« Early valve surgery versus conventional treatment in infective endocarditis patients with high risk of embolism: a randomized superiority clinical trial»

CHIRURGENDO

PHRC

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Scientific justification

- **Infective endocarditis (IE) : in-hospital mortality rate : 15-25%**
- **Leading causes of mortality:**
  - heart failure (HF)
  - **stroke caused by vegetation embolization.**
- **Symptomatic embolic events after antibiotic initiation: 15%**
- **Benefit of Valve surgery:**
  - clearly demonstrated in pts with periannular complications and moderate to severe HF resulting from acute valve regurgitation.
  - Indications of valve surgery for prevention of embolic complications are less clearly defined.
- **Timing of surgery to prevent embolism : critical since the risk of new embolic event is highest during the first weeks of antibiotic treatment.**

Scientific justification

Points in favor of early valve surgery (EVS) in pts with high embolic risk include the following

1. **Pts with high risk of embolism are identified by ETO**
2. **Low postoperative mortality**
3. **IE guidelines state that valve surgery**
   - should be performed in IE with vegetation above 10 mm AND an embolic event occurring while patients are receiving antibiotic (grade I/B)
   - should be considered in IE with vegetation above 30 mm (Grade IIaB) and may be above 10 mm and severe valve regurgitation,
4. **Korean RCT: showed that EVS in patients with high risk of embolism and severe valve regurgitation was associated with a significantly reduced risk of embolism compared with conventional treatment.**
5. **However,**
   - less than 80 pts enrolled ,
   - Pts characteristics (age, type of microorganisms) are completely different from those of IE patients in Europe and the USA,

Table : Indications and timing of surgery in left-sided valve infective endocarditis, and Class and Lev
of the recommendation (2015 European Guidelines) (15).

Indications for surgery	Timing[a]	Class[b]	Level[c]	Ref.[d]
1. Heart failure				
Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction or fistula causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B	111,115, 213,216
Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance	Urgent	I	B	37,115, 209,216, 220,221
2. Uncontrolled infection				
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B	37,209, 216
Infection caused by fungi or multiresistant organisms	Urgent/ elective	I	C	
Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	Urgent	IIa	B	123
PVE caused by staphylococci or non-HACEK gram-negative bacteria	Urgent/ elective	IIa	C	
3. Prevention of embolism				
Aortic or mitral NVE or PVE with persistent vegetations >10 mm after one or more embolic episode despite appropriate antibiotic therapy	Urgent	I	B	9,58,72, 113,222
Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	Urgent	IIa	B	9
Aortic or mitral NVE or PVE with isolated very large vegetations (>30 mm)	Urgent	IIa	B	113
Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery[e]	Urgent	IIb	C	

HACEK = *Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Haemophilus paraphrophilus*, *Haemophilus influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae* and *Kingella denitrificans*; HF = heart failure; IE = infective endocarditis; NVE = native valve endocarditis; PVE = prosthetic valve endocarditis.
[a]Emergency surgery: surgery performed within 24 h; urgent surgery: within a few days; elective surgery: after at least 1–2 weeks of antibiotic therapy.
[b]Class of recommendation.
[c]Level of evidence.
[d]Reference(s) supporting recommendations.
[e]Surgery may be preferred if a procedure preserving the native valve is feasible.

urgent (within a few days, <7 days)

Primary objective

- **To compare clinical outcomes of EVS (as soon as possible within 72 hours of randomization) with those of a conventional management based on current guidelines in patients with left-sided native-valve IE and high risk of embolism.**

Secondary objectives

1. **Six-months and one-year**
    1. all-cause death and clinical embolic events
    2. Mortality
    3. symptomatic embolic event rates
    4. neurological disability
    5. infective IE relapse
    6. cardiac congestive heart failure
    7. surgery recurrence rate
    8. valve prosthesis severe adverse event
2. **Quality of life in survivors at 6 months and 1 year.**

Experimental design

National multicenter prospective randomized open blinded end-point (PROBE) sequential superiority trial

Inclusion criteria

1. Age ≥ 18 years
2. Definite IE based on the modified Duke criteria (ESC 2015)
3. Length of vegetation on native aortic and/or mitral valve, as assessed by TOE
   - between 10 and 15 mm [ ] AND (severe regurgitation OR previous symptomatic or asymptomatic embolic events)
   - OR above or equal to 15 mm
4. Pts agree to the protocol (informed written consent)
5. Initiation of IE active AB < 5 days (≤120 hours) before inclusion
6. National health or universal health plan affiliation coverage

Non-inclusion criteria

1. Pts with “emergent” indication of surgery based on 2015 European Guidelines
2. Pts who are not candidates for surgery due to high risk post-surgery mortality based on the judgment of a multidisciplinary evaluation (endocarditis team) including for example coexisting major embolic stroke with a risk of hemorrhagic transformation, symptomatic hemorrhagic stroke; poor medical status, such as coexisting malignancies…
3. Pregnancy

Intervention / Primary outcome

- Intervention arm: Cardiac surgery as soon as possible within 72 hours of randomization
- Comparison arm: Conventional care according to the 2015 European guidelines.

- **Composite Primary outcome:**

  All cause death and symptomatic embolic event within 6 weeks of randomisation

Autorisations réglementaires

- En attente de l'accord du CPP et ANSM
- Mise en place en septembre 2018

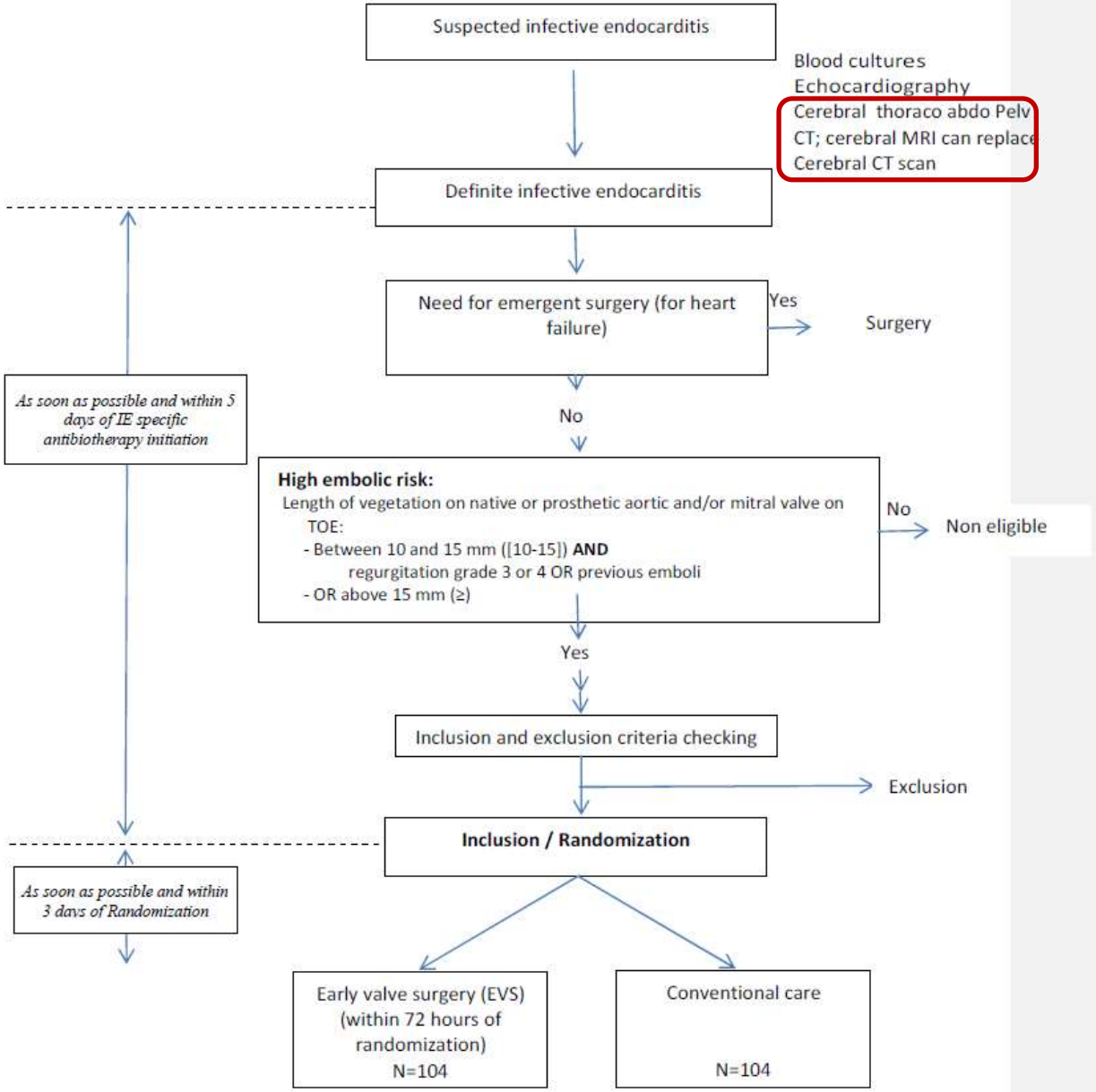
Participating centers

Civility	Name	First Name	City	Health facility	Speciality
Mr.	Duval Iung Nataf	Xavier Bernard Patrick	Paris	Bichat hospital	Infectious diseases Cardiology Cardiac surgery
Mr.	Le Moing	Vincent	Montpellier	CHU Montpellier	Infectious diseases
Mr.	Tattevin	Pierre	Rennes	CHU Rennes	Infectious diseases
Mr.	Boutoille	David	Nantes	CHU Nantes	Infectious diseases
Mr.	Bernard	Louis	Tours	CHRU de TOURS	Infectious diseases
Mr.	Selton-Suty Goehringer	Christine François	Nancy	CHU Nancy	Cardiologist Infectious diseaes
Mr.	Beraud	Guillaume	Poitiers	CHU Poitiers	Infectious diseases
Mr.	Piroth	Lionel	Dijon	CHU Dijon	Infectious diseases
Mr.	Nazeyrollas	Pierre	Reims	CHU Reims	Cardiologist
Mr.	Chirouze	Catherine	Besançon	CHU Bensançon	Infectious diseases
Mr.	Lucht	Fréderic	Saint Etienne	CHU St Etienne	Infectious diseases
Mr.	Delahaye Ferry Obadia	François Tristan Jean-François	Lyon	CHU Lyon	Cardiologist Infectious diseases Cardiac surgery
Mr.	Hoen	Bruno	Point à Pitre	CHU Guadeloupe	Infectious diseases
Mr.	Porte	Lydie	Toulouse	CHU Toulouse	Infectious diseases
Mr.	Lansac	Emmanuel	Paris	Montsouris	Cardiologist
Mr.	Tribouilloy	Christophe	Amiens	CHU Amiens	Cardiologsit

Statistical analysis

- **With a sequential design, a maximum sample size of 99 patients per arm would provide 90% power to detect a significant difference with respect to the primary end point at the 2-sided significance level of 0.05,**
- **assuming that the combined in-hospital event rate (death and symptomatic embolic event) would be**
  - 20% in the conventional treatment group
  - 5 % in the early surgery group.
- **Considering that 5 % of patients will be lost-to-follow up at 6 weeks, or no data available,**
- **we plan to include 208 patients (*104 patients per arm*)**
- ***16 medical centers in France***

Figure: Study Flow



	Baseline (Selection period)	*D1* ***Inclusion visit /randomization***	*Surgical intervention (within 72 hours post randomization)*	*1 wk +/- 2d*	*2 wk +/- 2d*	*3 wk +/- 2d*	*4 wk +/- 3d*	*6 wk +/- 3d*	*3 M +/- 7d*	*6 M +/- 7d*	*12 M +/- 7d*
Informed consent	X										
Eligibility	X										
Demographics	X										
Medical History	X			X	X	X	X	X	X	X	X
Physical Examination	X			X	X	X	X	X	X	X	X
Blood culture	X[1]			X				X			
Laboratory test	X[1]*							X**	X**	X**	X**
Cerebral CT (or cerebral MRI)	X[1]			←	←	←	X[3]	→	→	→	→
Abdomino pelvi CT	X[1]			←	←	←	X[3]	→	→	→	→
Transthoracic Echo	X[1]			X				X		X	X
Transesophageal Echo	X[1]										
Medications	X			X	X	X	X	X	X	X	X
Randomization		X[2]									
Cardiac surgery			X[2]	←	←	←	X[4]	→	→	→	→

[1] *not performed if previously performed within the 7 preceding days*

[2] *in patients randomized in the "urgent valve surgery (EVS) arm", cardiac surgery should be performed as soon as possible within the 72 hours.*

[3] *in case of the occurrence of clinical symptoms which may suggest extracardiac complications (including emboli) of IE*

[4] *in patients randomized in the "conventional care group", cardiac surgery may be performed according to guidelines, at the convenience of the investigator, throughout the follow-up of the patient.*

* Blood cell and platelet count, serum creatinine, liver function tests (transaminases, alkaline phosphatase, γ-GT), HIV serology, urinary or blood β-HCG for women of child-bearing age, latex waaler rose and urinary leukocytosis if currently performed; ** serum creatinine.

Table: 2015 IE European guidelines as compared to CHIRURGENDO surgical strategy

2015 IE European Guidelines (15)		**CHIRURGENDO inclusion criteria**	
Prevention of embolism	**Timing**		**Timing for the EVS arm**
Aortic or mitral NVE or PVE with persistent vegetations ≥10 mm after one or more embolic episode despite appropriate antibiotic therapy		Length of vegetation on aortic and/or mitral valve on TOE: Between 10 and 15 mm ([10-15]) ASSOCIATED with previous symptomatic or asymptomatic emboli (regardless patients were or not on appropriate antibiotic therapy)	
Aortic or mitral NVE with vegetations ≥10 mm associated with severe valve stenosis or regurgitation, and low operative risk	Urgent (within a few days before day 7 of IE antibiotherapy)*	Length of vegetation on aortic and/or mitral valve on TOE: Between 10 and 15 mm ([10-15]) ASSOCIATED with severe regurgitation	As soon as possible within 72 hours of randomization
Aortic or mitral NVE or PVE with isolated very large vegetations (≥30 mm)		(included in the situation below)	
Aortic or mitral NVE or PVE with isolated large vegetations (≥15 mm) and no other indication for surgery		Length of vegetation on aortic and/or mitral valve on TOE above 15 mm (≥) independently of regurgitation grade	

* In the French population-based epidemiological study on IE, median time interval between initiation of antibiotic and surgery for the prevention of emboli was 7 days (interquartile range 25-75%: 3-17 days; personal data).

Table: Comparison of inclusion criteria in the Korean protocol and in the French current protocol.

Korean protocol (34)		**Current French CHIRURGENDO protocol**	
Inclusion Criteria:		**Inclusion Criteria:**	
1.	Male or female		
2.	Age: 15-80 years	1.	Age ≥ 18 years
3.	Diagnosis of definite infective endocarditis according to the modified Duke criteria	2.	Diagnosis of definite infective endocarditis according to the **2015**-modified-Duke criteria
4.	Length of vegetation > 10 mm	3.	Length of vegetation on native or prosthetic aortic and/or mitral valve on TOE: - Between 10 and 15 mm AND regurgitation grade 3 or 4 OR previous emboli - OR above 15 mm
5.	Severe mitral or aortic valve disease	4.	
6.	The patient agrees to the study protocol and provides informed, written consent, as approved by the Institutional Review Board.	5.	The patient agrees to the study protocol and provides informed, written consent, as approved by the Institutional Review Board.
		6.	Initiation of IE active antibiotic less than 5 days (≤120 hours) before inclusion.
		7.	National health or universal health plan affiliation coverage
Exclusion Criteria		**Non-Inclusion Criteria:**	
1.	Patients with urgent and emergent indication of surgery based on current guidelines; aortic abscess, moderate to severe heart failure due to valvular regurgitation, periannular complications, fungal endocarditis, IE complicated by heart block, or destructive penetrating lesions.	1.	Patients with emergent indication of surgery based on 2015 European guidelines
2.	Prosthetic valve endocarditis.		
3.	Patients who were not candidates for surgery based on age > 80 years, coexisting major embolic stroke with a risk of hemorrhagic transformation, and/or poor medical status, such as coexisting malignancies.	2.	Patients who are not candidates for surgery due to high risk post-surgery mortality based on the judgment of a multidisciplinary evaluation (endocarditis team) including for example coexisting major embolic stroke with a risk of hemorrhagic transformation, symptomatic haemorrhagic stroke; poor medical status, such as coexisting malignancies…
4.	Patients with right-sided vegetations or small vegetations with diameter ≤ 10 mm.		
5.	Patients referred from other hospitals more than 7 days after the diagnosis of IE		
6.	Patients who did not consent to participate		
7.	Pregnancy	3.	Pregnancy