
# What is the right timing for valve surgery in IE?

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# Agenda

- Impact of early valve surgery (EVS) on the prognosis of IE
  - is the earlier the better?
- Very early valve surgery (VEVS) for prevention of embolism
- Valve surgery after cerebral embolism in IE

# 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

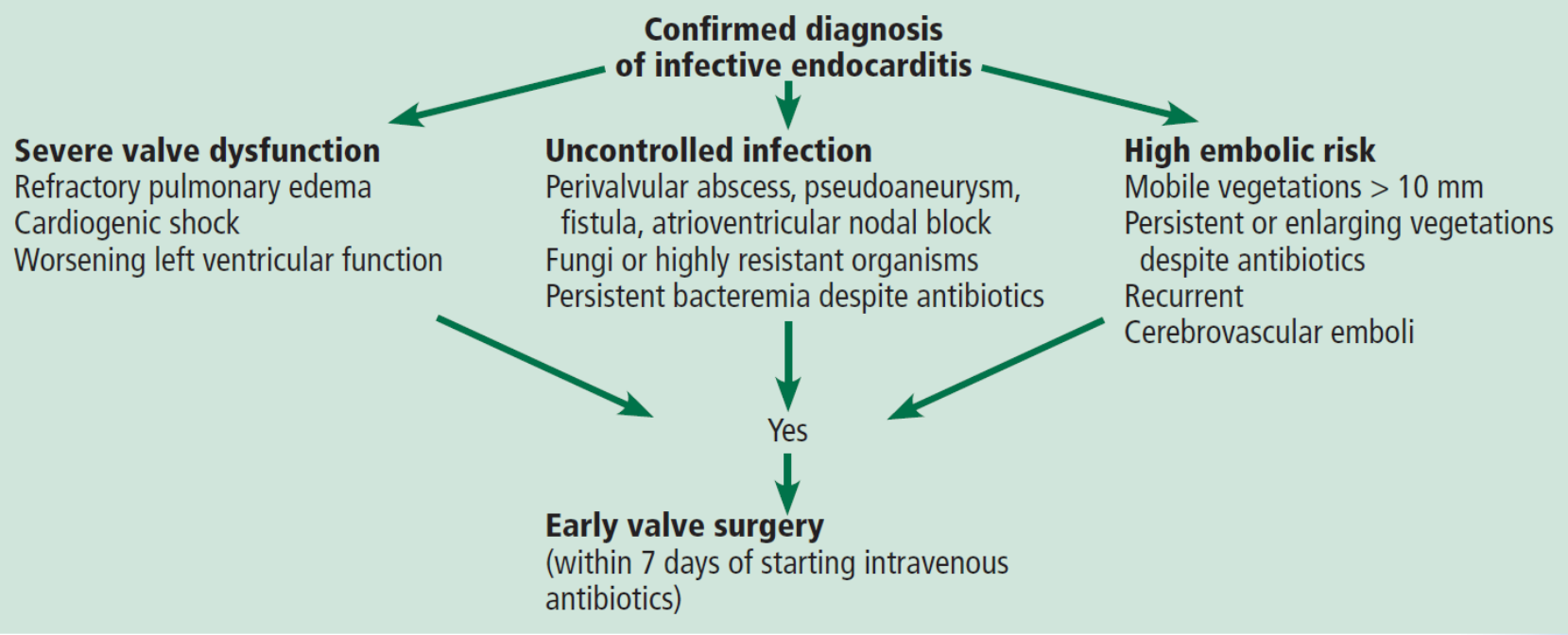
within days

within weeks

- Based on timing (for descriptive epidemiology)
  - Early: during antibiotic course
  - Very early: within first days of care

# How soon should patients with IE be referred for valve surgery?

## Indications for early valve surgery based on the currently available evidence




Soud M, Clev Clin J Med 2018;85:363

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# Surgery & mortality rates as a function of different variables in 390 patients with IE

| Variable | Total No. (%) | Surgery | | Mortality | |
|---|---|---|---|---|---|
| | | No. (%) | *P* Value | No. (%) | *P* Value |
| All | 390 (100) | 191 (49) | . . . | 62 (16) | . . . |
| Sex | | | | | |
| Women | 113 (29) | 42 (37) | .03 | 20 (18) | .53 |
| Men | 277 (71) | 150 (54) | | 42 (15) | |
| Location | | | | | |
| Only mitral valve | 112 (29) | 52 (46) | <.001 | 20 (18) | .67 |
| Only aortic valve | 136 (35) | 82 (60) | | 22 (16) | |
| Aortic and mitral | 55 (14) | 40 (73) | | 11 (20) | |
| Right-sided or bilateral | 45 (12) | 14 (31) | | 4 (9) | |
| Pacemaker | 18 (5) | 5 (28) | | 2 (11) | |
| Unknown | 24 (6) | 0 | | 3 (13) | |
| Previous heart disease | | | | | |
| Native valve disease | 119 (31) | 67 (56) | .29 | 14 (12) | .20 |
| Prosthetic valve | 63 (16) | 29 (46) | | 15 (24) | |
| Miscellaneous | 23 (6) | 11 (48) | | 3 (13) | |
| No known heart disease | 185 (47) | 83 (45) | | 30 (16) | |
| Microorganisms | | | | | |
| Streptococci | 196 (50) | 106 (54) | .02 | 22 (11) | .02 |
| Enterococci | 29 (7) | 15 (52) | | 5 (17) | |
| Staphylococci | 115 (29) | 43 (37) | | 29 (25) | |
| Others or ≥2 | 31 (8) | 20 (63) | | 5 (17) | |
| No microorganism | 19 (5) | 9 (45) | | 2 (10) | |
| Valve surgery | | | | | |
| Yes | 191 (49) | . . . | . . . | 11% | .02 |
| No | 199 (51) | . . . | | 20% | |

Hoen et al., JAMA 2002;288:75-81

# Indications for surgery in IE

- Benefits of surgery in IE are more supported by clinical experience than evidence
  - Only one (small) RCT
  - Unavoidable biases of observational studies
    - overall, sicker patients are selected for surgery
    - the sickest patients are not operated on

# Bedside prognostication in IE (complicated left-sided IE)

- Retrospective observational cohort of 513 patients with complicated left-sided IE
  - Derivation cohort: 250 patients
  - Validation cohort: 254 patients
- Predictors of 6-month mortality:

| | RR | score |
|---|---|---|
| Altered mental status | 1.98 | 4 |
| Comorbidity | 1.76 | 3 |
| Heart failure | 1.91 | 3 |
| Pathogen ≠ viridans strep | 4.87 | 8 |
| No surgery | 2.45 | 5 |

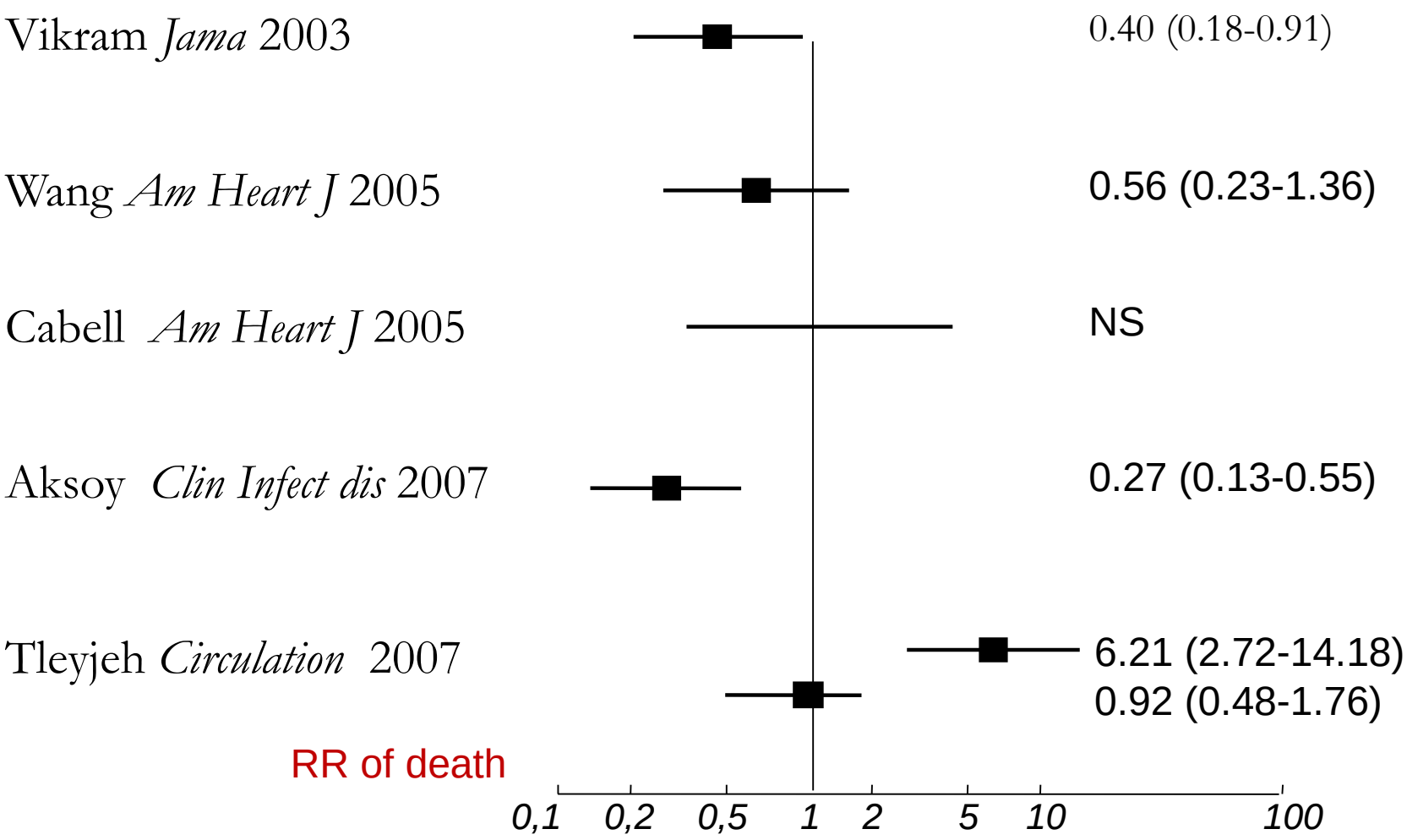
Hasbun R et al. JAMA 2003;289:1933-1940

# Impact of valve surgery on 6-month mortality in adults with complicated LS NV IE: a propensity analysis

- Methods
  - Propensity analyses to control for bias in treatment assignment and prognostic imbalance
  - Observational cohort study (1990 – 2000) of 513 pts:
    - 230 (45%) underwent valve surgery
    - 283 (55%) received medical therapy alone
- Results: mortality at 6 months (overall mortality: 26%)
  - Unadjusted: HR 0.43 (CI 0.29-0.63)
  - Adjusted for heterogeneity: HR 0.35 (CI 0.23-0.54)
  - 218 propensity-matched: HR 0.45 (CI 0.23-0.86)
    - Adjusted for confounding: HR 0.40 (CI 0.18-0.91)
    - Moderate to severe CHF: HR 0.22 (CI 0.09-0.53)

Vikram et al., JAMA 2003;290:3207-14

# Overview of the first 5 propensity analyses of the relation between EVS and outcome of IE



# Overview of the first 5 propensity analyses of the relation between EVS and outcome of IE

| | **Vikram 2003** | **Wang 2005** | **Cabell 2005** | **Aksoy 2007** | **Tleyjeh 2007** |
|---|---|---|---|---|---|
| N | 513 | 367 | 1516 | 426 | 546 |
| Valves | N–L | P–L/R | N–L/R | N/P–//R | N/P–L |
| Format EVS | Binary | Binary | Binary | Binary | Time-dep |
| Endpoint | 6 mo | Hospit | Hospit | 5 years | 6 mo |
| Mortality | ↓ | ↔ | ↔ | ↓ | ↑ |

# How to explain these discrepancies?

- They could be due to real differences (e.g. differences in patient characteristics, differences in hospital management…)
- We hypothesized that they were rather due to differences in methodological approaches (i.e. patient selection, follow-up duration, and modeling methods)
- Actually, methods used in these 5 studies were different for at least 2 essential items:
  - Surgery coding
  - Follow-up duration

# How controversial results may be not that controversial…

## …and propensity analysis may not be the magic bullet some thought it could be

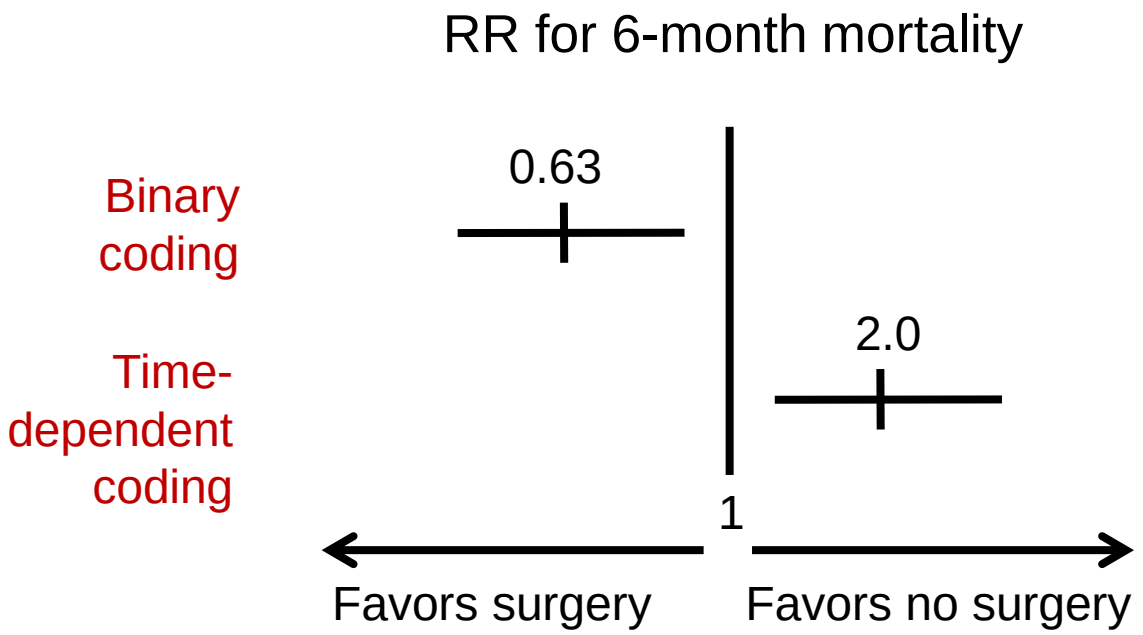
| | | Vikram[8] 2003 | Wang[9] 2005 | Cabell[6] 2005 | Aksoy[5] 2007 | Tleyjeh[7] 2007 |
|---|---|---|---|---|---|---|
| 1. Previous studies: statistical methods and results | **Population definition** | Complicated [a] left-sided native valve IE | prosthetic valve IE | native valve IE | All IE | left-sided IE |
| | **Follow-up duration** | 6 months | Inhospital | Inhospital | 5 years | 6 months |
| | **N° of patients** | 513 | 367 | 1516 | 426 | 546 |
| | **Modelling** | Cox model | Logistic regression | Logistic regression | Cox model | Cox model |
| | **Surgery coding** | Binary variable | Binary variable | Binary variable | Binary variable | Partitioned time-dependent covariate: Short-term [c] / Mid-term [d] |
| | **Adjusted death rate HR or OR (95%CI) of valve surgery** | 0.40 (0.18-0.91) | 0.56 (0.23-1.36) | NS[b] | 0.27 (0.13-0.55) | 6.21 (2.72-14.18) / 0.92 (0.48-1.76) |

A. Bannay et al, Eur Heart J, 2011

# Provisional conclusions (1)

- Discrepencies observed between the 5 propensity studies were largely analytical
  - Analysis methods were incorrect for most of them
    - Survivor bias not addressed (4/5)
    - Follow-up too short (4/5)
    - EVS not entered as a time-dependent variable (4/5)

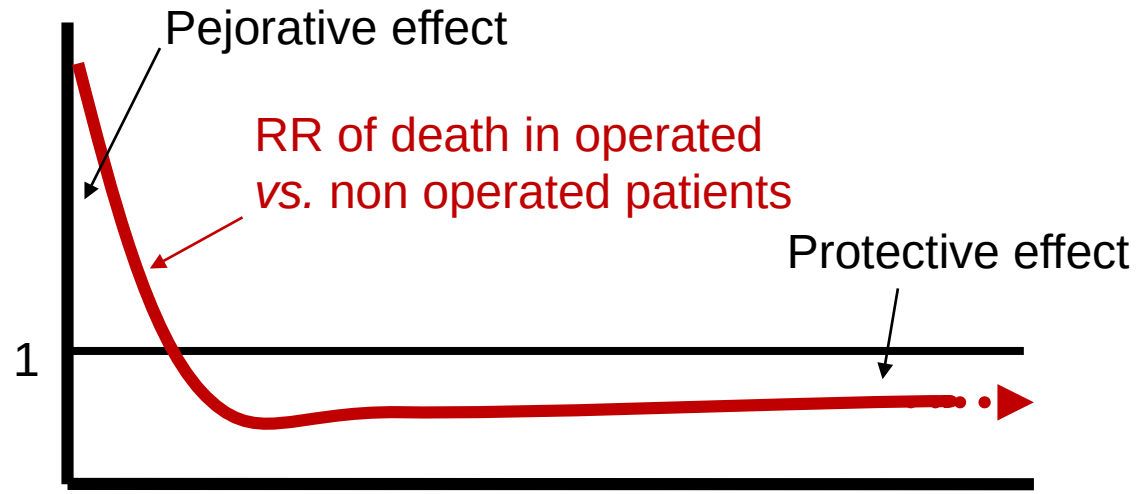
# 1. Surgery coding and survivor selection bias




Data from Hoen JAMA 2002

# 2. Follow-up duration

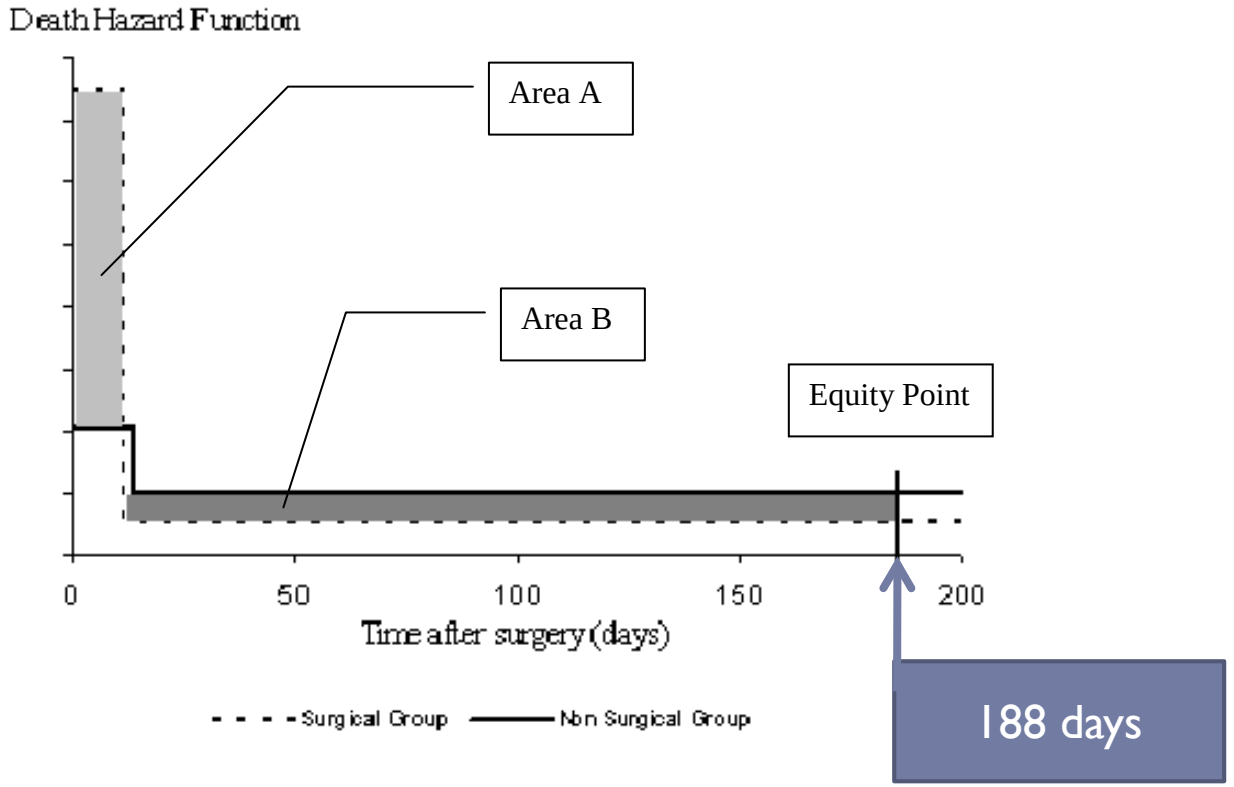
- The relationship between surgery and survival is not linear over time




- Two RRs must be calculated (a short-term and a long-term RR)
- Follow-up duration must be long enough for the high early post-operative risk be offset by the long-term protective effect of surgery

# Death hazard functions over time and equity point

- The equity point is the time at which the area between the surgical group curve and the non surgical group curve during the short-term period (area A) is equal to the area between the surgical group curve and the non surgical group during the long-term period (area B)



# Interpreting results of observational IE studies: what to look at carefully

- Patient population
  - Native valve IE, prosthetic valve IE or both
- Follow-up duration – date of endpoint
  - In-hospital, 6-month, 1-year, or 5-year
- Modeling method
  - Cox or logistic regression
- Adjusting method and bias control
  - Adjustment on propensity or prognosis score, or both (or none!)
  - Control for survivor bias (or not)
- Variable coding (especially for surgery)
  - Binary or time-dependent (one or two time-dependent covariates)

# Provisional conclusions (2)

- Discrepencies observed between the 5 propensity studies may largely be analytical
  - Analysis methods were incorrect for most of them
    - Survivor bias not addressed (4/5)
    - Follow-up too short (4/5)
    - EVS not entered as a time-dependent variable (4/5)
- When analysis fulfills quality criteria, EVS
  - is associated with a higher short-term (< 6 mo) mortality
  - is associated with a lower long-term (≥ 1 year) mortality

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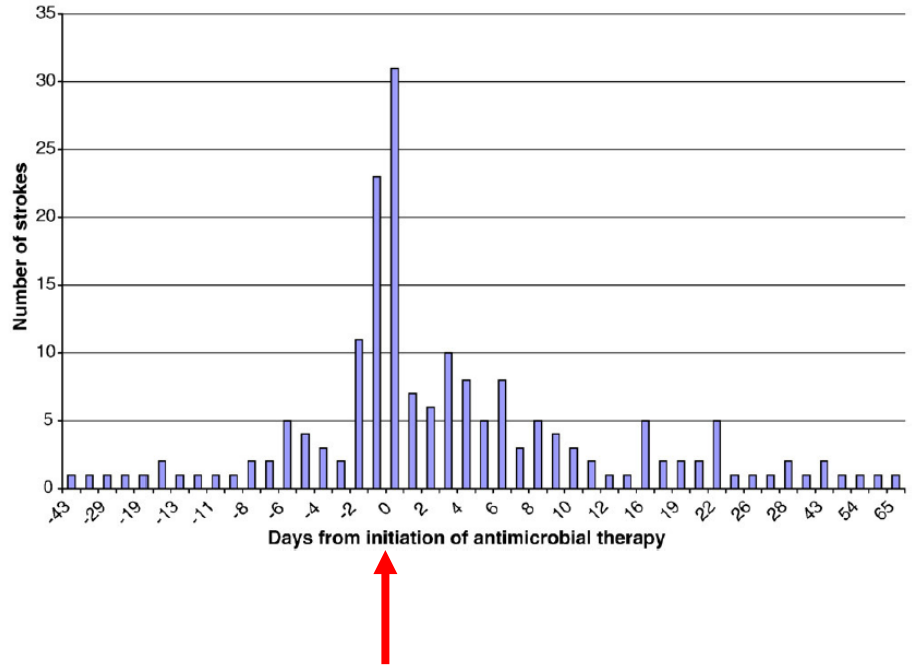
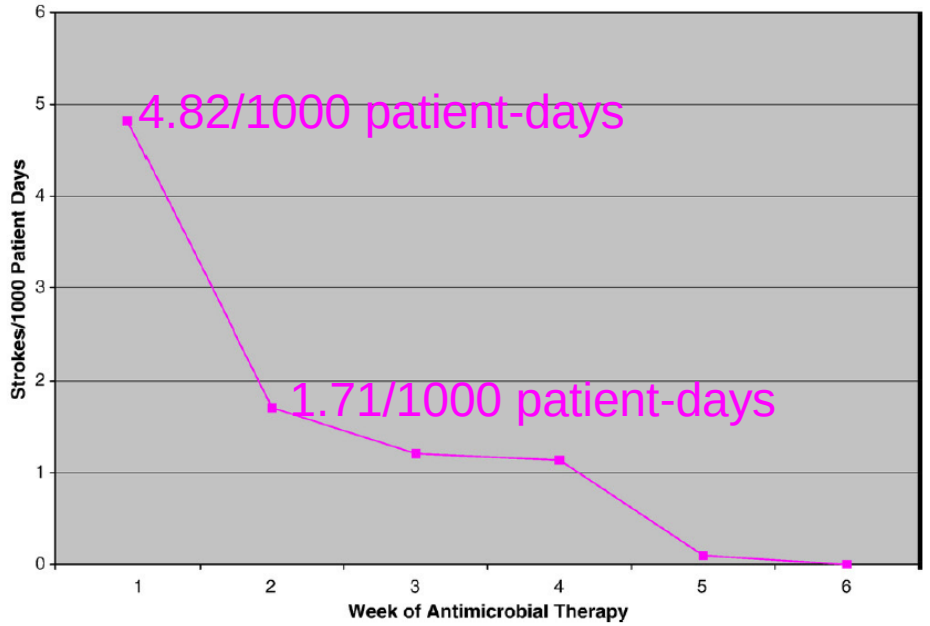
# Relationship between the initiation of antimicrobial therapy and the incidence of stroke in IE

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

**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

| | | | |
|---|---|---|---|
| *S bovis* | 0.19 | 1.9 | 0.73–4.74 |
| *S aureus* | 0.12 | 2 | 0.84–4.76 |

Thuny F. Circulation 2005;112:69

Research

JAMA Intern Med. 2018;178(4):502-510

JAMA Internal Medicine | Original Investigation

# Association of Vegetation Size With Embolic Risk in Patients With Infective Endocarditis

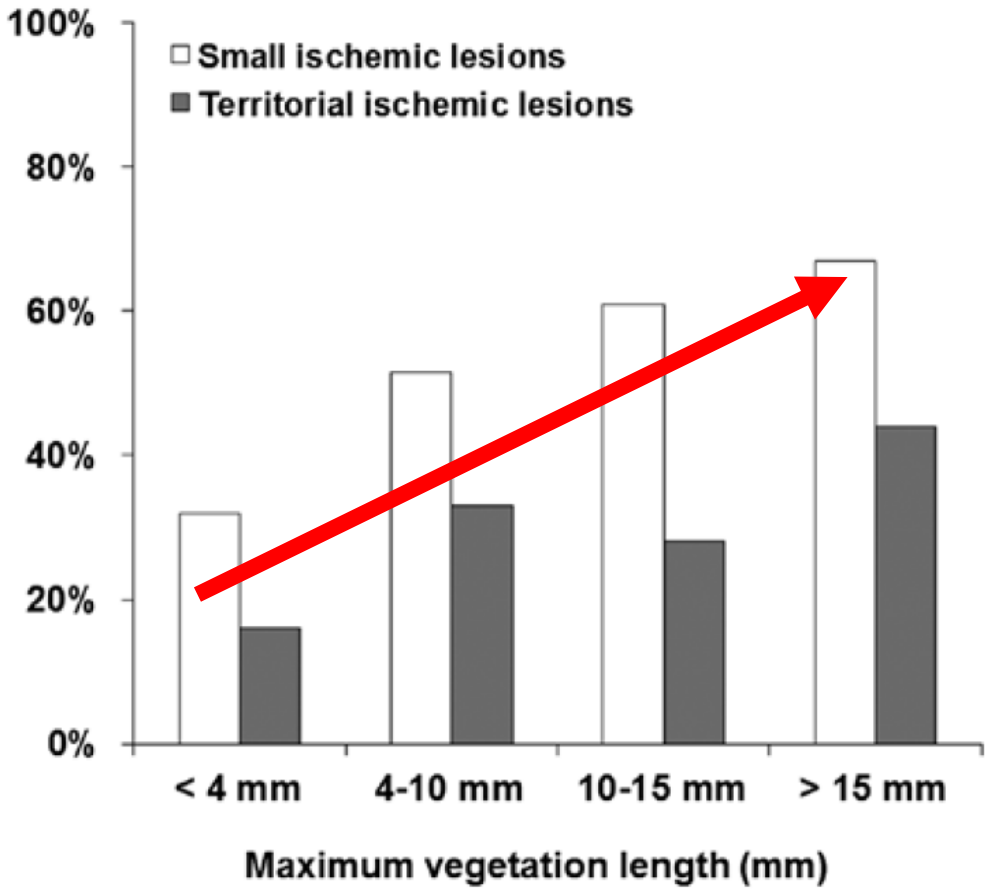
## A Systematic Review and Meta-analysis

Divyanshu Mohananey, MD; Ashley Mohadjer, DO; Gosta Pettersson, MD, PhD; Jose Navia, MD; Steven Gordon, MD; Nabin Shrestha, MD; Richard A. Grimm, MD; L. Leonardo Rodriguez, MD; Brian P. Griffin, MD; Milind Y. Desai, MD

- 21 studies from 1983 to 2016 with a total of 6646 unique patients with IE and 5116 vegetations with available dimensions
- Patients with vegetation >10 mm (vs <10 mm) had higher odds of
  - embolic events OR 2.28; 95%CI, 1.71-3.05; P < .001
  - death OR 1.63; 95%CI, 1.13-2.35; P = .009

# Factors associated with cerebral ischemic lesions

- 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




B. Iung, Stroke 2013;44:3056

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

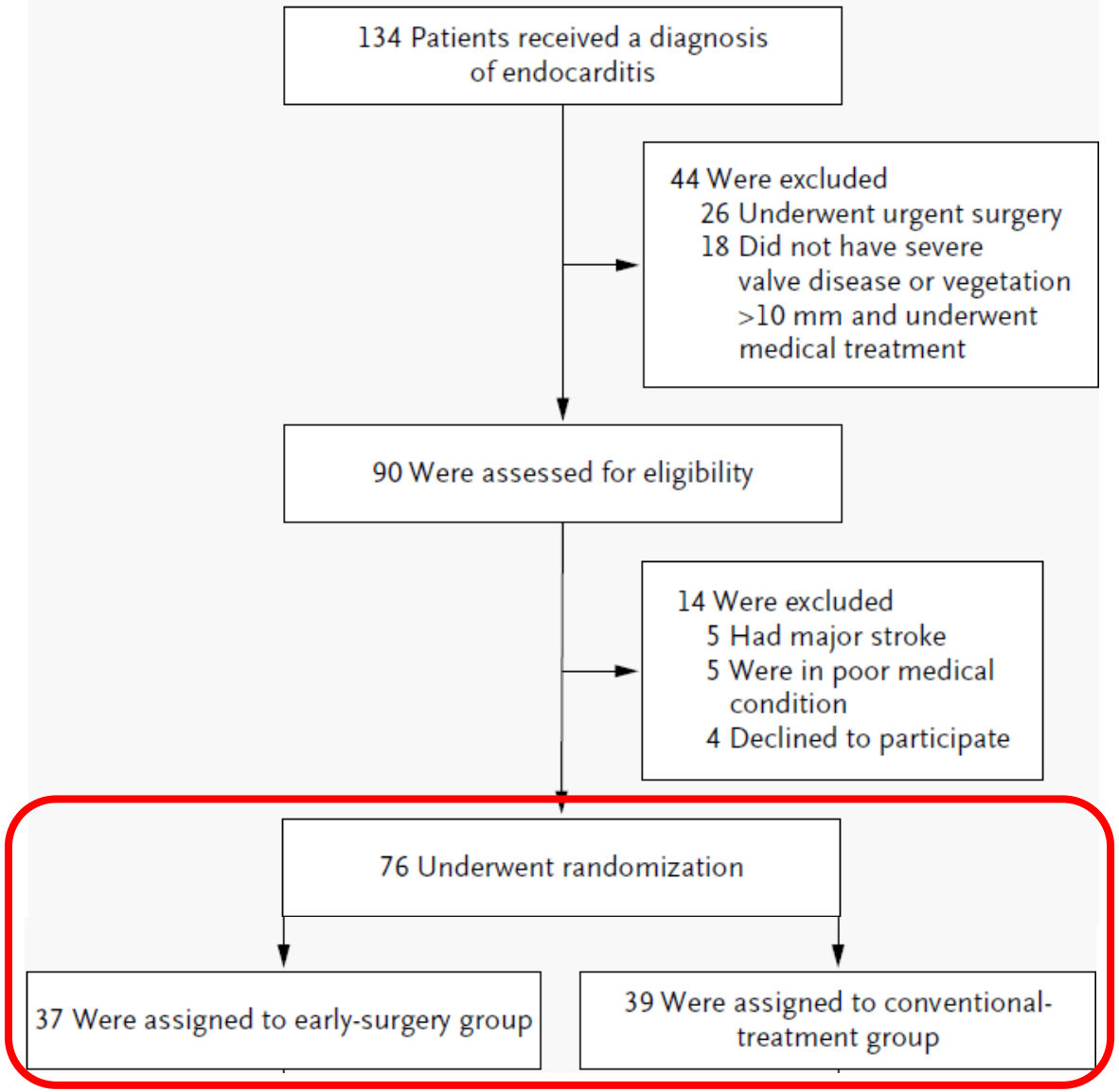
Kang DH, N Engl J Med 2012;366:2466-73

# 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)

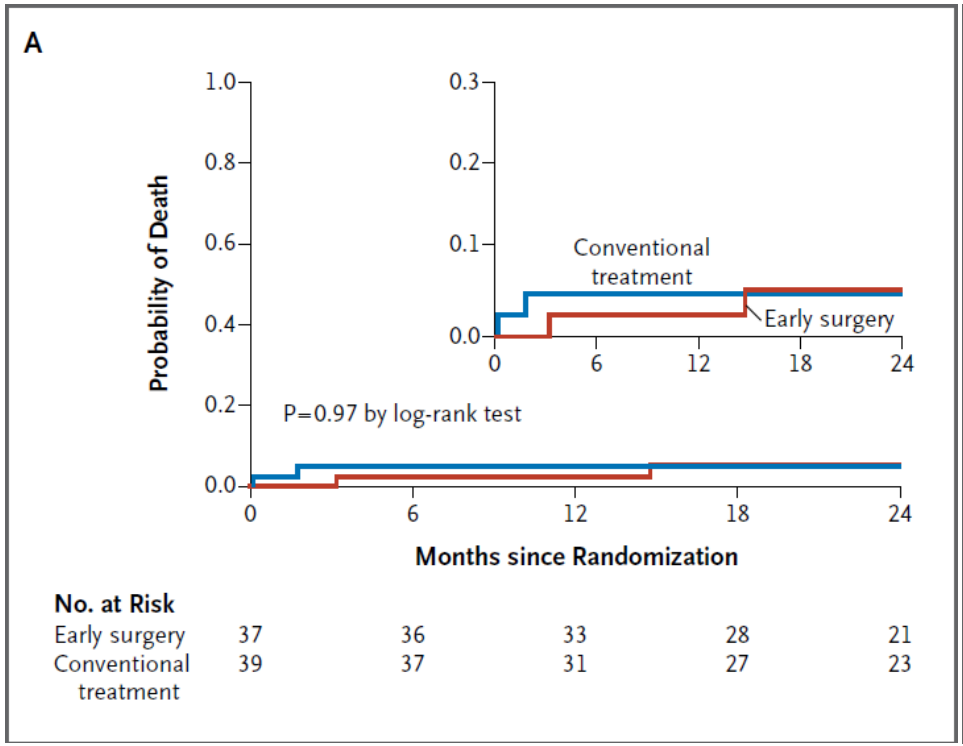
| Outcome | Conventional Treatment (N=39) | Early Surgery (N=37) | P Value |
|---|---|---|---|
| Primary end point — no. (%) | | | |
| In-hospital death or embolic event at 6 wk | 9 (23) | 1 (3) | 0.01 |
| In-hospital death | 1 (3) | 1 (3) | 1.00 |
| Embolic event at 6 wk | | | |
| Any | 8 (21) | 0 |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

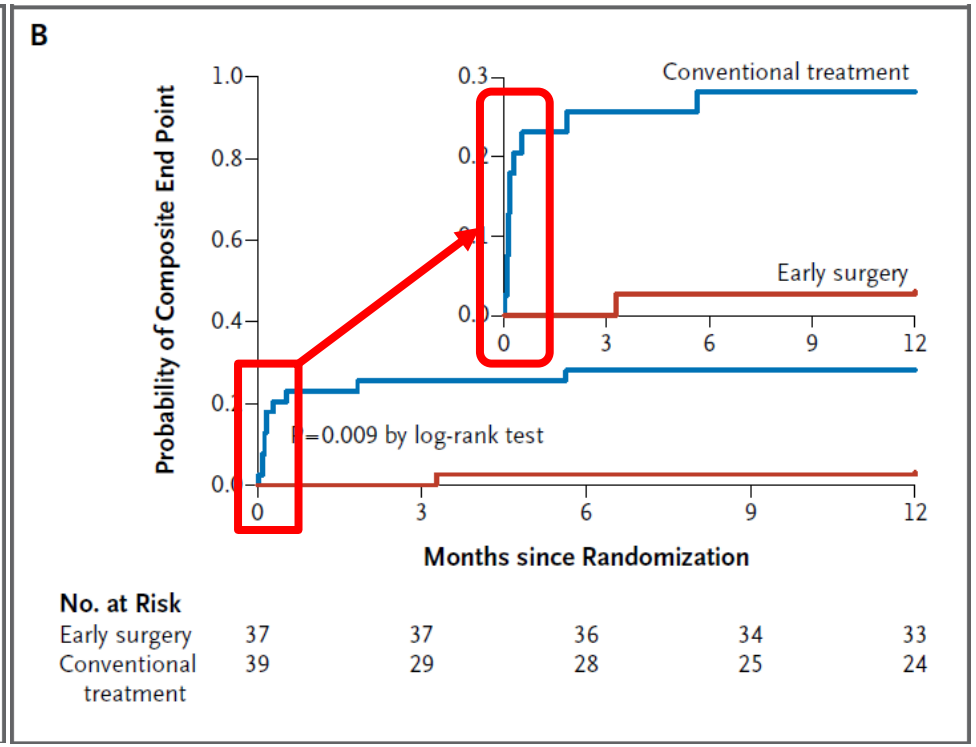
Kang DH, N Engl J Med 2012;366:2466-73

# 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

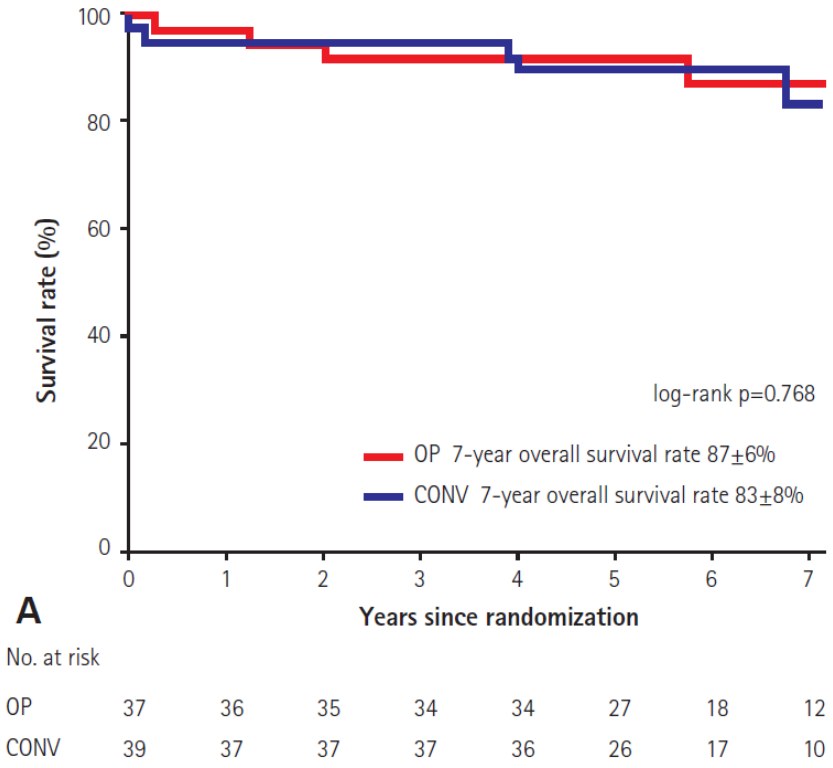
- Single-center study – Recruitment took 5 years
- Patients were young (mean age 46 years)
- Only patients with left-sided native valve IE were enrolled
- More than 60% of the cases were due to streptococci
- All-cause, 6-month mortality was 3% in ES and 5% in CT
- 77% of the patients randomized to the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

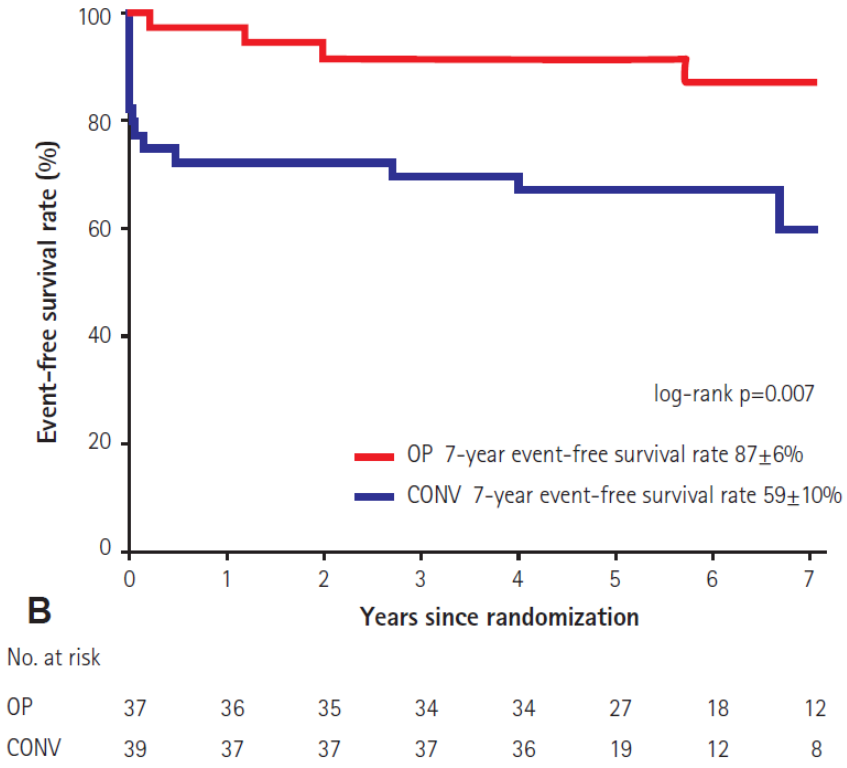
**Results of this trial cannot be generalized to support EVS routinely**

# Long-term results of the EASE trial

- Death from any cause, embolic events or recurrence of IE at 4 years was
  - 8.1% in the EVS group
  - 30.8% in the CT group

  (HR, 0.22; 95% CI, 0.06-0.78; p=0.02)
- No embolic event or recurrence of IE occurred in the EVS group
- 2 embolic events and 1 recurrence of IE in the CT group




Kang, Korean Circ J 2016;46:846

# 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, 2011;32:2027

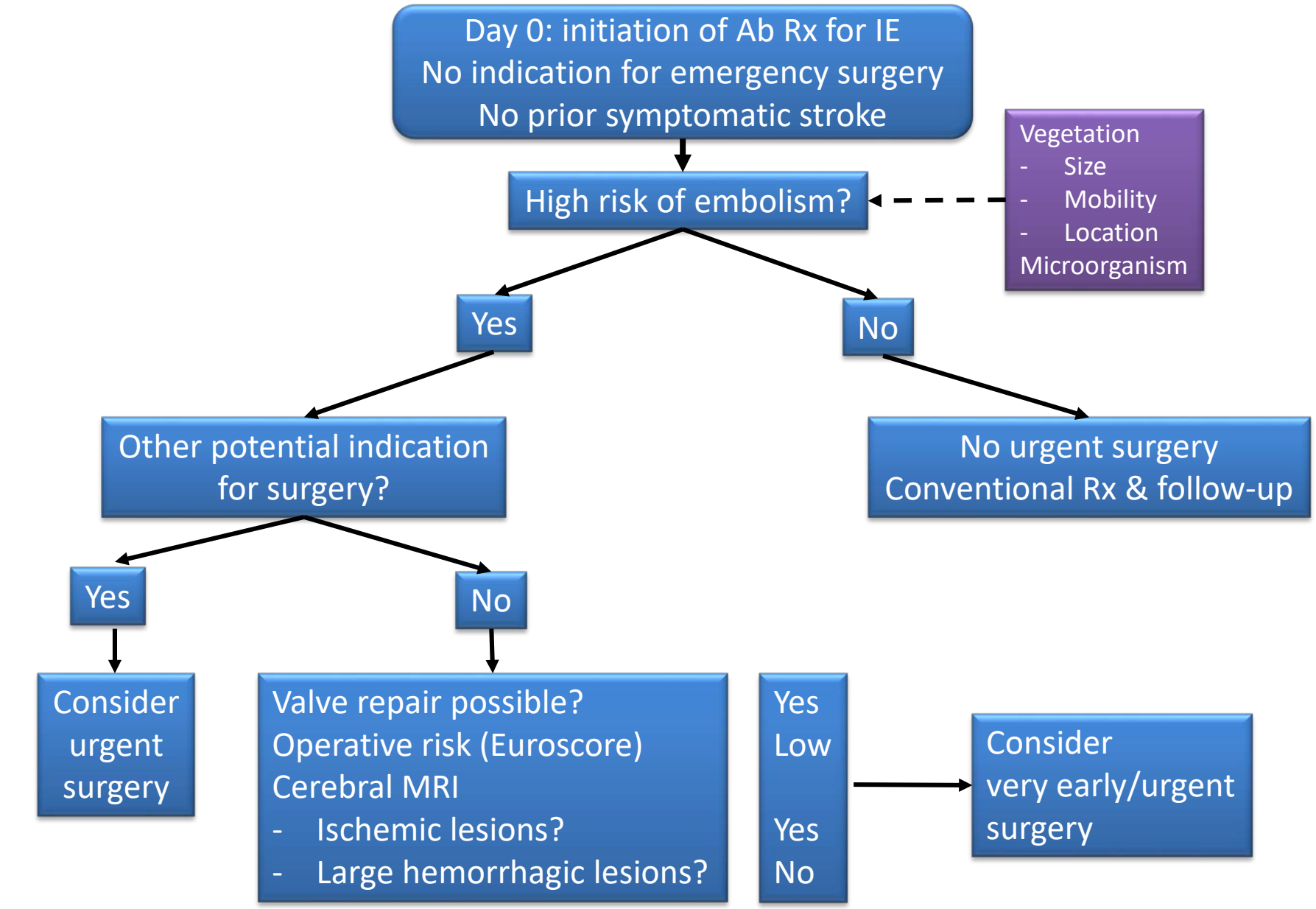
# Chirurgendo

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

Pr Xavier Duval
Centre d'Investigation Clinique – Hôpital Bichat

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

# Indication of EVS for prevention of embolism in an individual patient



# Agenda

- Impact of early valve surgery (EVS) on the prognosis of IE
  - is the earlier the better?
- Very early valve surgery (VEVS) for prevention of embolism
- Valve surgery after cerebral embolism in IE

# Current guidelines: AHA 2017 – ESC 2015

| Organization | American Heart Association | European Society of Cardiology |
|---|---|---|
| Recommendations for surgical timing in patients with endocarditis complicated with an ischemic stroke | (1) Operation without delay may be considered in patients with IE and an indication for surgery who have suffered a stroke but have no evidence of intracranial haemorrhage or extensive neurological damage<br>COR IIb<br>LOE B-NR | (1) After a silent embolism or transient ischemic attack, cardiac surgery, if indicated, is recommended without delay<br>COR I<br>LOE B<br>(2) After a stroke, surgery indicated for HF, uncontrolled infection, abscess, or persistent high embolic risk should be considered without any delay as long as coma is absent and the presence of cerebral haemorrhage has been excluded by cranial CT or MRI<br>COR IIa<br>LOE B |
| Recommendations for surgical timing in patients with endocarditis complicated with a haemorrhagic stroke | (1) Delaying valve surgery for at least 4 wk may be considered for patients with IE and major ischemic stroke or intracranial haemorrhage if the patient is haemodynamically stable<br>COR IIb<br>LOE B-NR | (1) After intracranial haemorrhage, surgery should generally be postponed for ≥1 mo<br>COR IIa<br>LOE B |

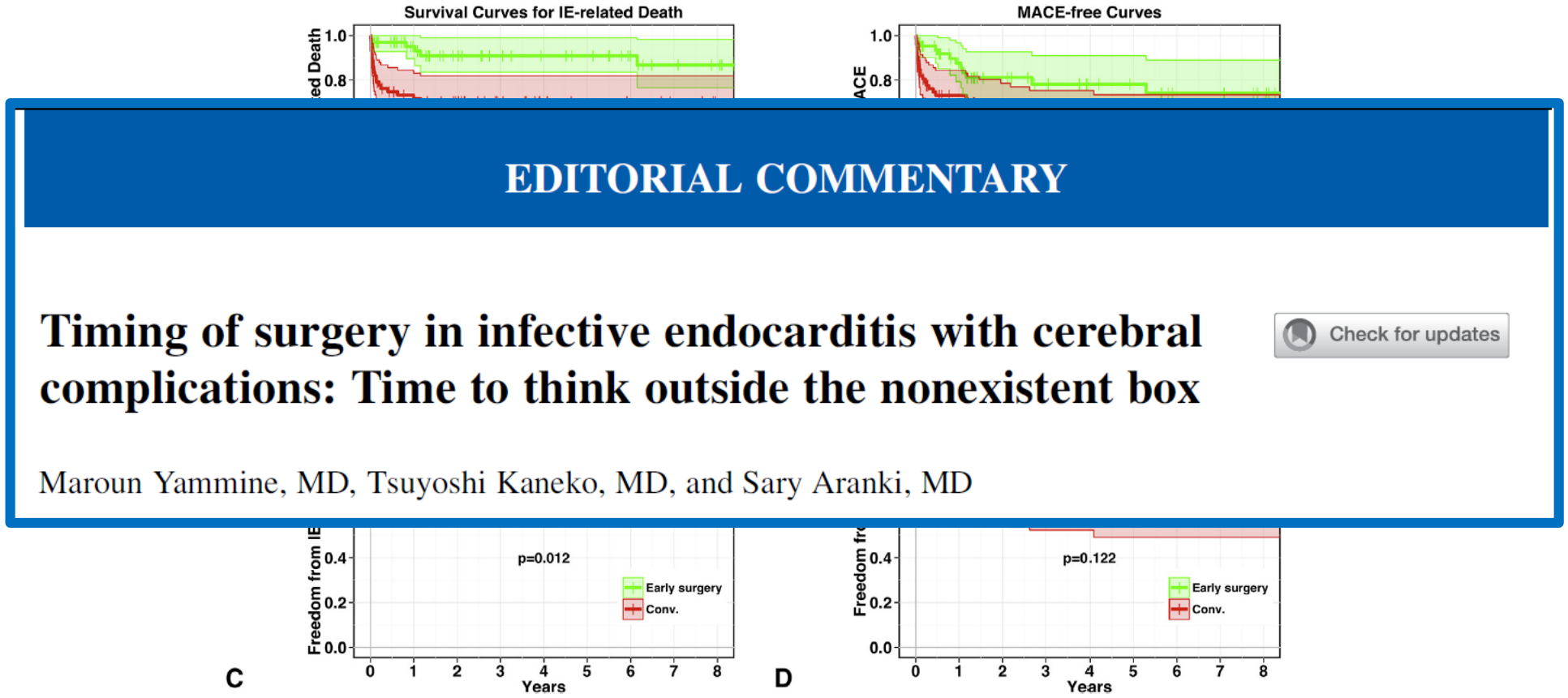
# EVS in patients with mitral valve IE and acute stroke is safe

- 243 patients underwent surgery for active MV IE
  - 72% (174 of 243 patients) with no preoperative stroke
  - 28% (69 of 243 patients) with stroke (33% asymptomatic)
- Postoperative strokes were confirmed in all patients with brain CT or MRI and examination by a neurologist
- Median time from admission to operation: 5 days
- Postoperative stroke
  - 4% among patients with no preoperative stroke
  - 4% among patients with preoperative stroke
  - 1 patient developed an infarct hemorrhagic conversion
- Postoperative mortality
  - 7% among patients with no preoperative stroke
  - 7% among patients with preoperative stroke

Ghoreishi M, Ann Thorac Surg 2018;105:69

# Outcomes of EVS for IE with moderate cerebral complications

Comparison of IE-related mortality and major adverse cardiac events (MACE) between EVS and conventional treatment in patients with nonsevere stroke (NIHSS ≤10)




Murai R, J Thorac Cardiovasc Surg 2017;153:831-40)

# Early vs late valve surgery for patients with IE and neurological injury: a systematic review and meta-analysis

- 27 observational studies
- Using early and late thresholds defined in each study (7 or 14 days), EVS vs LVS in ischemic/hemorrhagic stroke was associated with
  - elevated perioperative mortality (RR 1.74; 95% CI 1.34-2.25)
  - greater neurological exacerbation (RR 2.09; 95% CI 1.32- 3.32)
- In subgroup analysis
  - for ischemic stroke, EVS before 7 vs before 14 days exhibited similar perioperative mortality and neurological exacerbation
  - for hemorrhagic stroke, performing surgery before 21 vs before 28 days showed trends toward
    - higher perioperative mortality (RR 1.77 vs 0.63)
    - neurological exacerbation (RR 2.02 vs 0.44)

DY Tam, Can J Cardiol, 2018;34:1185

# Take home messages

- In 2019, there are no evidence-based data to support the performance of EVS in IE on a systematic basis
- If EVS is indicated, the outcome is better if it is performed
- When indicated, EVS for MVIE complicated by stroke should not be delayed
- VEVS (within 48 hours of diagnosis)
  - CANNOT be recommended on a systematic basis
  - is the ONLY OPTION for patients with severe hemodynamic condition
  - MAY save lives by reducing the risk of embolism in situations associated with a high risk of embolic events
  - BUT is associated with
    - improved survival (both short-term and long-term)
    - higher risk of relapse and/or prosthetic dehiscence

# THANK YOU FOR YOUR ATTENTION