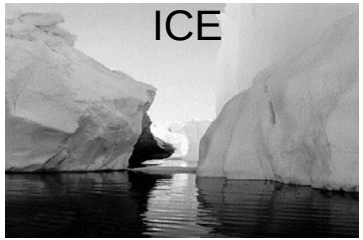
JNI 16es Journées Nationales d'Infectiologie
Nancy et l'interrégion Est
du mercredi 10 au vendredi 12 juin 2015
Centre Prouvé
Grand Nancy Congrès & Événements

Quelles stratégies pour le diagnostic, la prévention et le traitement des accidents emboliques cérébraux dans l'endocardite infectieuse ?

Bruno Hoen



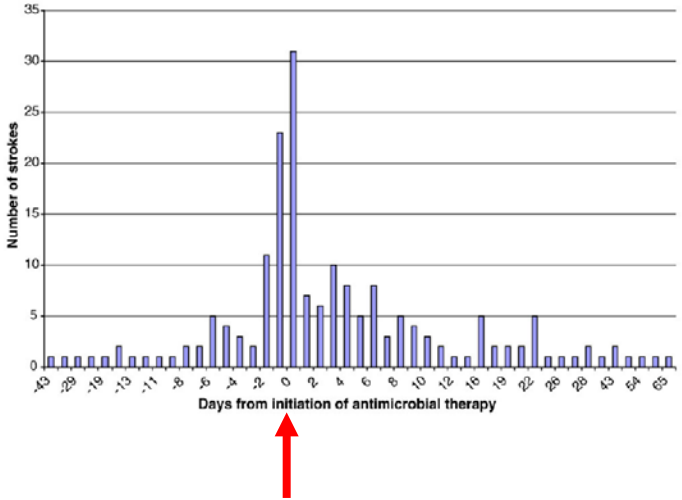
Déclaration d'intérêts de 2012 à 2015

Je n'ai rien à déclarer

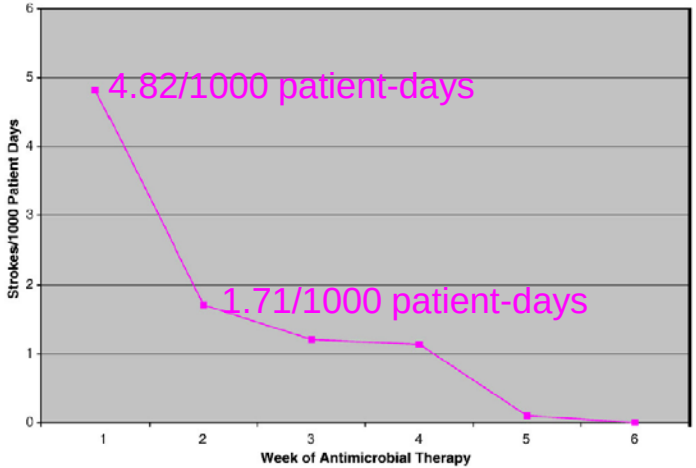
Relationship between the initiation of antimicrobial therapy and the incidence of stroke in IE

1437 consecutive patients with left-sided IE admitted directly to ICE centers
15.2% (219/1437) had a stroke

Daily incidence of stroke in the ICE-PCS cohort



Stroke rate after initiation of antimicrobial therapy



After 1 week of antimicrobial therapy, only 3.1% of the cohort experienced a stroke

Dickerman S, Am Heart J 2007;154:1086

Risk of Embolism in IE: A Prospective Multicenter Study

Prospective study – 384 consecutive patients with Duke-definite IE

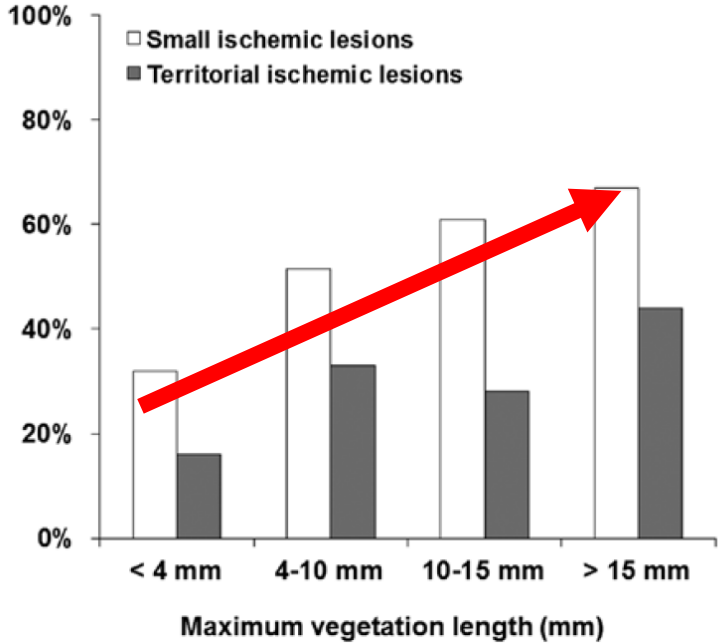
	P	Adjusted Odds Ratio	95% CI
Vegetation length >10 mm	0.004	9	1.98–40.8
Severe vegetation mobility	0.04	2.4	1.02–5.42
S bovis	0.19	1.9	0.73–4.74
S aureus	0.12	2	0.84–4.76

Typical profile of IE with high risk of embolism:
- large (10 to 15 mm) and mobile vegetation
- on the mitral valve
- caused by *S. aureus* or group D streptococci

Thuny F. Circulation 2005;112:69

Factors associated with cerebral ischemic lesions (IMAGE study)

- Multivariate analysis
  - Vegetation length
    - OR 1.10 per mm
    - 95% CI 1.03–1.16
    - *P*=0.003
  - IE due to *S. aureus*
    - OR 2.65
    - 95% CI 1.01–6.96
    - *P*=0.05



Above 4 mm, every 1-mm increase in vegetation size is associated with a 10%-increased risk of ischemic lesion

B. Iung, Stroke 2013;44:3056

Predicting the occurrence of embolic events: an analysis of 1456 episodes of IE

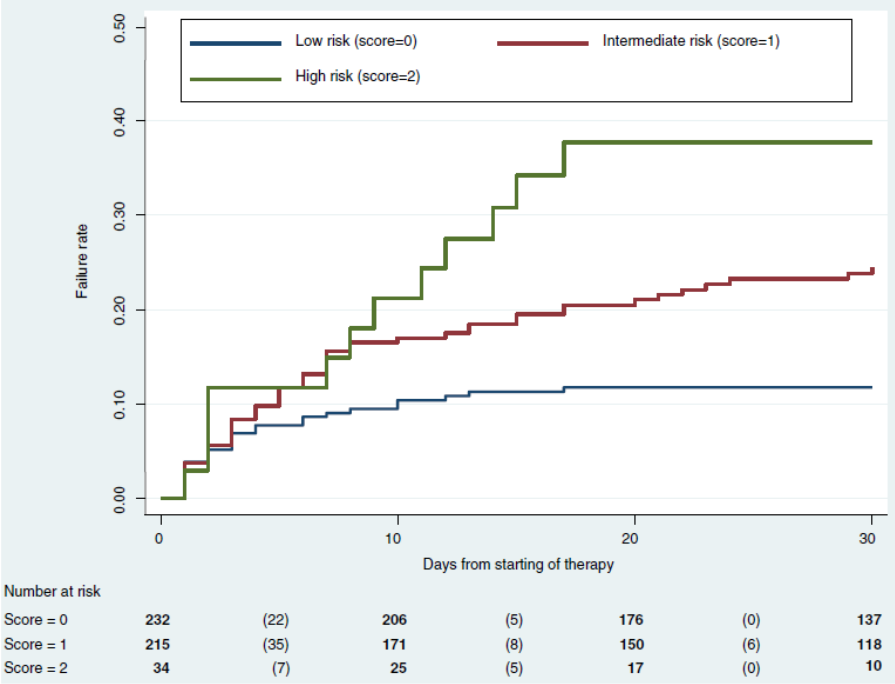
	Odds ratio	95% CI	p ≤ †
Age	1.0	1.0 – 1.0	NS
HIV infection	0.8	0.3 – 2.0	NS
Cancer	1.10	0.7 – 1.9	NS
Chronic liver disease	1.4	0.9 – 2.2	NS
Mitral vs aortic valve	1.0	0.7 – 1.3	NS
Prosthetic vs native valve	**1.8**	**1.2 – 2.9**	**0.011**
Righ-sided IE	**3.9**	**2.0 – 7.7**	**<0.0001**
Size of vegetation ≥ 13 mm	**1.9**	**1.3 – 2.6**	**<0.0001**
Staphylococcus aureus	**2.2**	**1.5 – 3.4**	**<0.0001**

Rizzi et al. BMC Infect Dis 2014, 14:230

Predicting the occurrence of embolic events: an analysis of 1456 episodes of IE

30-day cumulative incidence of embolism

- Low risk : 11.8% [7.2-19.2]
  - Non *S. aureus* etiology
  - and vegetation <13 mm
- Intermediate risk: 24.5% [20.3-37.0]
  - *S. aureus* etiology
  - or vegetation ≥ 13 mm
- High risk: 37.7 [22.1-64.9]
  - *S. aureus* etiology
  - and vegetation ≥ 13 mm



Rizzi et al. BMC Infect Dis 2014, 14:230

Annals of Internal Medicine | ARTICLE

Effects of Early Cerebral Magnetic Resonance Imaging on Clinical Decisions in Infective Endocarditis, the IMAGE study

Xavier Duval , Bernard Iung , Isabelle Klein , Eric Brochet , Gabriel Thabut , Florence Arnoult , Laurent Lepage , Jean Pierre Laissy , Michel Wolff and Catherine Leport and the IMAGE study group.

130 patients admitted to Bichat Claude Bernard Hospital, Paris

(June 2005-Sept 2008)

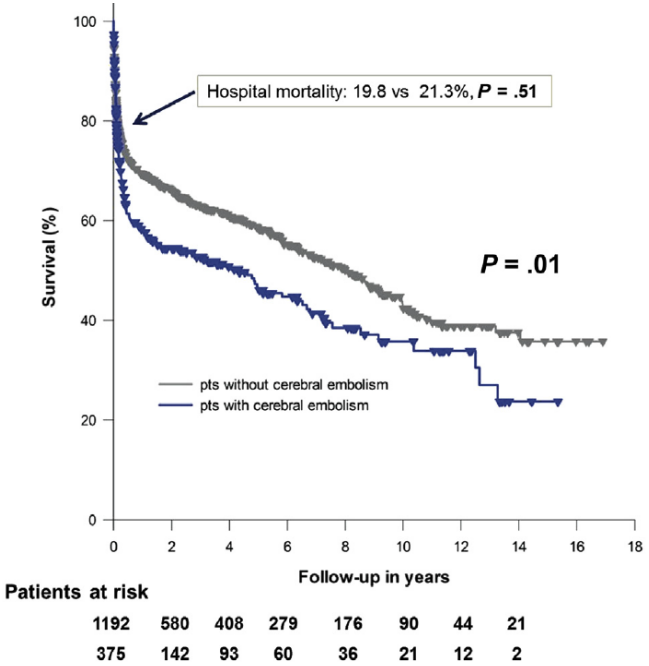
with systematic cerebral MRI (including MRA)

Neurological Complications n=106 — **82%**

16/16 (100%) symptomatic pts
90/114 (79%) asymptomatic pts

Cerebral embolism, whether sysmptomatic or not, is associated with a poorer outcome of IE

- Rate of CV embolism
  - 24% (375/1571 patients)
- 5-year survival
  - w/ CV embolism 46%
  - w/o CV embolism 57% (P<.01)
- 10-year survival
  - w/ CV embolism 42%
  - w/o CV embolism 35% (P<.01)



Misfield, J Thorac Cardiovasc Surg 2014;147:1837-46

How to mitigate the risk of embolism?

- 30-year-old man, known bicuspid aortic valve
  - Admitted to hospital because of high-grade fever
  - New mitral regurgitation murmur
  - Blood cultures: *Haemophilus paraphrophilus*
  - TEE: large (20 mm), oscillating vegetation on the MV, no other complication
  - Afebrile within 48 h of AbRx
- 34 year-old female, no known valve disease
  - Admitted to hospital because of high-grade fever
  - No cardiac murmur
  - Blood cultures: *S. aureus*
  - TEE by day 2 of AbRx: very large vegetation (34 mm) on the aortic valve, no abscess, no regurgitation

How to mitigate the risk of embolism?

1. Keep on with AbRx, and do nothing else
2. Keep on with AbRx, and pray
3. Keep on with AbRx, and push the patient right away to the OR for emergency valve surgery
4. Keep on with AbRx, and do something else

Interventions to reduce embolic risk in IE

- Pharmacologic interventions
  - Anticoagulants
  - Antiplatelet agents
    - Aspirin
    - Other agents

Antiplatelet agents and embolism in IE

Experimental

Nicolau et al 1995, AAC; 39:2748	ASA, impoved Rx... no prevention
Nicolau et al 1996, IJAA; 7:271	Ticlopidine, impoved Rx... no prevention
Nicolau et al 1999, IJAA; 11:159	ASA +ticlo, impoved Rx... no prevention
Kupferwasser et al 1999, Circ; 99:2791	ASA, anti-S. aureus... no prevention
Kupferwasser et al 2003, JCI; 112:222	ASA, pleotropic anti-S. aureus (sigma, arg,sar)
Veloso et al 2015, JID; 211:72	ASA, ticlo, abciximab, dabigatran … prevention

Clinic

Chan et al 2003, JACC; 42:775	ASA during IE, emboli idem, increased hemorrhage
Anavekar et al 2007, CID; 44:1180	ASA pre-IE, less emboli, no hemorrhage increase
Chan et al 2008, CID; 46:37	ASA pre-IE, emboli idem, increased hemorrhage
Pepin et al 2009, CMI; 15:193	ASA pre-IE, emboli idem, decreased mortality
Eisen et al 2009, J Infect; 58:332	ASA pre S.aureus IE, decreased surgery and complications, increased mortality
Anavekar et al 2011, MCP; 86:1068	ASA or statins, less emboli
Snygg-Martin et al 2011, SJID;43:899	AP pre-IE, emboli idem, mortality?
Eisen et al 2015, JID; 2015; corresp.	meta-analysis, less emboli, …more death

Interventions to reduce embolic risk in IE

- Pharmacologic interventions
  - Anticoagulants
  - Antiplatelet agents
    - Aspirin
    - Other agents
  - Thrombolytic agents
    - r-TPA

Successful treatment of IE with r-TPA

- Methods
  - 7 infants/young children with septic shock/MOF and catheter-related IE failing antimicrobial Rx and catheter removal.
  - BC+ in 6 infants (Candida, staphylococci, enterococci)
  - r-TPA given intravenously until vegetation vanishing.
- Results
  - Patients afebrile and BC negative after 3 days.
  - Vegetations no longer visualized after 4 days.
  - Weaning from cardiorespiratory support after 6 days.
  - No bleeding and full recovery in all patients.

Levitas et al J Pediatr 2003

Intravenous thrombolysis is unsafe in stroke due to infective endocarditis

Patient	Age/sex	Presentation	Baseline NIHSS	Time to tPA	Time to IE diagnosis	IE risk factors	Complications	Follow-up NIHSS
1[5]	56/M	Right hemiparesis, dysphasia, HH	15	2 h, 36 min	48 h	None	None reported	4
2[6]	46/M	Left hemiparesis	15	1 h, 50 min	<6 h	IVDU	Multifocal parenchymal haemorrhage	Death
3[6]	65/F	Right hemiplegia, dysphasia, HH	21	2 h, 0 min	24 h	Immunosuppression	Multifocal parenchymal and subarachnoid haemorrhage	NR
4[6]	61/M	Right hemiparesis, dysphasia	21	1 h, 30 min	24 h	None	Multifocal parenchymal and subarachnoid haemorrhage	NR
5[7]	70/M	Right hemiparesis, dysphasia	13	2 h, 30 min	<6 h	Occult malignancy	None reported	5
6[8]	68/M	Right hemiparesis, dysphasia	12	2 h, 15 min	24 h	None	Multifocal parenchymal and subarachnoid haemorrhage	1
7	27/F	Right hemiparesis, dysphasia	15	2 h, 20 min	<6 h	Poor dentition	Early neurological deterioration not due to ICH	1

Brownlee WG, Intern Med J 2014;44:195

Interventions to reduce embolic risk in IE

- Pharmacologic interventions
  - Anticoagulants
  - Antiplatelet agents
    - Aspirin
    - Other agents
  - Thrombolytic agents
    - r-TPA
- Surgical intervention

Indications for surgery in IE Recommendations by the ESC, 2009

Recommendations: Indications for surgery	Timing*	Class[a]	Level[b]
A - HEART FAILURE			
Aortic or mitral IE with severe acute regurgitation or valve obstruction causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B
Aortic or mitral IE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or shock	Emergency	I	B
Aortic or mitral IE with severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor haemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent	I	B
Aortic or mitral IE with severe regurgitation and no HF	Elective	IIa	B
B - UNCONTROLLED INFECTION			
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B
Persisting fever and positive blood cultures > 7–10 days	Urgent	I	B
Infection caused by fungi or multiresistant organisms	Urgent/elective	I	B
C - PREVENTION OF EMBOLISM			
Aortic or mitral IE with large vegetations (> 10 mm) following one or more embolic episodes despite appropriate antibiotic therapy	Urgent	I	B
Aortic or mitral IE with large vegetations (> 10 mm) and other predictors of complicated course (heart failure, persistent infection, abscess)	Urgent	I	C
Isolated very large vegetations (> 15 mm)[#]	Urgent	IIb	C

C: consensus of experts' opinion

Habib G. Eur Heart J 2009;30:2369

Definitions

- Based on emergency level (patient-based)

Indications for surgery	Timing
A. HEART FAILURE	
Aortic or mitral IE with severe acute regurgitation or obstruction causing refractory pulmonary edema or cardiogenic shock	Emergency
Aortic or mitral IE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or shock	Emergency
Aortic or mitral IE with severe acute regurgitation or obstruction and persisting heart failure or signs of poor hemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent
Aortic or mitral IE with severe regurgitation and heart failure easily controlled with medical treatment	Elective

within hours

within days

within weeks

- Based on timing (for descriptive epidemiology)
  - Early: during antibiotic course
  - Very early: within 1st week of treatment

Early Surgery versus Conventional Treatment for Infective Endocarditis

Duk-Hyun Kang, M.D., Ph.D., Yong-Jin Kim, M.D., Ph.D.,
Sung-Han Kim, M.D., Ph.D., Byung Joo Sun, M.D., Dae-Hee Kim M.D., Ph.D.,
Sung-Cheol Yun, Ph.D., Jong-Min Song, M.D., Ph.D.,
Suk Jung Choo, M.D., Ph.D., Cheol-Hyun Chung, M.D., Ph.D.,
Jae-Kwan Song, M.D., Ph.D., Jae-Won Lee, M.D., Ph.D.,
and Dae-Won Sohn, M.D., Ph.D.

N Engl J Med 2012;366:2466-73.

ABSTRACT

BACKGROUND

The timing and indications for surgical intervention to prevent systemic embolism in infective endocarditis remain controversial. We conducted a trial to compare clinical outcomes of early surgery and conventional treatment in patients with infective endocarditis.

Early Surgery versus Conventional Treatment for Infective Endocarditis

- All patients suspected of IE underwent blood cultures and echocardiography within 24 hrs after hospitalization

Inclusion Criteria	Exclusion Criteria
▪ Age: 15-80 years ▪ Definite left-sided native valve IE according to Duke criteria ▪ Severe mitral or aortic valve disease ▪ Vegetation length > 10mm	▪ Pts with urgent indication of surgery moderate to severe CHF, heart block, annular or aortic abscess, penetrating lesions, fungal endocarditis ▪ Pts not candidates for early surgery age > 80 yrs, coexisting major embolic stroke or poor medical status ▪ Prosthetic valve IE ▪ Right-sided vegetations ▪ Small vegetations ≤ 10mm

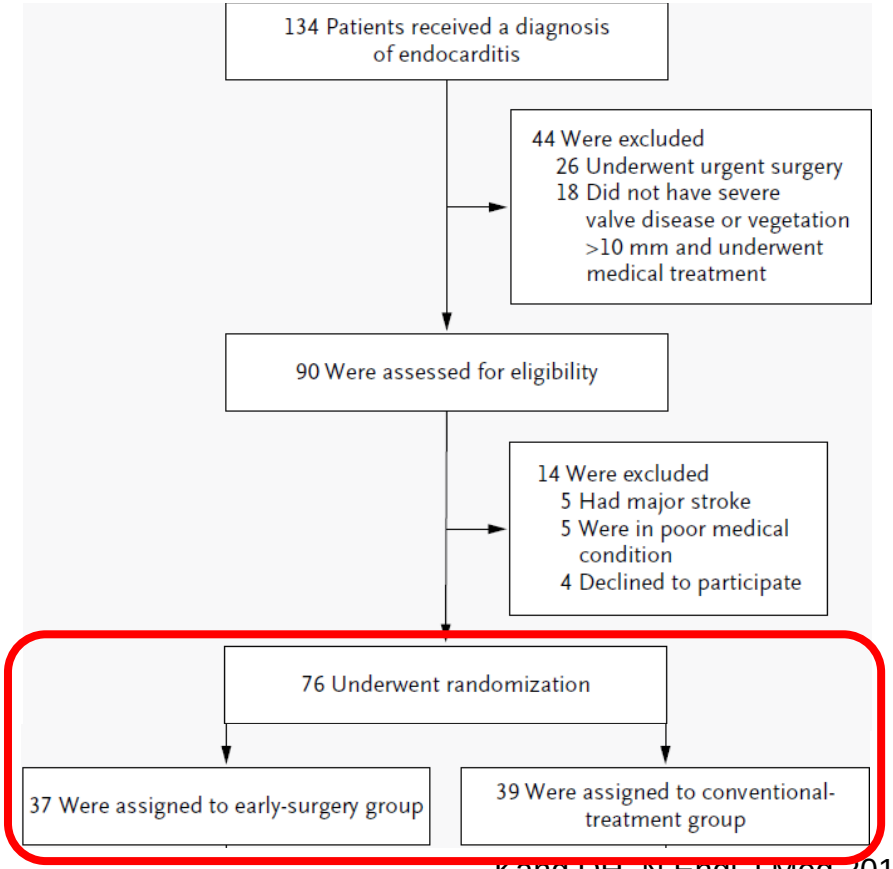
Kang DH, N Engl J Med 2012;366:2466-73

Early Surgery versus Conventional Treatment for Infective Endocarditis

- Randomization arms
  - early surgery (ES): surgery within 48 hours
  - conventional treatment (CT): according to current guidelines
- Primary endpoint (composite):
  - In-hospital death or clinical embolic events within 6 weeks after randomization
- Clinical embolic event:
  - acute onset of clinical symptoms or signs of embolism and the occurrence of new lesions, confirmed by imaging studies.
- Cutaneous manifestations or metastatic abscesses were NOT regarded as embolic events

Kang DH, N Engl J Med 2012;366:2466-73

Early Surgery versus Conventional Treatment for Infective Endocarditis



Kang DH, N Engl J Med 2012;366:2466-73

Early Surgery versus Conventional Treatment for Infective Endocarditis

Primary endpoint (death or major embolic event within 6 weeks)

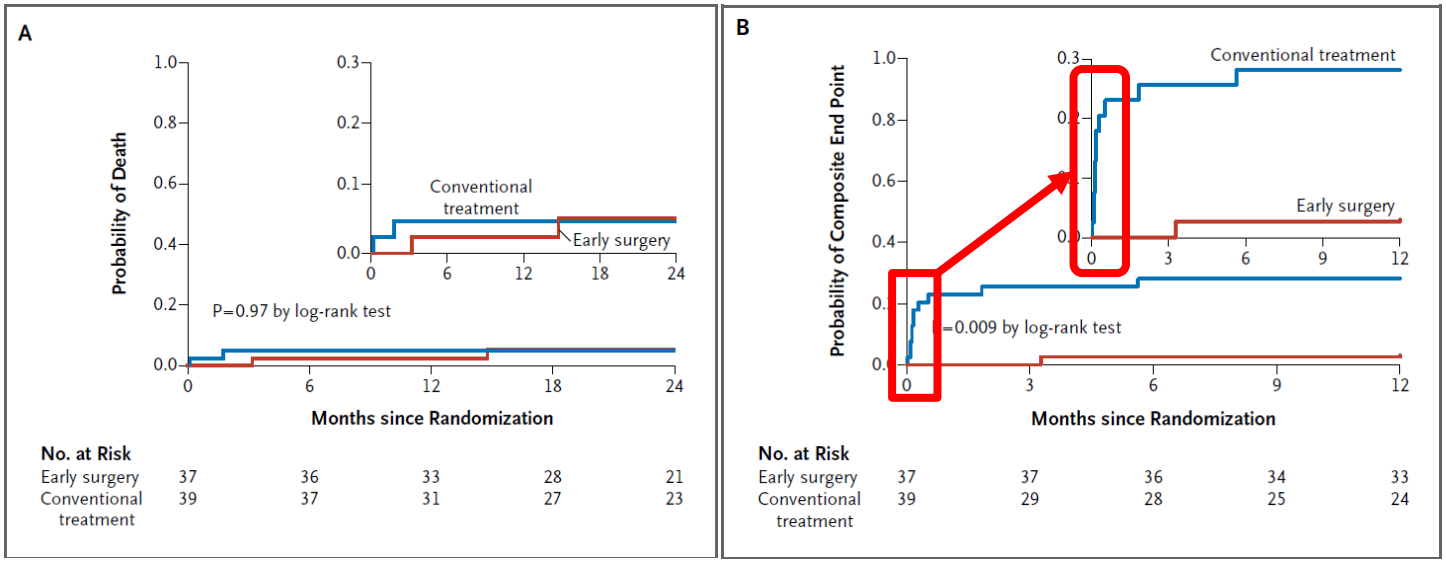
Outcome	Conventional Treatment (N = 39)	Early Surgery (N = 37)	P Value
Primary end point — no. (%)			
In-hospital death or embolic event at 6 wk	9 (23)	1 (3)	0.01
In-hospital death	1 (3)	1 (3)	1.00
Embolic event at 6 wk			
Any	8 (21)	0	0.005

Kang DH, N Engl J Med 2012;366:2466-73

Early Surgery versus Conventional Treatment for Infective Endocarditis

Cumulative probability of death

Cumulative probability of composite endpoint (death or embolic event or recurrence of IE or CHF)



Kang DH, N Engl J Med 2012;366:2466-73

The limitations of the study by Kang et al

- Single-center study – Recruitment took 5 years
- Patients were young (mean age 46 years)
- Only patients with left-sided native valve IE were enrolled
- More than 60% of the cases were due to streptococci
- All-cause, 6-month mortality was 3% in ES and 5% in CT
- 77% of the patients randomized to the CT arm underwent early valve surgery
- Benefit resulted only from the decreased rate of embolic events
  - no impact on short-term mortality

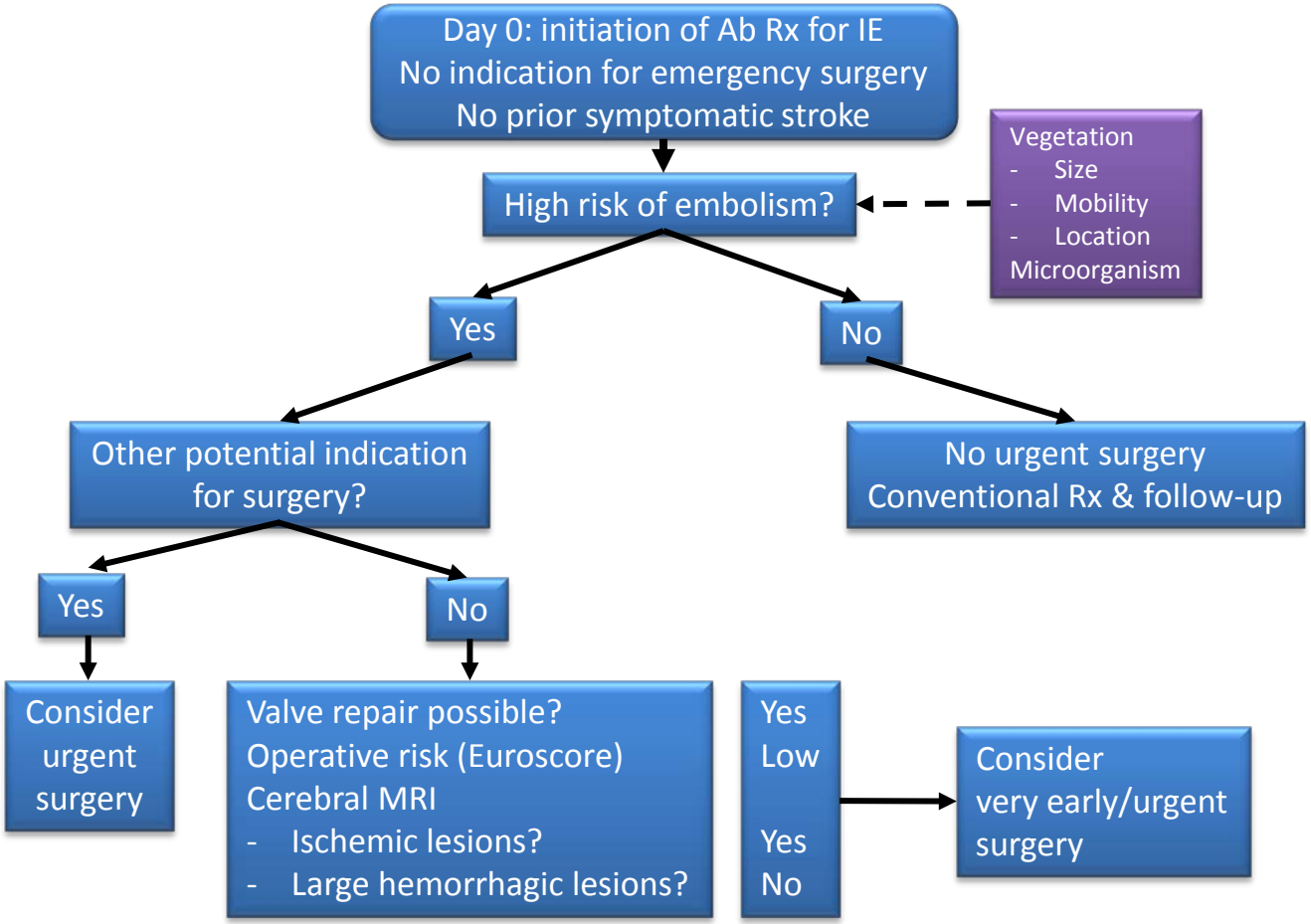
Results of this trial cannot be generalized to support EVS

The timing of surgery influences mortality and morbidity in adults with severe complicated IE: a propensity analysis

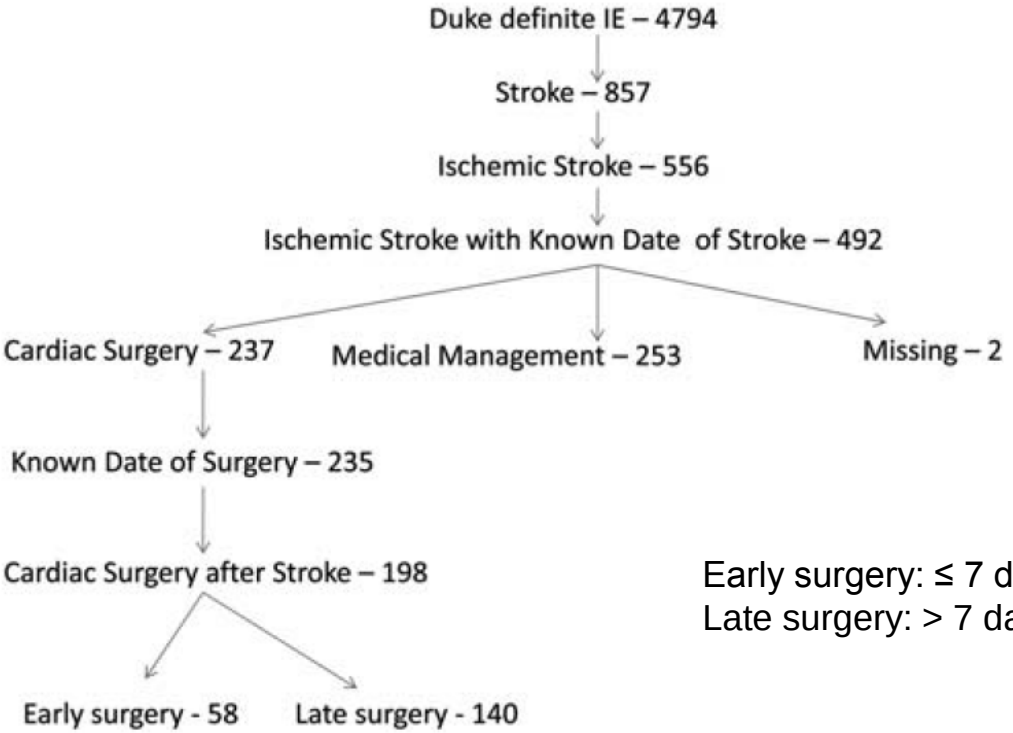
	≤1st week surgery group ($n = 95$)	>1st week surgery group ($n = 196$)	*P*-value
6-month mortality	14 (15)	23 (12)	0.47
Relapses and postoperative valvular dysfunction	15 (16)	7 (4)	0.0005
Relapses	8 (8)	4 (2)	0.02
Postoperative valvular dysfunction	7 (7)	3 (2)	0.02

Thuny F, Eur Heart J, 2009

Indication of EVS for prevention of embolism in an individual patient



Influence of the Timing of Cardiac Surgery on the Outcome of Patients With IE and Stroke

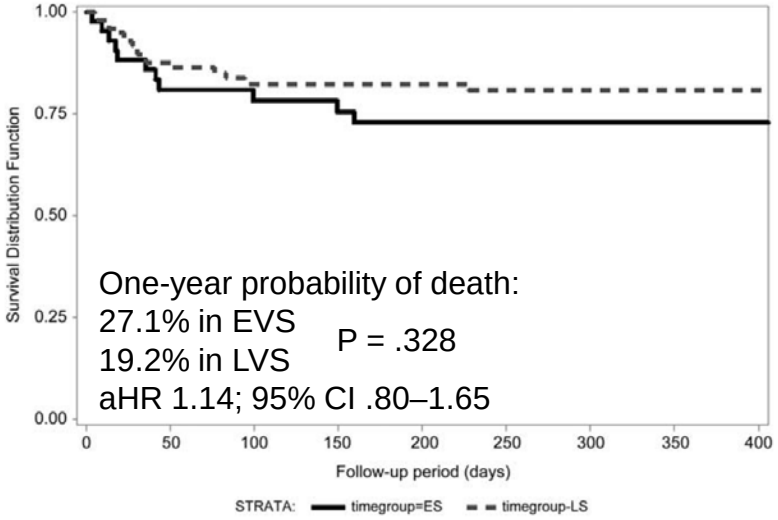


Early surgery: ≤ 7 days after stroke
Late surgery: > 7 days after stroke

Barsic B. et al, Clin Infect Dis 2012

Influence of the Timing of Cardiac Surgery on the Outcome of Patients With IE and Stroke

Indications for Surgery	Time to Surgery Poststroke: 1–7 d (n = 58)	Time to Surgery Poststroke: >7 d (n = 140)	*P* Value
Other systemic embolization (excluding stroke)	26 (44.8)	57 (40.7)	.637
Intracardiac abscess	14 (24.1)	46 (32.9)	.240
Congestive heart failure	20 (34.5)	69 (49.3)	.061
Persistent positive blood cultures	8 (13.8)	10 (7.1)	.174
Mycotic aneurism	1 (1.7)	0 (0.0)	.293
Valve perforation	11 (19.0)	22 (15.7)	.676
Intracardiac fistula formation	1 (1.7)	3 (2.2)	1.000
Hospital mortality	13 (22.4)	17 (12.1)	.082



Variable	In-Hospital Mortality Logistic Regression Analysis: Adjusted OR	95% CI	*P* Value	One-Year Mortality Cox Regression Analysis: Adjusted HR	95% HR Confidence Limits	*P* Value
Early surgery	2.308	.942–5.652	.065	1.138	.802–1.650	.481
Intracardiac abscess	4.529	1.921–11.152	.001	0.990	.688–1.455	.957
Healthcare- associated infection	4.574	1.919–11.093	.001	1.533	.995–2.481	.066

Barsic B. et al, Clin Infect Dis 2012

Neurologic complications and outcomes of infective endocarditis in critically ill patients

- 198 patients with left-sided IE, admitted to ICU
  - 108 (55%) had at least one neurologic complication
    - Ischemic stroke (n=79)
    - Meningitis (n=41)
    - Mycotic aneurysm (n=10)

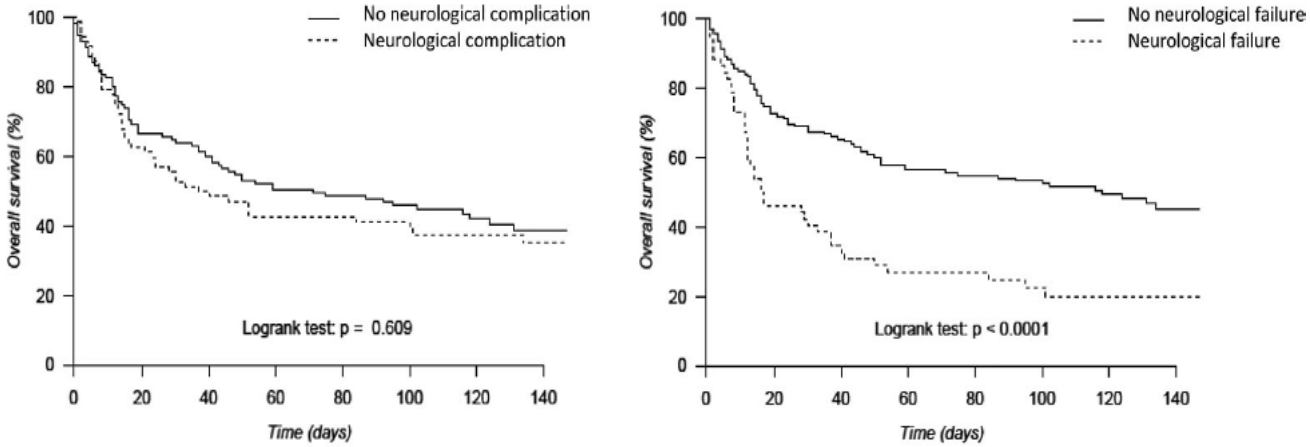
    Hemorrhagic stroke (n=53)

    Intra-cerebral abscess (n=14)
- Factors associated with 3-month mortality (multivariate)
  - Neurologic failure (GCS <10): OR 7.41 [2.89 –18.96],
  - *S. aureus* IE : OR 3.26 [1.53– 6.94],
  - severe comorbidities before admission (Charlson >2): OR 3.16 [1.47– 6.77]

Sonneville, Crit Care Med 2011;39:1474

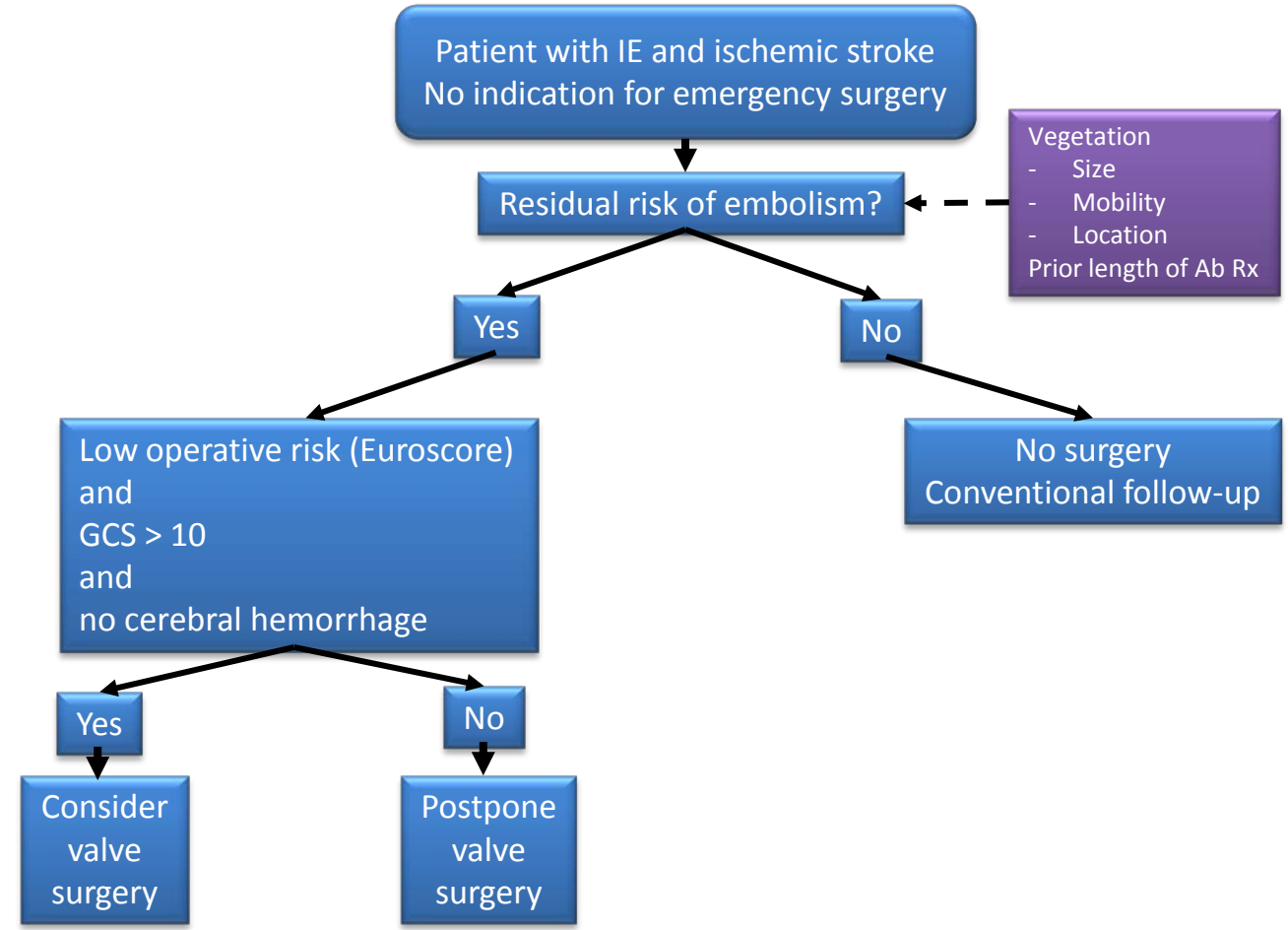
Neurologic complications and outcomes of infective endocarditis in critically ill patients

- Outcome of IE is poorer when neurologic complications were associated with neurologic failure (GCS < 10 on admission to ICU)



Sonneville, Crit Care Med 2011;39:1474

Timing of valve surgery in patients with IE and ischemic stroke



Take home messages

- In 2015, there are no evidence-based data to support the performance of EVS in IE on a systematic basis, for whatever reason
  - (SA)PVIE
  - Fungal endocarditis
  - High embolic risk
- Very early valve surgery (within 48 hours of diagnosis)
  - is the only option for patients with untractable hemodynamic condition
  - may decrease the incidence of embolism in some high-risk situations
  - BUT is associated with higher risk of relapse and/or prosthetic dehiscence
  - therefore CANNOT be recommended on a systematic basis
- The indication of EVS for prevention of embolism MUST be discussed in any IE patient on the 1st day of treatment
- Patient management should involve a multidisciplinary team with expertise in cardiology, cardiac surgery, and infectious diseases

Acknowledgments

- Univ – CHU Besançon
  - Catherine Chirouze
  - Joël Leroy
  - Sidney Chocron
  - Yvette Bernard
  - Isabelle Patry
  - Patrick Plésiat
- Univ – CHU Nancy
  - Christine Selton-Suty,
  - François Alla,
  - Thanh Doco-Lecompte
  - Aurélie Bannay
  - Jean-Pierre Carteaux †
- APH-Paris
  - Xavier Duval
  - Bernard Iung
  - Catherine Leport
- Univ – CHU Lyon
  - François Delahaye
  - Jean-François Obadia
  - Marie Celard
  - François Vandenesch
- Univ – CHU Montpellier
  - Vincent le Moing
- Univ – CHU Rennes
  - Pierre Tattevin, Mathieu Revest

AEPEI

- ICE Coordinating Center (DCRI, Durham, NC)
  - GR Corey
  - V Chu
  - T Harding
  - K Anstrom
  - K Baloch
  - L Clevenger
  - C Dixon
  - M Molina
  - P Pappas
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  - P Moreillon
  - L Olaison,
  - E Rubinstein
  - D Sexton
- Duke Medical Center Endocarditis Service
- Members of the ICE project