Faculty Disclosure

Franck Thuny

I disclose the following financial relationships:
Philips, Philips, Sanofi, Actelion, Boehringer Ingelheim

Evolution of knowledge from the early clinical description down to the early days of surgery...

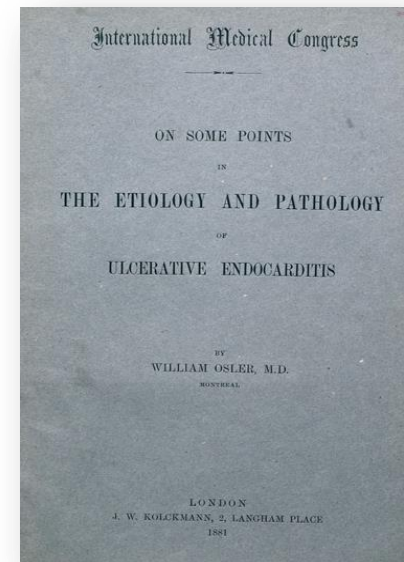Jean Fernel
(1497-1558)

Lazare Riviere
(1589-1655)

William Osler
(1849-1919)

Evolution of knowledge from the early clinical description down to the early days of surgery…

Evidence of endocardial lesions

- Histology
- New regurgitant murmur
- Predisposing heart disease

TTE   TEE   CT Scan   PET-CT Scan

1970s-1990s   1990s-2000s   2000s-2010s

years

- Valve culture
- Blood cultures

Serologies

- PCR
- Immunohistochemistry

Mass spectrometry

Evidence of infection

Evolution of knowledge from the early clinical description down to the early days of surgery…

Mortality (%)

Thuny F, et al. *Lancet* 2012;379:965-75
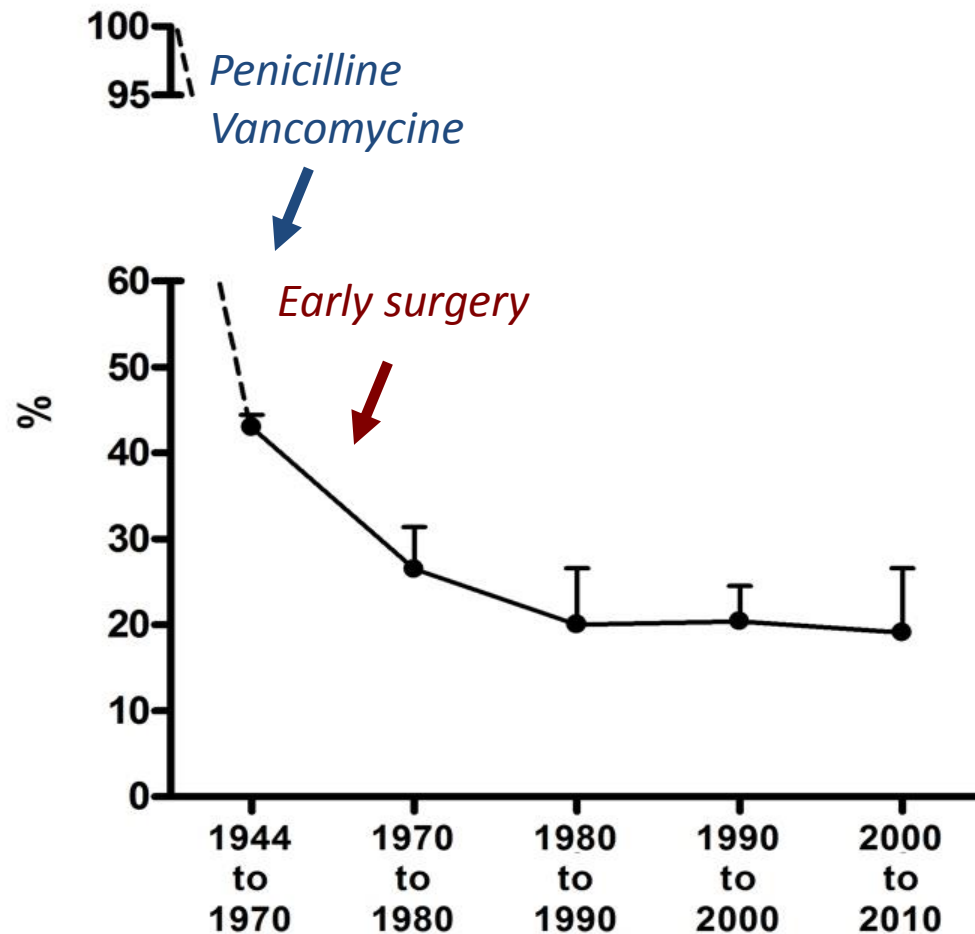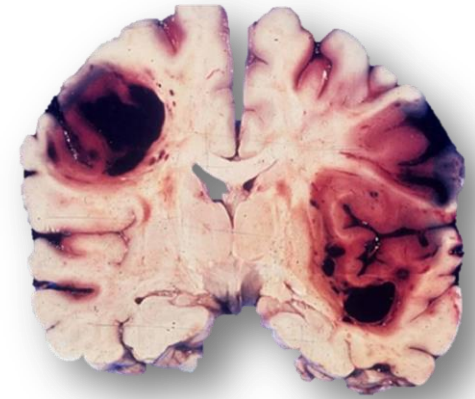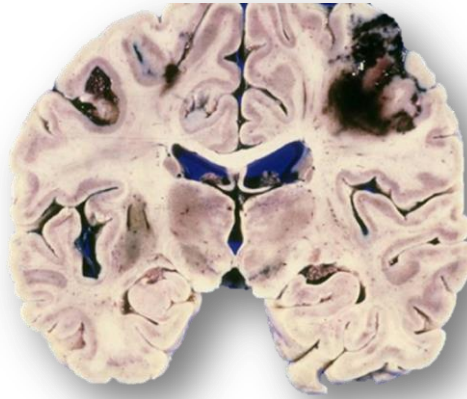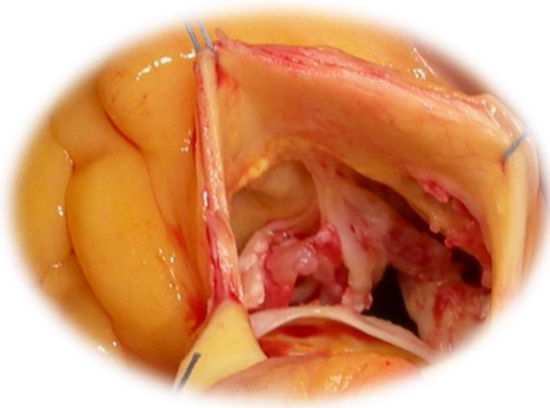
2000 people / year in France
17 000 people / year in USA

1/3 of patients
will die within the 1ˢᵗ year of diagnosis

Research in IE remains very dynamic and offer hope to improve prognosis

WHAT'S NEW IN ENDOCARDITIS ?
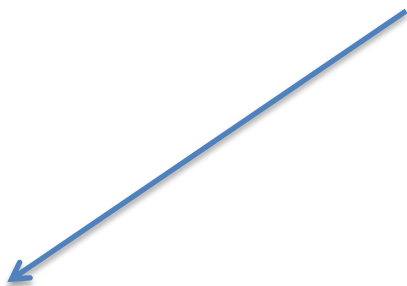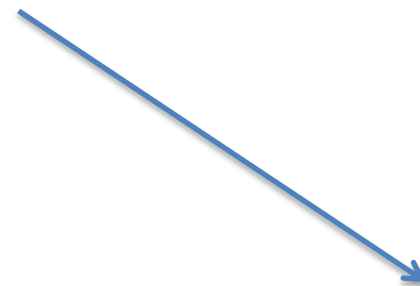
EPIDEMIOLOGY   **PREVENTION**   **MANAGEMENT**

EPIDEMIOLOGY

EPIDEMIOLOGY

Prevention strategies have not lowered the incidence of this life-threatening disease

Incidence per million inhabitant-years

3 successive French Population-based surveys

■ 1991   ■ 1999   ■ 2008

P=0.98

Duval X, et al. J Am Coll Cardiol 2012;59:1968-76
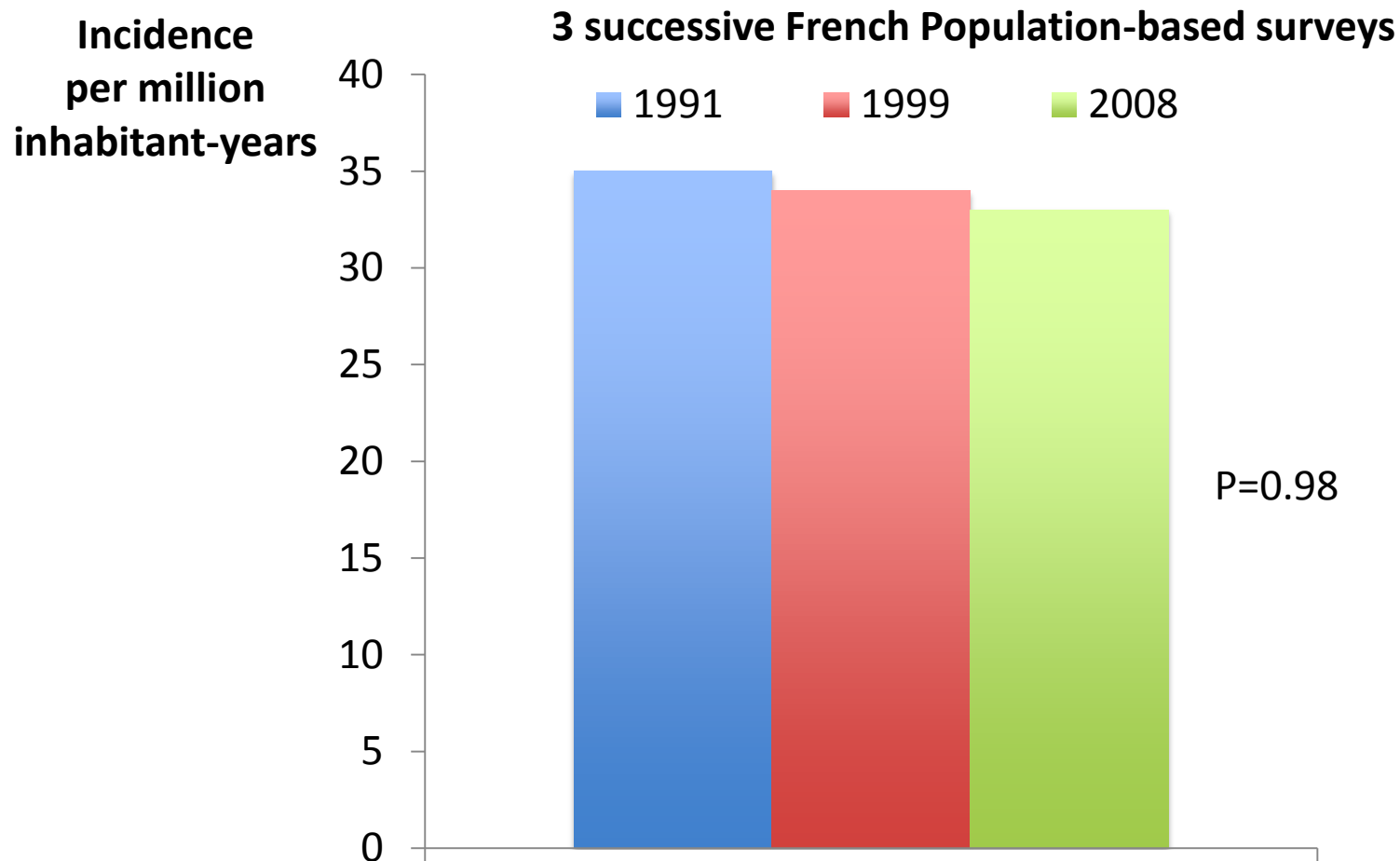
EPIDEMIOLOGY

Epidemiological profile has changed
Increasing proportion of «Health care-associated IE»
30% of cases

Nosocomial
Long-term IV therapy
Hemodialysis
Home care

Federspiel JJ et al, et al. *Arch Intern Med* 2012;172:364-365

Sy RW, et al. *Eur Heart J* 2010;31:1890-1897
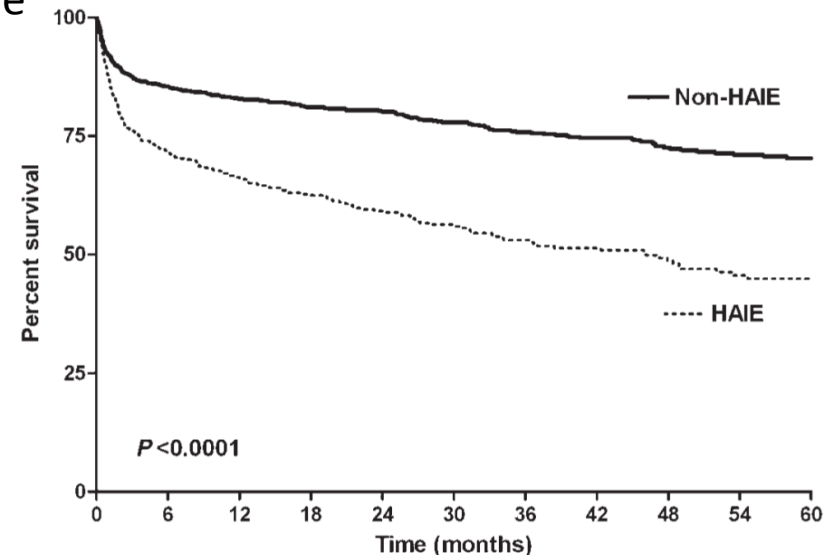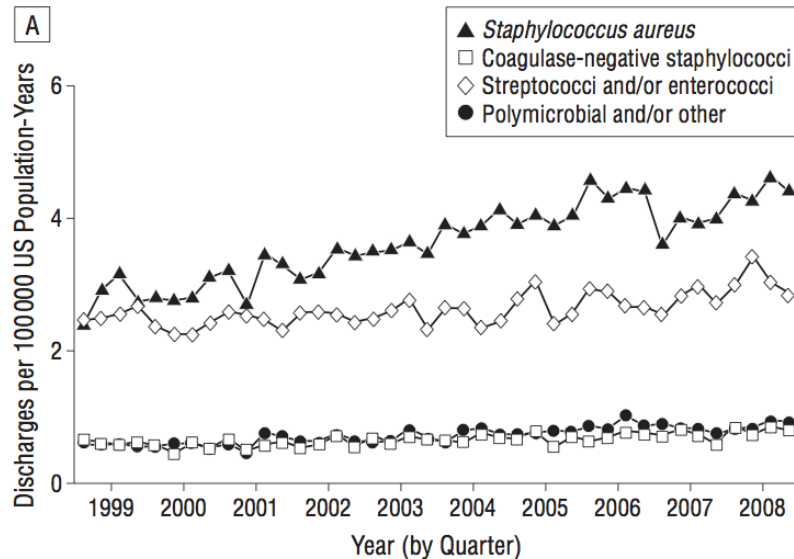
EPIDEMIOLOGY

Epidemiological profile has changed
S aureus is the first causative pathogen

The 2008-French Survey

Selton-Suty C, et al. Clin Infect Dis 2012;54:1230-9
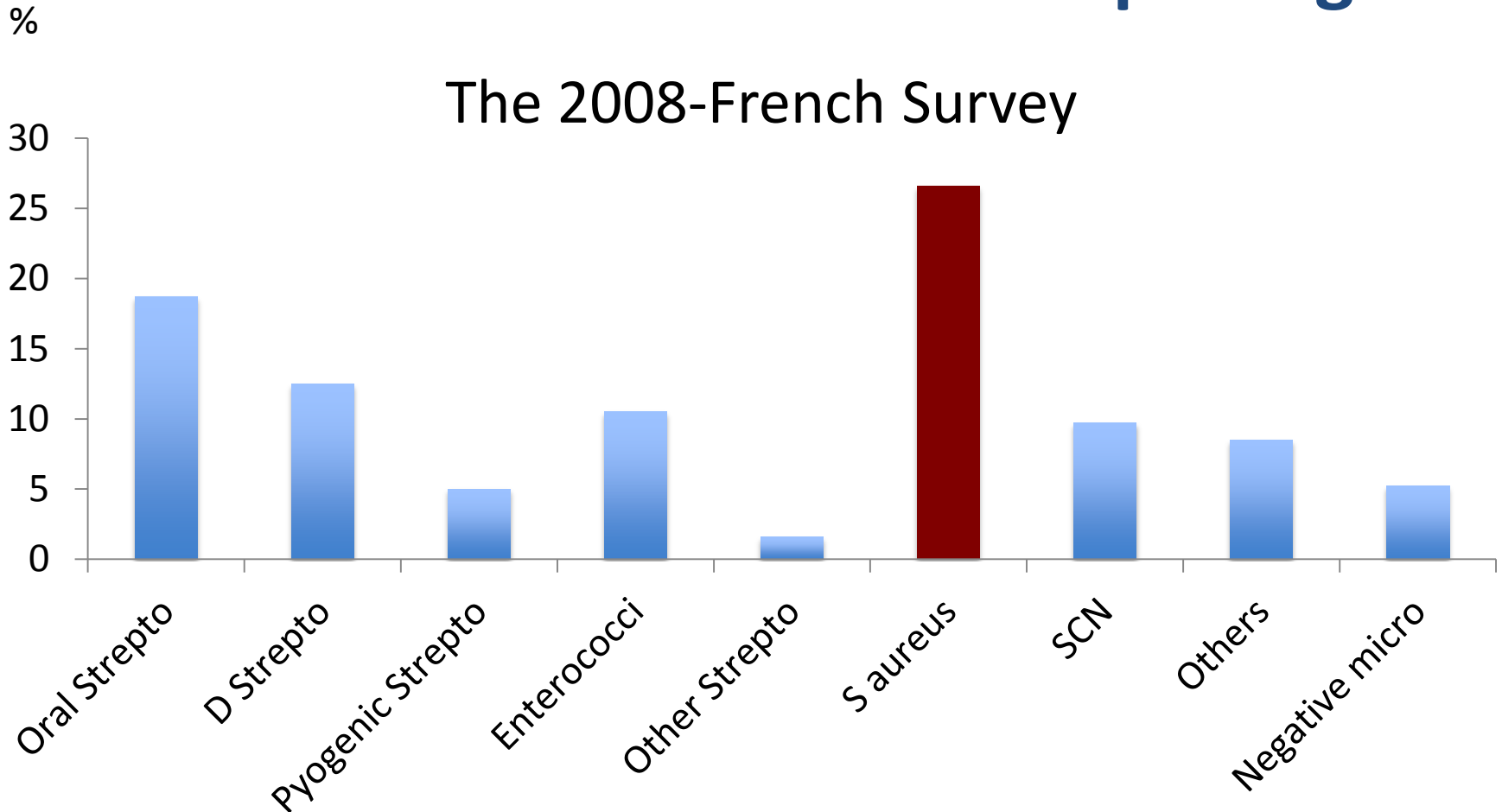
EPIDEMIOLOGY

Epidemiological profile has changed

Prosthetic valve endocarditis

- 1% per patient–year
- Increasing of the number of implantation (plus 5-7% per year)
- PVE=20-30% of all IE
- Emergence of new forms: TAVI++

Pacemaker/ICD leads endocarditis

- 2 per 1000 implants/year
- Increasing of the number of implantation CDIE=15% of all IE

PARTNER Trial
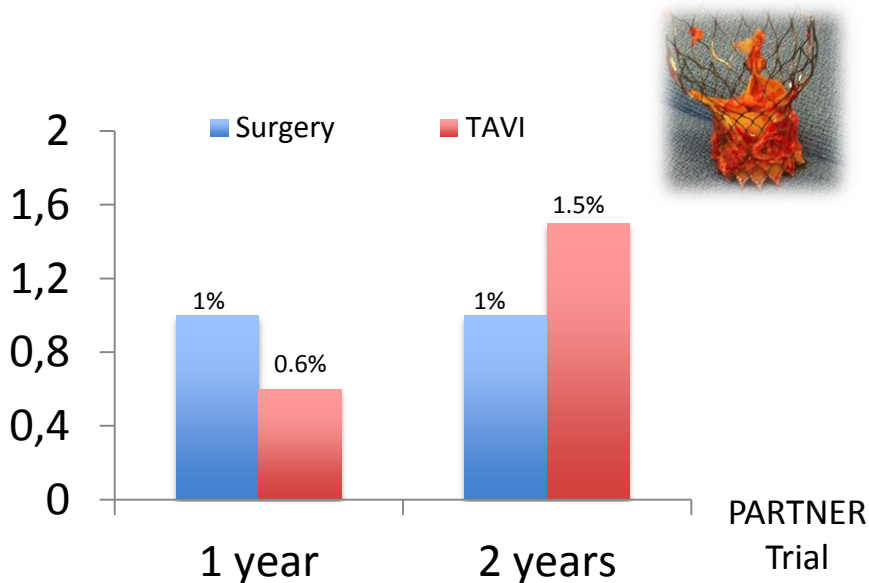
Kodali SK, et al. New Engl J Med 2012;366:168695

Uslan DZ, et al. Arch Intern Med 2007;167:669–75

PREVENTION

PREVENTION

Restriction of the indications of antibioprophylaxis

ESC and ACC/AHA GUIDELINES

Patients

Recommendations: prophylaxis	Class[a]	Level[b]

Antibiotic prophylaxis should only be considered for patients at highest risk of IE
1. Patients with a prosthetic valve or a prosthetic material used for cardiac valve repair
2. Patients with previous IE
3. Patients with congenital heart disease
   a. cyanotic congenital heart disease, without surgical repair, or with residual defects, palliative shunts or conduits
   b. congenital heart disease with complete repair with prosthetic material whether placed by surgery or by percutaneous technique, up to 6 months after the procedure
   c. when a residual defect persists at the site of implantation of a prosthetic material or device by cardiac surgery or percutaneous technique
	IIa	C

Procedure

Recommendations: prophylaxis	Class[a]	Level[b]
A - Dental procedures: **Antibiotic prophylaxis should only be considered for** dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa	IIa	C

Drug

		Single dose 30–60 minutes before procedure	
Situation	Antibiotic	Adults	Children
No allergy to penicillin or ampicillin	Amoxicillin or ampicillin*	2 g p.o. or i.v.	50 mg/kg p.o. or i.v.
Allergy to penicillin or ampicillin	Clindamycin	600 mg p.o. or i.v.	20 mg/kg p.o. or i.v.

PREVENTION

Restriction of the indications of antibioprophylaxis

NICE British GUIDELINES

NEVER !

PREVENTION

Restriction of the indications of antibioprophylaxis

NICE British GUIDELINES

Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study

Antibioprophylaxis presciption
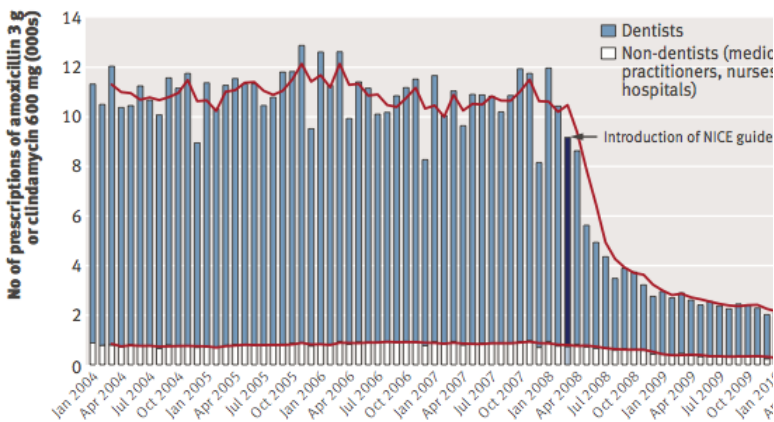
P<0.001

Number of endocarditis cases

P=0.61

Thornhill MH, et al. BMJ 2011;342:d2392
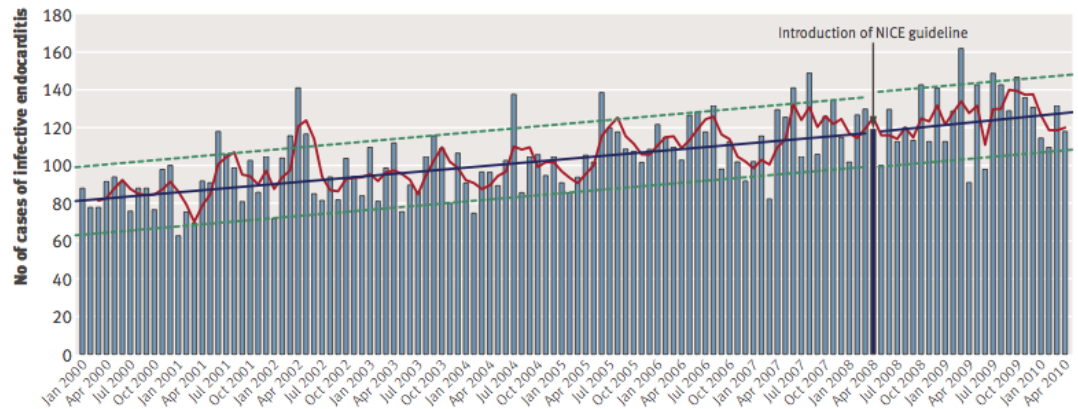
MANAGEMENT

MANAGEMENT

Mortality has not decreased since the last decades

« Residual deaths »

Early surgery

In-hospital mortality
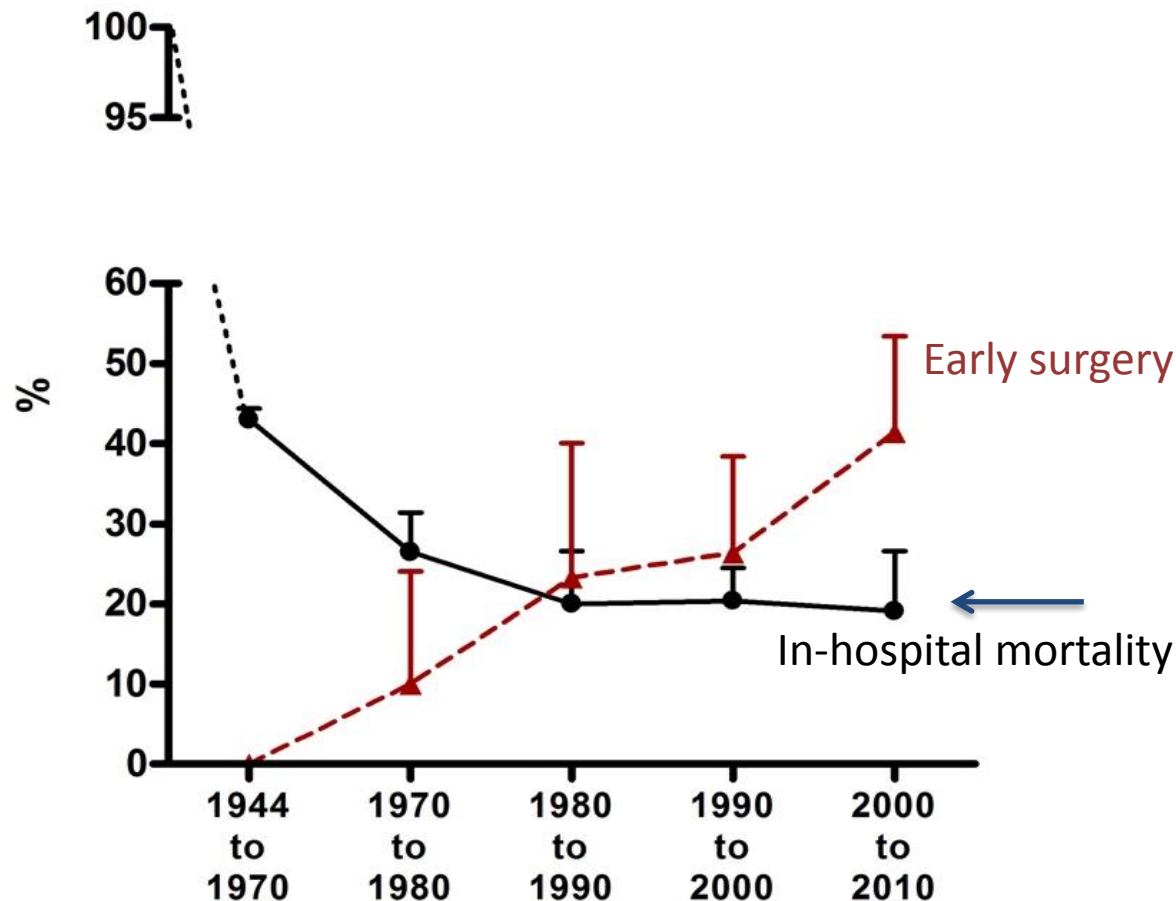
Persistence of high in-hospital fatality rate ≈ 20%

Thuny F, et al. *Lancet* 2012;379:965-75

MANAGEMENT

« Residual deaths »

Causes of death re...

The diagnosis is often done too late

Insufficiencies in prognostic assessment

Thuny F, et al. *Am Heart J* 2012;164:94-101

MANAGEMENT

Challenges in the management

1. Improve the **diagnostic** strategies to reduce the delay of the start of appropriate treatment

2. Improve **prognostic** assessment to identify patients requiring close monitoring and urgent surgery

3. Develop new **medico-surgical strategies**

Improvement of Diagnostic Strategies
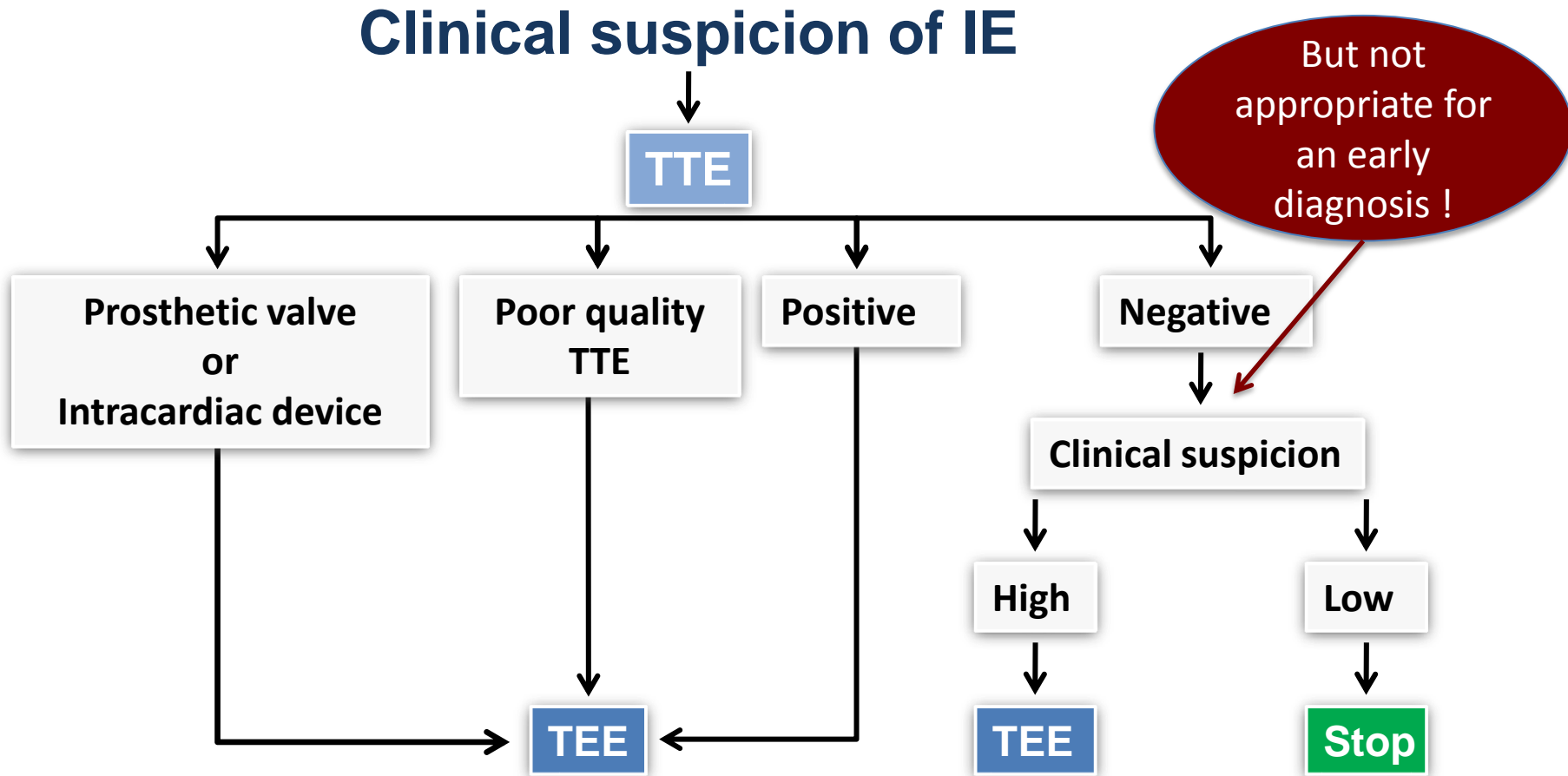
Current Recommendations in Imaging Testing

Clinical suspicion of IE

TTE

But not appropriate for an early diagnosis !

| Prosthetic valve or Intracardiac device | Poor quality TTE | Positive | Negative |

Clinical suspicion

High → TEE

Low → Stop

TEE

If initial TEE is negative but persistent suspicion of IE: repeat TEE within 7-10 days

Improvement of Diagnostic Strategies

Current Recommendations in Imaging Testing

Intitial Echo is Negative or Inconclusive in 20%-30%

(prosthetic valves and intracardiac devices)

Stop

If initial TEE is negative but persistent suspicion of IE: repeat TEE within 7-10 days

Improvement of Diagnostic Strategies

Innovations in the diagnostic strategy have emerged through new Imaging Methods

Systematic Cerebral MRI

Cardiac CT scan

PET-CT Molecular imaging
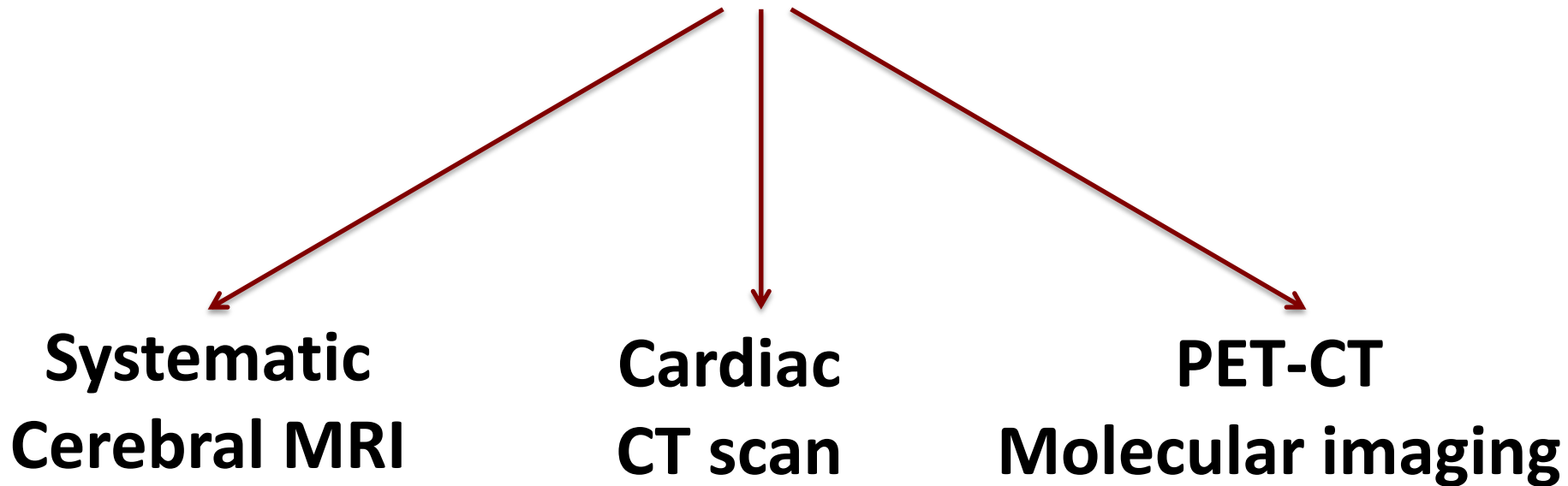
Improvement of Diagnostic Strategies

News in Imaging Testing

Systematic Cerebral MRI

Diffusion
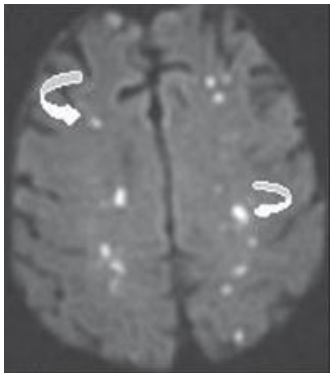
Cerebral infarcts (60%)

T2*
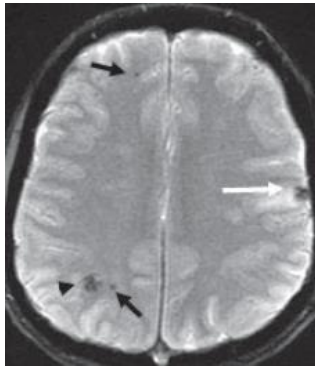
Micro-hemorrhages (60%)

MR angiography
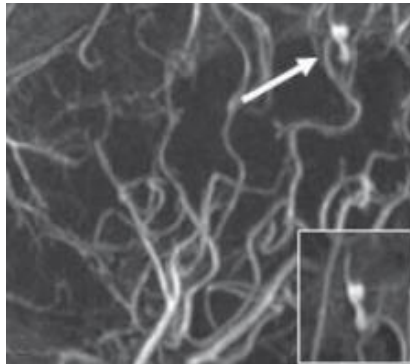
Infectious aneurysms (8%)

- Incidence of neurological events: **65% to 82%**

- Diagnostic reclassification: **32%**

- Therapeutic plans modifications: **18%**

Duval X, et al. Ann Intern Med 2010;152:497-504
Cooper HA, et al. Circulation 2009;120:585-91
Snygg-Martin U, et al. Clin Inf Dis 2008;47:23-30

Improvement of Diagnostic Strategies

News in Imaging Testing

Cardiac ECG-gated CT scan+whole body CT
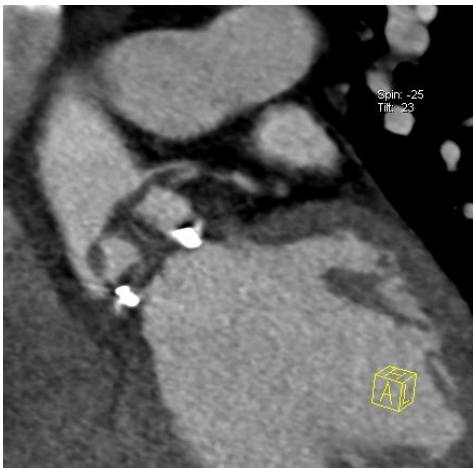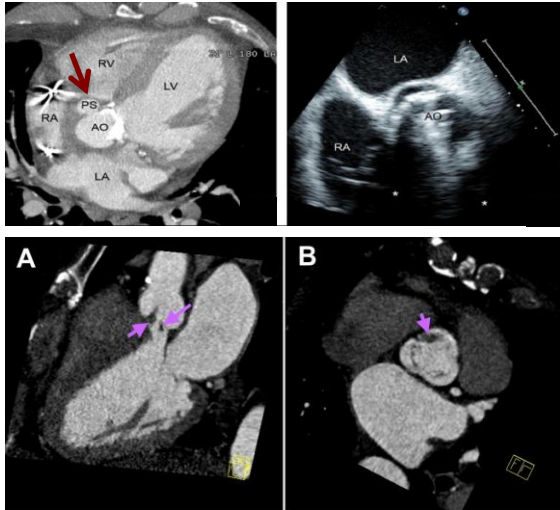
- Good results in detecting valvular abnormalities in IE

- In PVE, could detect **periannular complications** (anterior) not seen by TEE

- Preoperative **exclusion of coronary artery disease**

- Screening of **silent emboli**

- *!! Risk of acute renal failure*

Feuchtner GM, et al. J Am Coll Cardiol 2009;436-44
Fagman E, et al. Eur Radiol 2012;22:2407-14

Improvement of Diagnostic Strategies

News in Imaging Testing

18F-FDG PET-CT

- **Echo** provides **morphological imaging** without accurate information on the activity of IE = **insensitive for very early diagnosis**

- **PET/CT** provides **a functional imaging of inflammation** and has been tested in the diagnosis **of cardiovascular implantable devices (CIED) infections** and **embolism-metastatic infections of IE**

- **Clinical cases** suggesting the interest of PET/CT in PVE
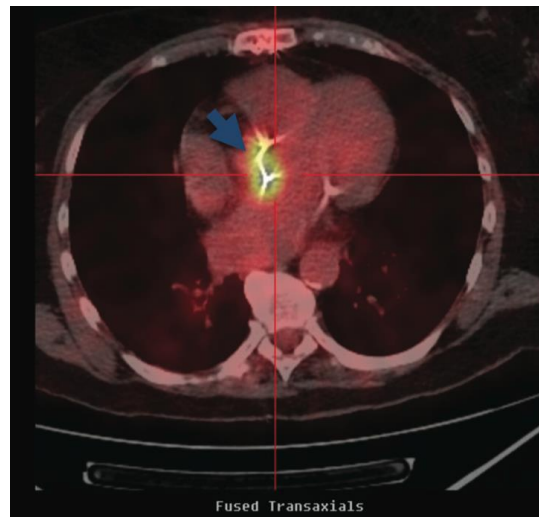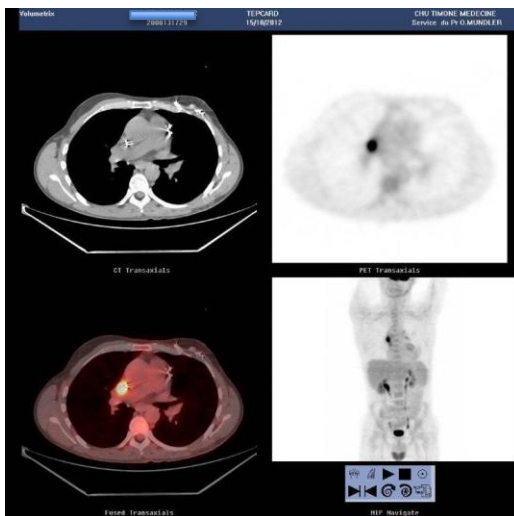
Bensimhon L, et al. Clin Microbiol Infect 2011;17:836-44
Ploux S, et al. Heart Rhythm 2011;8:1478-81
Sarrazin JF, et al. J Am Coll Cardiol 2012;59:1616-25
Saby L, et al. Circulation 2013;126:e217-220
Thuny F, et al. Arch Cardiovasc Dis 2013;106:52-62

News in Imaging Testing

18F-FDG PET-CT

Cardiac Imaging in Endocarditis

Positron Emission Tomography/Computed Tomography for Diagnosis of Prosthetic Valve Endocarditis

Increased Valvular ^{18}F-Fluorodeoxyglucose Uptake as a Novel Major Criterion

Ludivine Saby, MD,* Olivia Laas, MD,† Gilbert Habib, MD,* Serge Cammilleri, MD, PhD,†
Julien Mancini, MD, PhD,‡ Laetitia Tessonnier, MD,† Jean-Paul Casalta, MD,§
Frederique Gouriet, MD, PhD,§ Alberto Riberi, MD,‖ Jean-Francois Avierinos, MD,*
Frederic Collart, MD,‖ Olivier Mundler, MD, PhD,† Didier Raoult, MD, PhD,§
Franck Thuny, MD, PhD*§¶

Marseille, France

Pilot study

91 patients with suspicion of PVE — >1 month of surgery

Urgent surgery, 8 patients
Hemodynamic instability, 7 patients
Death, 2 patients
Glycaemia > 1.8 G/L, 1 patient
Poor PET/CT images quality, 1 patient

72 patients included →
- Clinical
- Mircrobiological
- Echo
- PET/CT

30 *definite* PVE | 22 *possible* PVE | 20 *rejected* PVE

Final diagnosis at 3 months

Saby et al, J Am Coll Cardiol 2013;61:2374–82
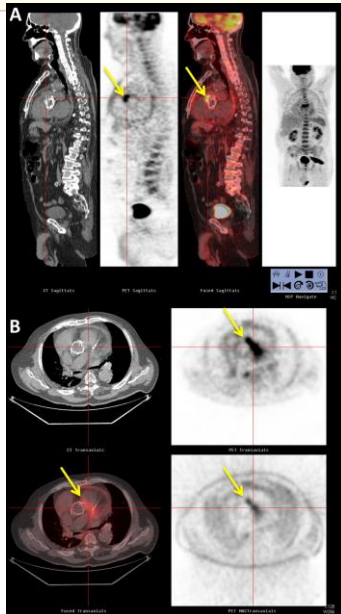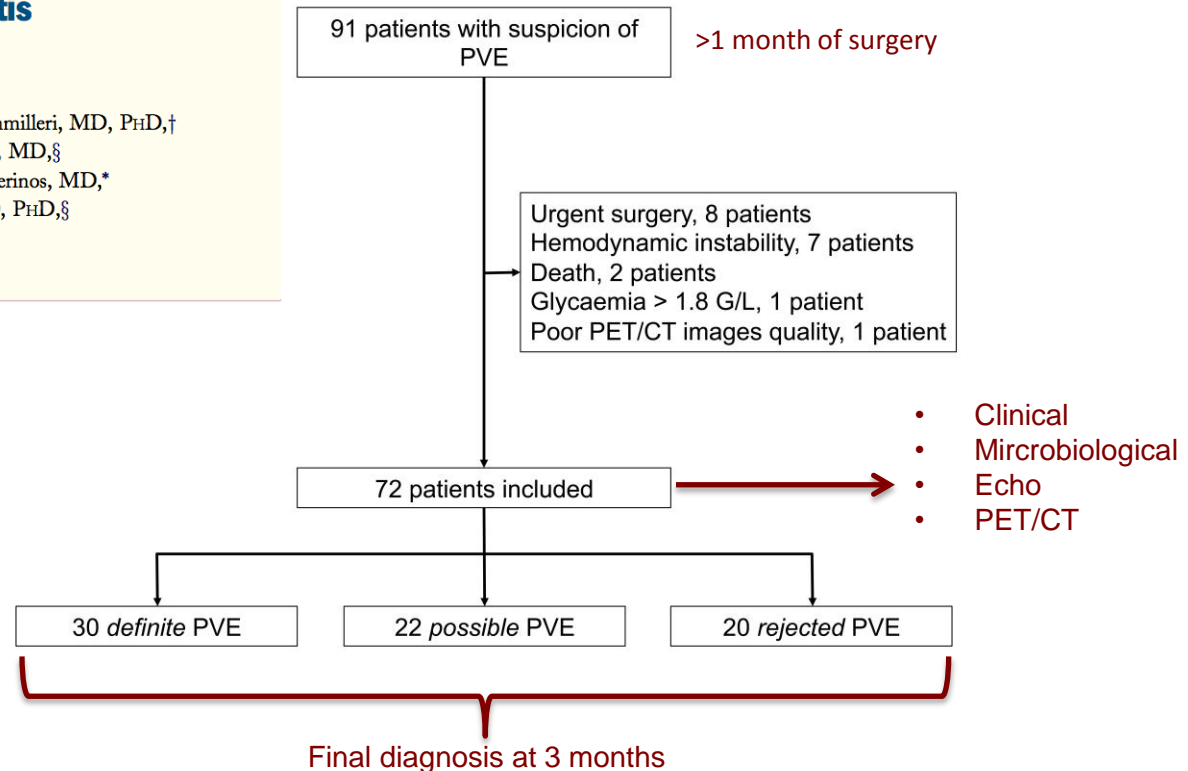
Improvement of Diagnostic Strategies

News in Imaging Testing

18F-FDG PET-CT

PET/CT median time=6 days after admission and 9 days after ATB

PET/CT diagnostic value
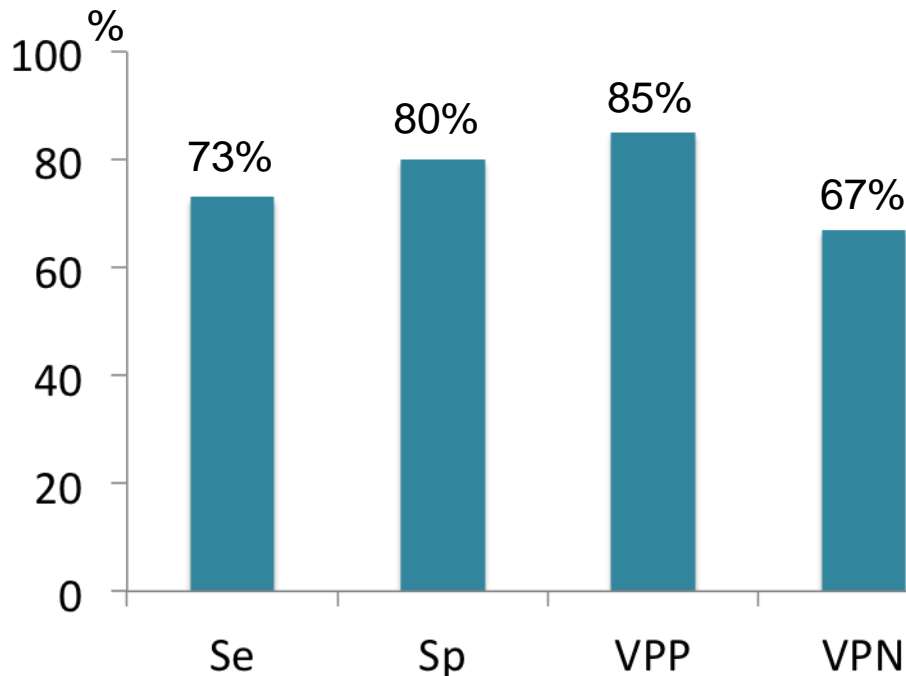
PET/CT as a novel major criterion
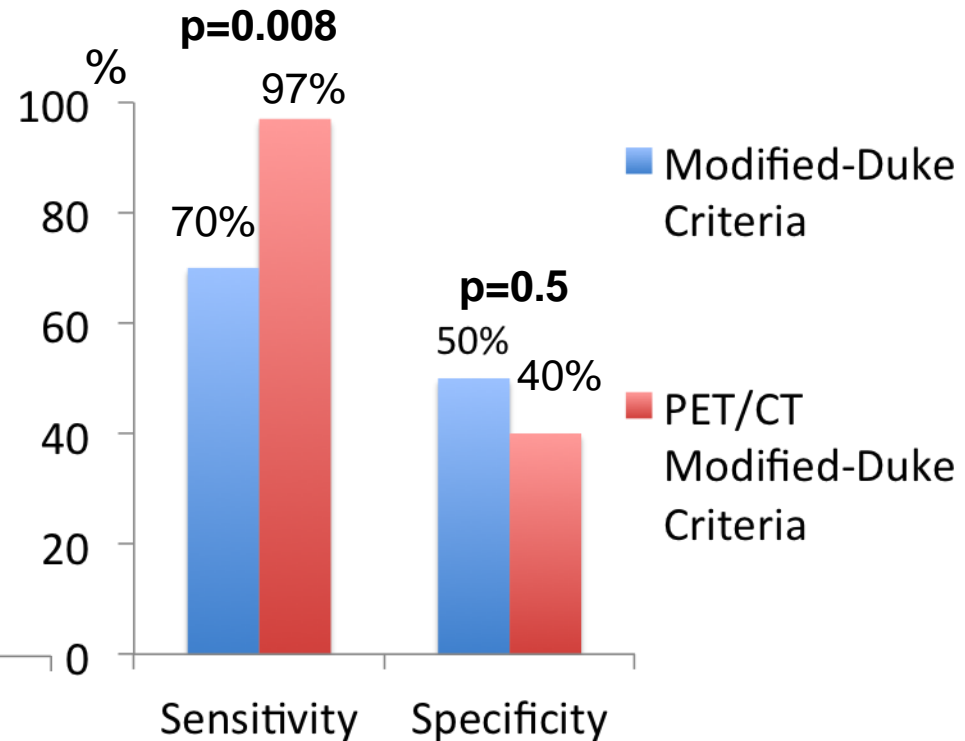
Saby et al, J Am Coll Cardiol 2013;61:2374–82

Improvement of Diagnostic Strategies

News in Imaging Testing

18F-FDG PET-CT

Saby et al, J Am Coll Cardiol 2013;61:2374–82
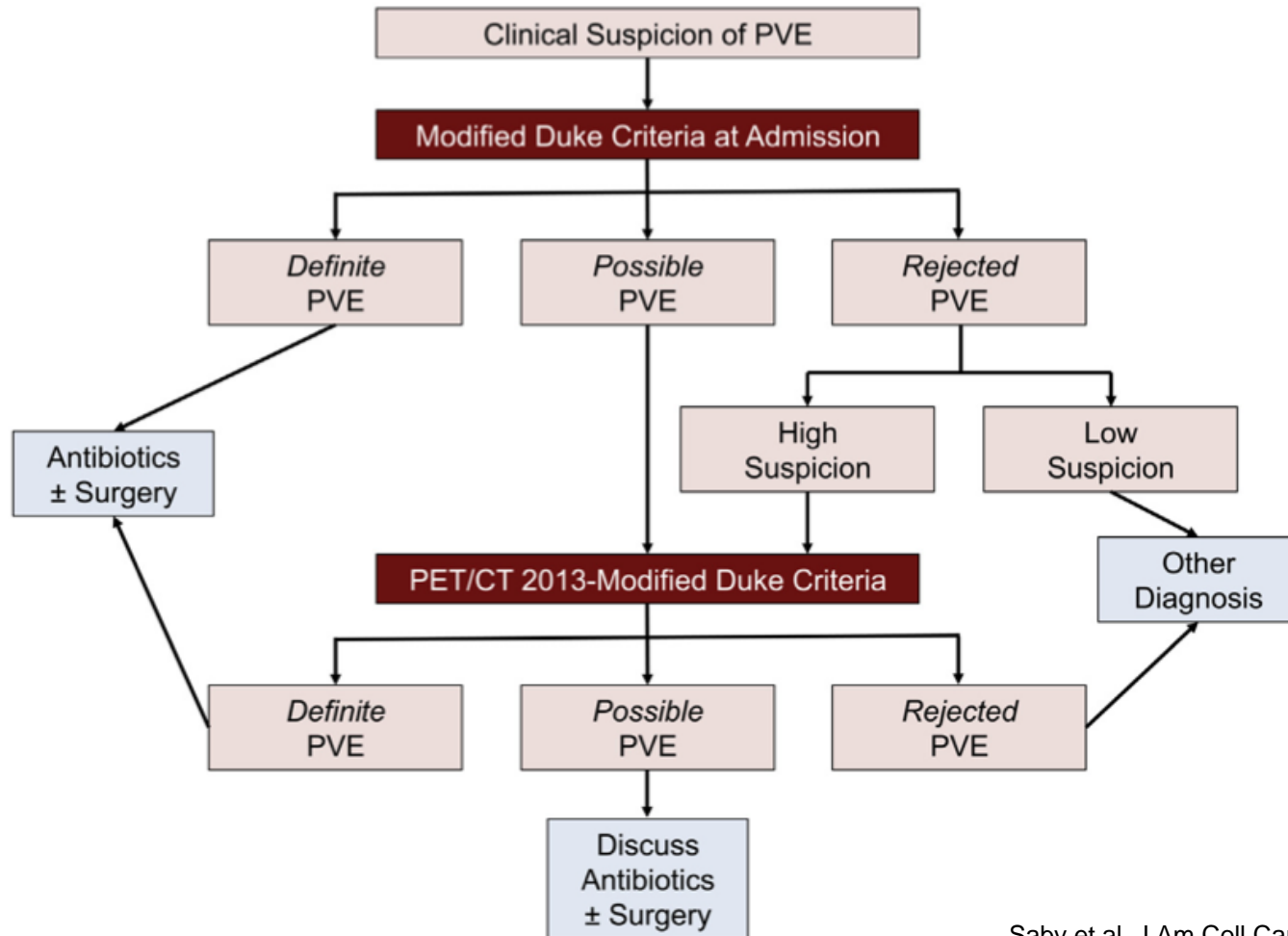
Improvement of Diagnostic Strategies

News in Imaging Testing
ECG-Gated CARDIAC CT/PET-CT
FUSED

Tanis W, et al. JACC Cardiovasc Img 2013
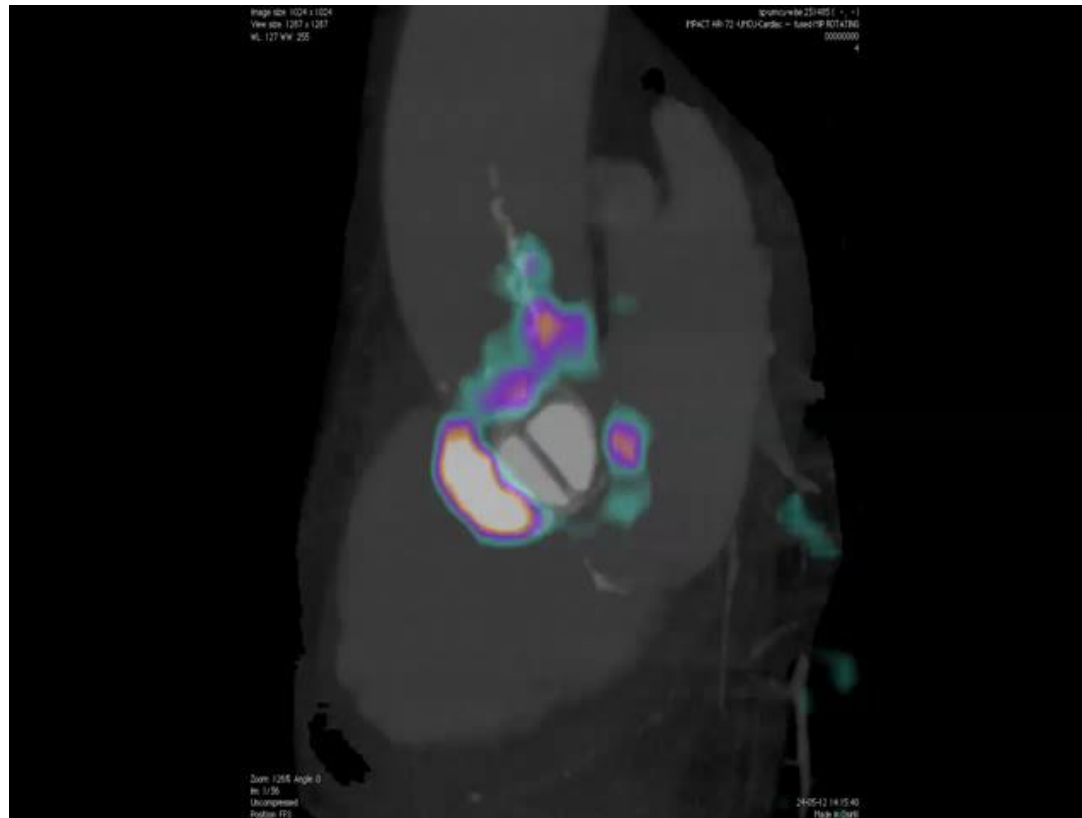
Improvement of Diagnostic Strategies

News in Imaging Testing

Radiolabeled leucocytes SPECT/CT

- Better specificity, lower sensitivity than PET/CT

- Time consuming (4-24 hours)

Hyafil F, et al. Eur Heart J Cardiovasc Imaging. 2013;14:586-94
Erba PA, et al. J Nucl Med 2012; 53:1235-43

Development of
New Medico-Surgical Strategies

Development of
New Medico-Surgical Strategies

Impact of a standardized multidisciplinary approach

1-year mortality
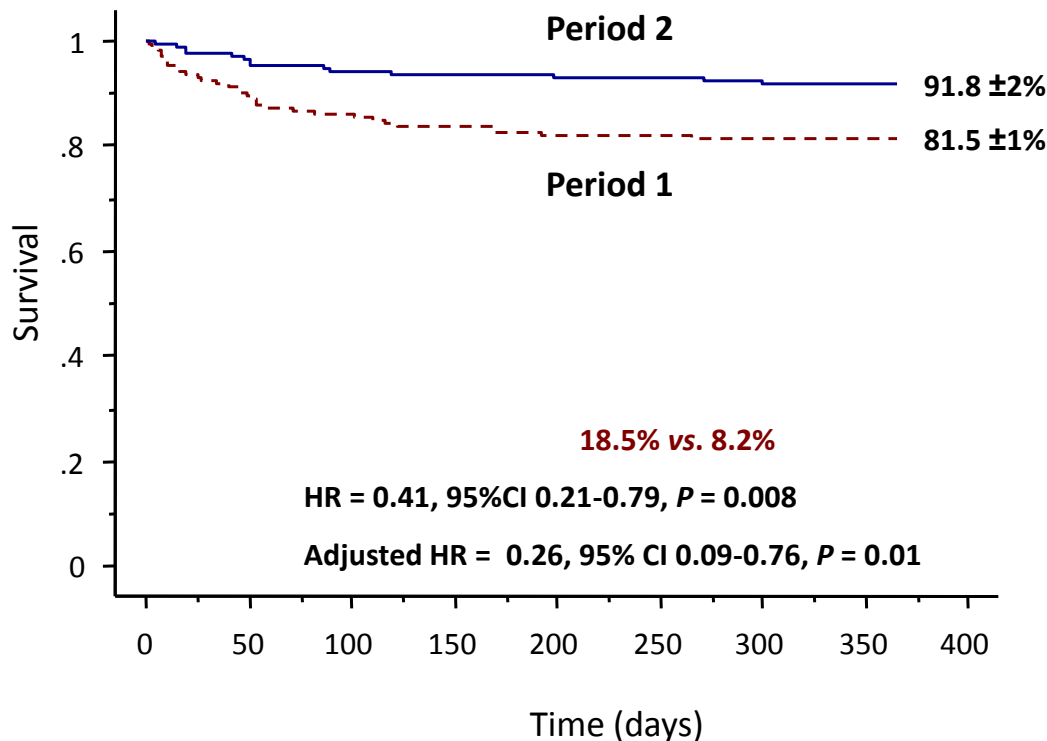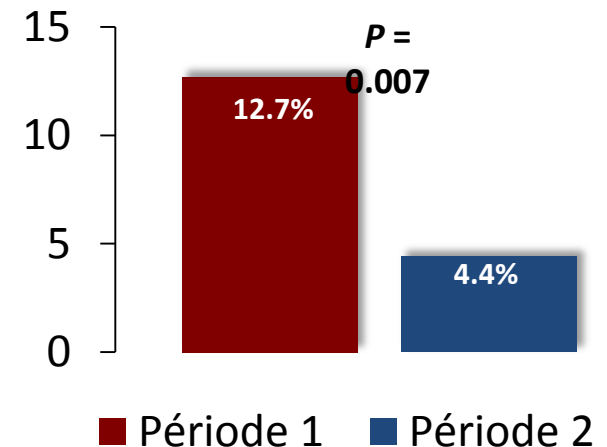
Period 2

91.8 ±2%

81.5 ±1%

Period 1

18.5% *vs.* 8.2%

HR = 0.41, 95%CI 0.21-0.79, *P* = 0.008

Adjusted HR = 0.26, 95% CI 0.09-0.76, *P* = 0.01

Survival

Time (days)

In-hospital mortality

P = 0.007

12.7%

4.4%

■ Période 1 ■ Période 2

Botelho-Nevers E, et al. Arch Intern Med 2009;169:1290-1298
Thuny F, et al. Arch Intern Med 2009;170:211-212

Development of New Medico-Surgical Strategies

Very Early Surgery to Prevent Embolism and Death

Recommendations: Indications for surgery	Timing	Level of evidence	
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 cardiogenic shock	Emergency	I	B
Aortic or mitral IE with severe acute regurgitation and persisting HF or echo-cardiographic signs of poor hemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent	I	B
Aortic or mitral IE with severe acute regurgitation and no HF	Elective	IIa	B
B. UNCONTROLLED INFECTION			
Locally uncontrolled infection	Urgent	I	B
Persisting fever and positive blood culture > 7-10 days		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 treatment	Urgent	I	B
Aortic or mitral IE with large vegetations (10 mm) and other predictors of complicated course (HF, persistent infection, abscess)	Urgent	I	C
Isolated very large vegetations (>15 mm)	Urgent	IIb	C

ESC 2009

Development of New Medico-Surgical Strategies

Very Early Surgery to Prevent Embolism and Death

1st Randomized trial

ORIGINAL ARTICLE

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.

134 Patients received a diagnosis of endocarditis

44 Were excluded
26 Underwent urgent surgery
18 Did not have severe valve disease or vegetation >10 mm and underwent medical treatment

90 Were assessed for eligibility

14 Were excluded
5 Had major stroke
5 Were in poor medical condition
4 Declined to participate

76 Underwent randomization

37 Were assigned to early-surgery group — Within 48h

39 Were assigned to conventional-treatment group

37 Underwent early surgery
3 Died

39 Underwent conventional treatment
3 Died

37 Were included in the analysis

39 Were included in the analysis — Surgery in 77%

Kang DH, et al. New Engl J Med 2012;366:2466-73

Development of New Medico-Surgical Strategies

Very Early Surgery to Prevent Embolism and Death

Table 3. Clinical End Points.

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
Cerebral	5 (13)	0	
Coronary	1 (3)	0	
Popliteal	1 (3)	0	
Splenic	1 (3)	0	
Secondary end points at 6 mo — no. (%)			
Any	11 (28)	1 (3)	0.003
Death	2 (5)	1 (3)	1.00
Embolic event	8 (21)	0	0.005
Recurrence of infective endocarditis	1 (3)	0	1.00

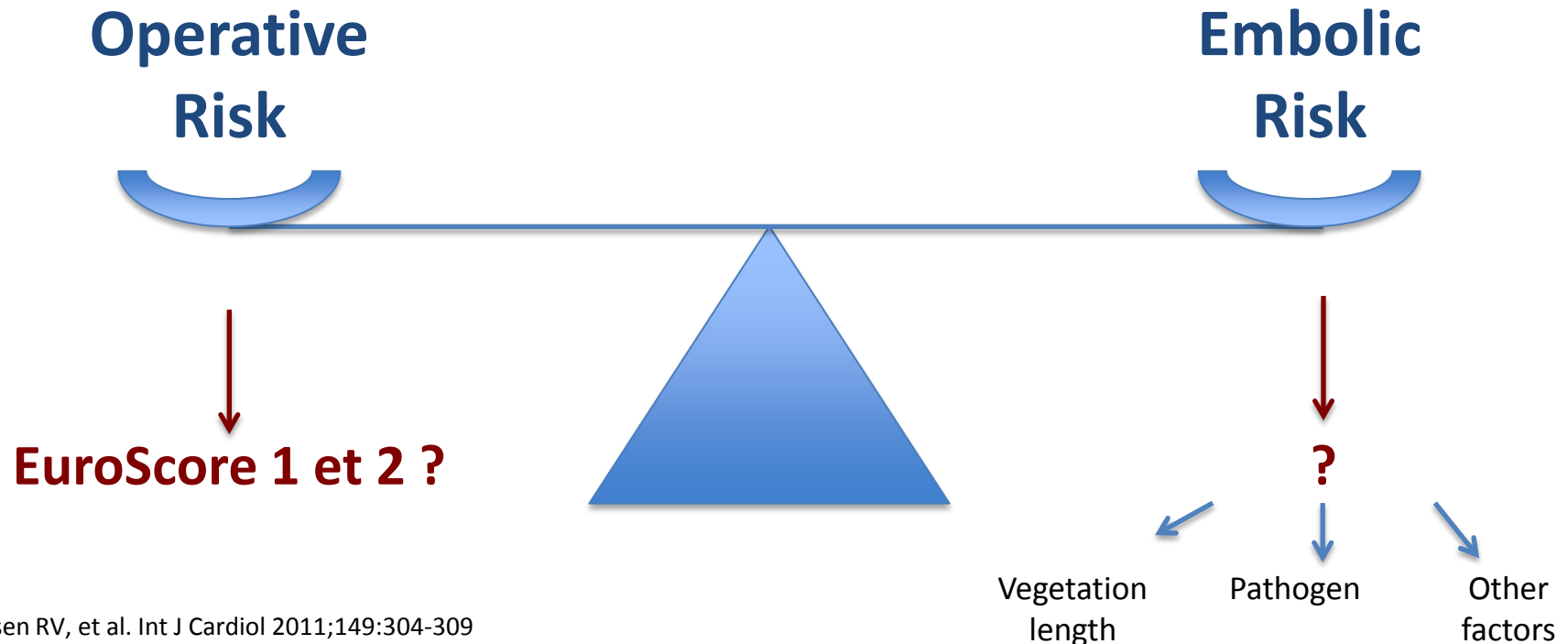**But**
- exclusion of patients with high comorbidities

- Vegetation length is not the only predictor of embolism

Kang DH, et al. New Engl J Med 2012;366:2466-73

Development of New Medico-Surgical Strategies

Prediction of Embolic Risk in Infective Endocarditis

Quantification of Benefit/Risk Ratio for surgery must be evaluated

Operative Risk

Embolic Risk

EuroScore 1 et 2 ?

?

Vegetation length

Pathogen

Other factors

Rasmussen RV, et al. Int J Cardiol 2011;149:304-309

Development of New Medico-Surgical Strategies

Prediction of Embolic Risk in Infective Endocarditis

Benefit/Risk Ratio <u>Quantification</u>
for surgery must be evaluated
"The Embolic Risk French Calculator"

Prediction of Symptomatic Embolism in Infective Endocarditis

Construction and Validation of a Risk Calculator in a Multicenter Cohort

Sandrine Hubert, MD,*† Franck Thuny, MD, PhD,*‡§ Noemie Resseguier, MD,‖
Roch Giorgi, MD, PhD,‖ Christophe Tribouilloy, MD, PhD,¶# Yvan Le Dolley, MD,*
Jean-Paul Casalta, MD,** Alberto Riberi, MD,† Florent Chevalier, MD,¶ Dan Rusinaru, MD,¶
Dorothée Malaquin, MD,¶ Jean Paul Remadi, MD,†† Ammar Ben Ammar, MD,‡‡
Jean Francois Avierinos, MD,* Frederic Collart, MD,† Didier Raoult, MD, PhD,‡** Gilbert Habib, MD*

Marseille and Amiens, France

Risk Calculator for 6-Month Embolic Risk for Infective Endocarditis

Collect the following clinical, echocardiographic, and microbiological variables at admission of patient with infective endocarditis.
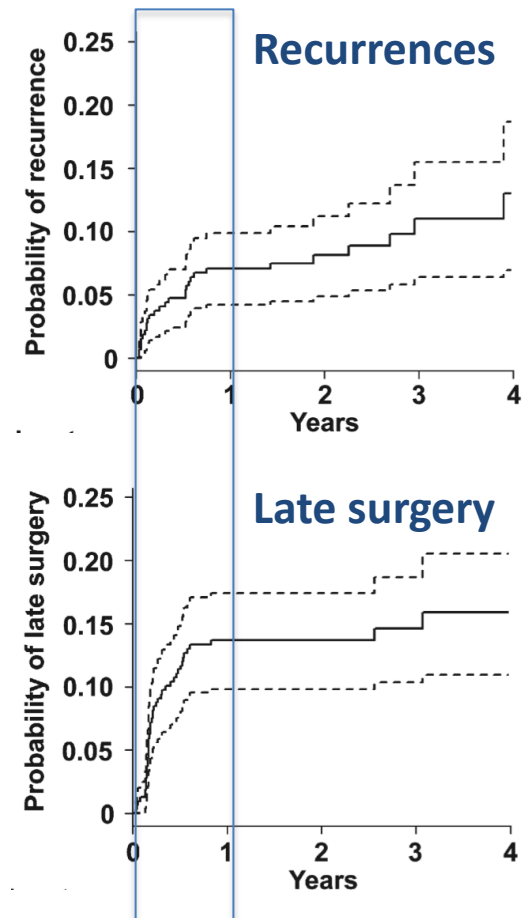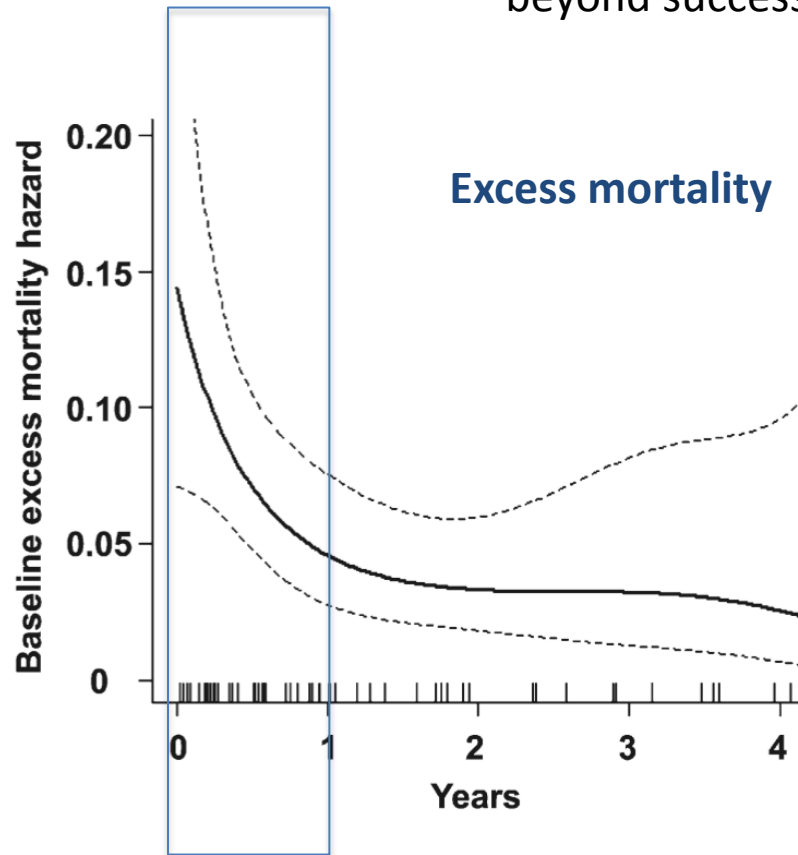Then, the predicted embolic risk is automatically calculated at different times.

DATA AT ADMISSION

Clinical Data	Age (years)	75
	Diabetes (0: no ; 1: yes)	1
	Previous embolism (0: no ; 1: yes)	1
	Atrial fibrillation (0: no ; 1: yes)	0
Echocardiography		
	Vegetation >0 to ≤10 mm (0: no ; 1: yes)	0
	Vegetation >10 mm (0: no ; 1: yes)	1
Microorganism		
	Staphylococcus aureus (0: no ; 1: yes)	1

PREDICTED EMBOLIC RISK CALCULATION

Time (Days)	Predicted Embolic Risk
1	5%
2	6%
3	10%
4	13%
5	14%
6	15%
7	16%
10	18%
11	18%
12	20%
13	22%
14	24%
18	24%
19	25%
23	26%
28	27%
35	27%
47	28%
48	28%
180	29%

Hubert S, et al. J Am Coll Cardiol 2013;62:1384–92

Development of New Medico-Surgical Strategies

Close Follow-up during the 1st Year after diagnosis

Mortality and morbidity may extend beyond successful treatment

Excess mortality

Recurrences

Late surgery

Thuny F, et al. Am Heart J 2012; Am Heart J. 2012;164:94-101

CONCLUSION

WHAT'S NEW IN ENDOCARDITIS ?

- The profile of IE is changing but the mortality remains high

- The indication of antibiotic prophylaxis has been restricted

- Novel methods offer hope in decreasing mortality by accelerating the diagnostic process and the risk stratification

Thank you

MARSEILLE

©Gilles Martin-Raget/Audi MedCup 2009

Development of New Medico-Surgical Strategies

Prediction of Embolic Risk in Infective Endocarditis

Benefit/Risk Ratio Quantification
for surgery must be evaluated
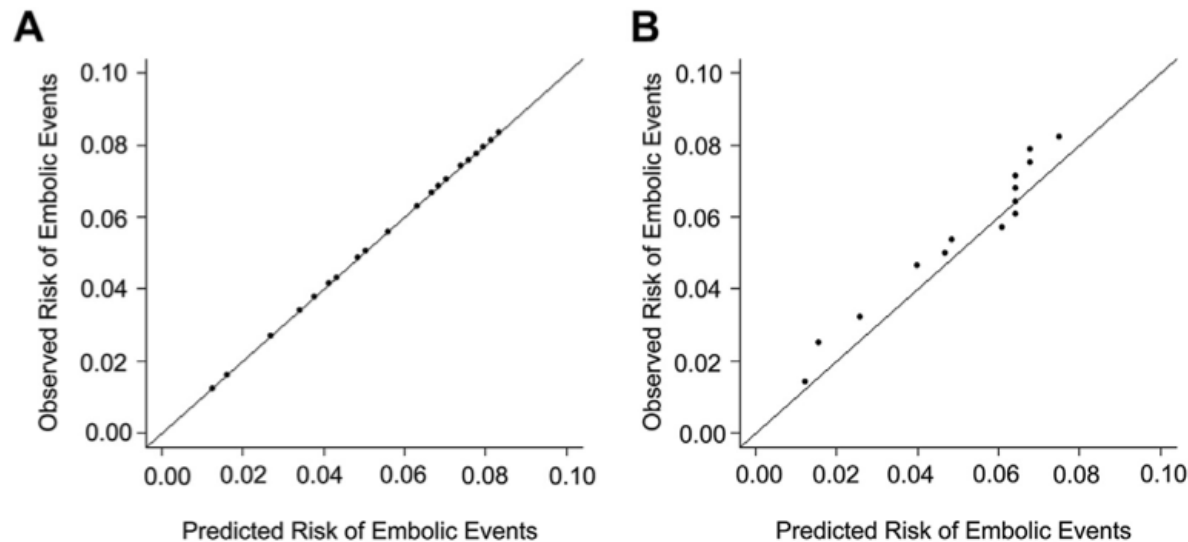*"The Embolic Risk French Calculator"*

Figure 2 — Comparison of Predicted Versus Observed Risk (Calibration) of Embolic Events for the Development Sample and the Validation Sample

Hubert S, et al. J Am Coll Cardiol 2013;62:1384–92