, periannular complications, persistent >10-mm vegetation after systemic embolization, or persistent signs of infection (fever or positive blood cultures after 7 days of correct antibiotic treatment once other sources of fever are ruled out). The specific surgical technique will be decided by the surgeon according to the degree of tissue destruction and will be aimed to remove the infected tissue and to repair the damaged structures or, if this is not feasible, to implant cardiovascular prosthesis.

**Table II.** Study schedule and procedures

	Baseline	Change in clinical status	Daily	Weekly until discharge
Clinic history	x			
Physical exam	x	x	x	x
Informed consent	x			
EKG	x	x		x
Blood sample *	x	x		x
Urine sample	x	x		x
Pregnancy test †	x			
TTE	x	x		x
TEE	x	x		x
Blood cultures (x3)	x	x		x
Chest radiograph	x	x		x
Adverse events evaluation	x	x	x	x

EKG, Electrocardiogram; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram.

\* Includes systematic and biochemistry, procalcitonine, globular sedimentation velocity.

† In every woman in fertile period.

**Table III.** Long-term study schedule and procedures

	1st month after discharge	6th month	12th month
Outpatient clinical visit	x	x	x
EKG	x	x	x
Blood sample	x	x	x
TTE		x	x
TEE		x	x
Blood cultures (x3)		x	x
Chest radiograph	x	x	x
Adverse events evaluation	x	x	x

If the patients meet any of the high-risk criteria, they are randomized to the state-of-the-art therapeutic strategy aforementioned or the early surgical strategy. In the latter, surgery must be performed within 48 hours after randomization. Therefore, the time from the first contact to the hospital to surgery cannot be >5 days (3 days to have the transesophageal exam and the blood cultures available and 2 days for randomization to surgery). The study flow chart is shown in Figure 1.

The only event to be considered in the statistical analysis will be death within 30 days of admission. The study will be prolonged and patients will be followed for 1 year. In the long-term analysis, death and a new episode of endocarditis will be considered the only events. Table II depicts the study schedule and procedures. Table III depicts the long-term substudy schedule and procedures.

The protocol has been approved by the local ethical committee of the following institutions: (1) University Clinic Hospital, Valladolid, Spain; (2) University Clinic Hospital San Carlos, Madrid, Spain; (3) University Clinic Hospital Valle Hebrón, Barcelona, Spain.

Enrollment will be initiated in the first semester of 2008. It is expected to be completed in 3 years and results will be

**Table IV.** Mortality rate in high-risk patients reported on by different groups

Author	Reference	n	Characteristics of the patients	Mortality rate
Habib et al	19	104	Prosthetic endocarditis	21%
Mourvillier et al	20	228	Patients admitted to an intensive care unit	45%
Wolf et al	21	122	Prosthetic endocarditis	34%
Akowuah et al	22	66	Prosthetic endocarditis	29%
Karth et al	23	33	Patients admitted to an intensive care unit	35%
Revilla et al	11	89	Urgent surgery	36%
López et al	24	66	Early-onset prosthetic endocarditis	38%

publicly presented in international meetings in the last semester of 2011.

## Statistical considerations

### Determination of sample size

The study will be powered to address the primary hypothesis that a decision to operate on patients with high-risk endocarditis on an urgent basis will decrease inhospital mortality compared to patients managed with the state-of-the-art strategy. Thus, the sample size was calculated based on the assumption of a 30% mortality in the state-of-the-art group<sup>11,17-22</sup> versus 13% in the early surgery group<sup>12,13</sup> (17% absolute reduction). Table IV shows the mortality rate in high-risk patients reported on by different groups. A sample size of 206 patients will produce a study power of 80% with a 2-sided  $\alpha$  level of .05. As a result, assuming a 5% loss during the study period, a sample size of 216 enrolled patients is needed with 108 in each group. Losses during long-term follow-up will be censored.

### Randomization

Once the patients have complied with protocol requirements and has signed the informed consent, they will be included in the study and randomized to one of the 2 strategies. Randomization will be performed with blocks of 4 and 6 patients by an automated assignment system. Blocks will be rerandomized to avoid knowing the block size. All calculations will be performed with the C4Study design pack (v 1.1, Glaxo Wellcome, Madrid, Spain).

Independence is guaranteed because the person who will make the process will be contacted by telephone and will not take any clinical decision about the patient.

### Safety issues

An intermediate analysis will be done to control the quality of the information collected and to contrast the hypothesis of the study. The study will be stopped if a rate of adverse event higher than expected is observed.

## Statistical analysis

Once that information has been collected and checked, the statistical analysis will begin. Statistical analysis of data will follow the intention-to-treat principle, that is, patients will be analyzed according to the treatment arm to which they were allocated, regardless of adherence to the assigned treatment. Continuous variables will be compared with Student *t* test and Mann-Whitney *U* test for nonnormally distributed variables and categorical variables will be compared with the  $\chi^2$  test and Fisher exact test when appropriate.

The distribution of time-to-event variables will be estimated by the Kaplan-Meier method; treatment effects will be compared with log-rank test. The Cox regression method will be used to estimate the hazard ratio and 95% CI. All tests will be 2 sided and *P* values <.05 will be considered to indicate statistical significance. Statistical analysis will be performed with SPSS software v 14.0 (SPSS, Inc, Chicago, IL).

## Study limitations

It has been decided to exclude patients with stroke, either ischemic or hemorrhagic, because it may potentially bias the results. Thus, the results of this study will not be applicable to patients with active endocarditis and stroke, a challenge in the management of this disease.

We would like to test the usefulness of early surgery in the early phase of the disease. Conceptually, therefore, patients whose diagnosis is established after >5 days shall be excluded. Again, our results will not be pertinent for patients after a few days of their diagnosis.

Although the sample size should be enough if the rate of death in both arms is close to that predicted, analysis of subgroups is expected not to bear any statistical power; thus, if our results are encouraging, future trials should deal with the benefits of early surgery in more specific groups, like prosthetic endocarditis or *S aureus* endocarditis.

Finally, we are aware that this will be the first randomized trial on endocarditis. Therefore, the level of evidence will not change from B to A, given that >1 randomized trial is necessary to increase the level of evidence. We hope, however, that our study will spur the minds of clinical investigators in this field, an area in which scientific evidence is highly demanded, and that a long series of randomized clinical studies on infective endocarditis will be initiated. We encourage investigators on infective endocarditis to give their best to help tip the balance in favor of science.

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