

Etudes observationnelles

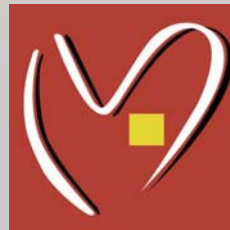
l'exemple des endocardites infectieuses

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DESC de Maladies Infectieuses

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Predisposing Factors Have Changed

1970



Rheumatic heart disease
Congenital cardiopathy

...

Congenital cardiopathy

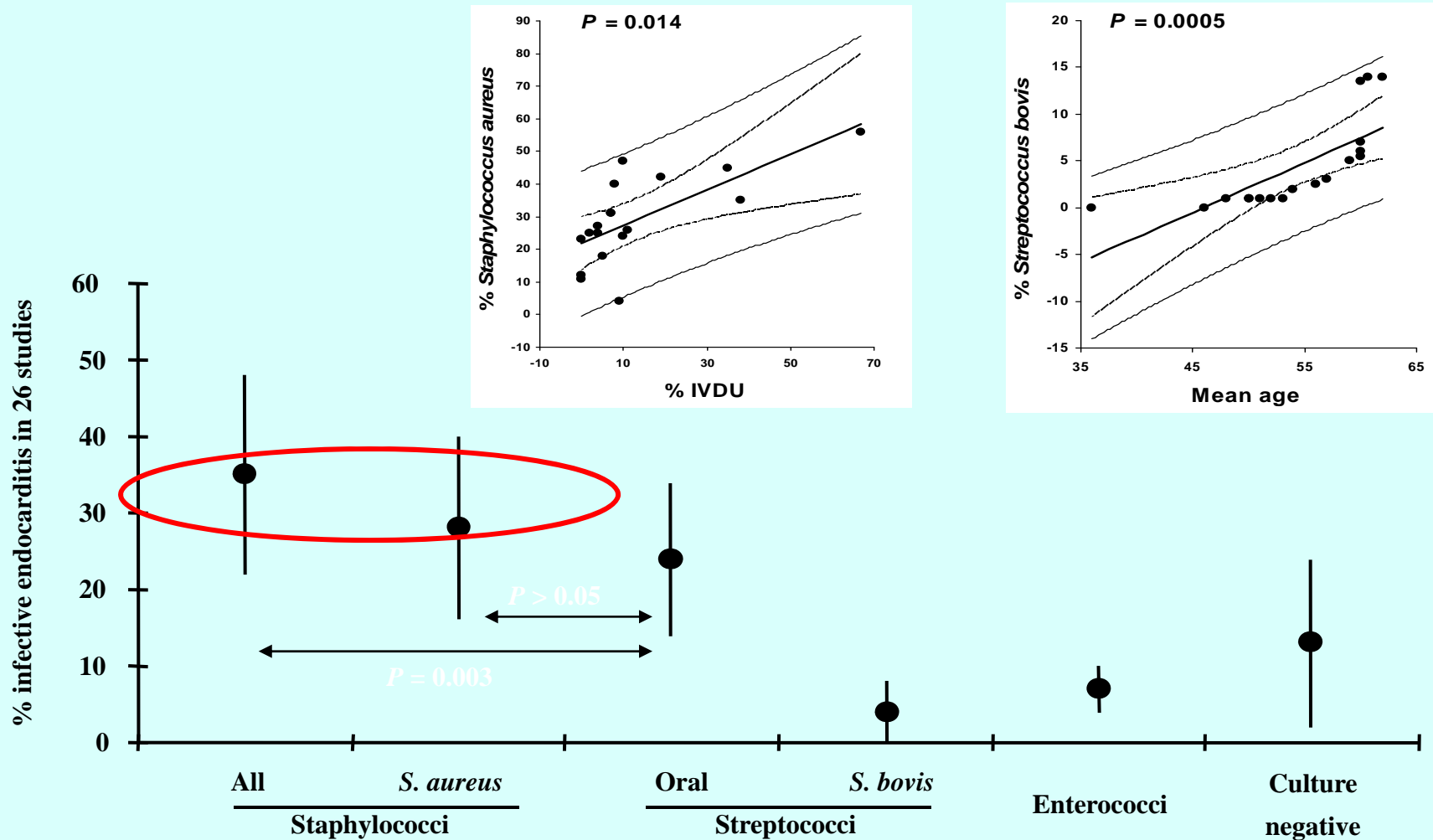
IVDU

Elderly patients/valve sclerosis

Prosthetic valves

**Nosocomial and healthcare-associated
endocarditis**

Organism frequency reported in IE in 26 studies between 1993 and 2003



Endocarditis Papers

Country of Origin March 2008-March 2009

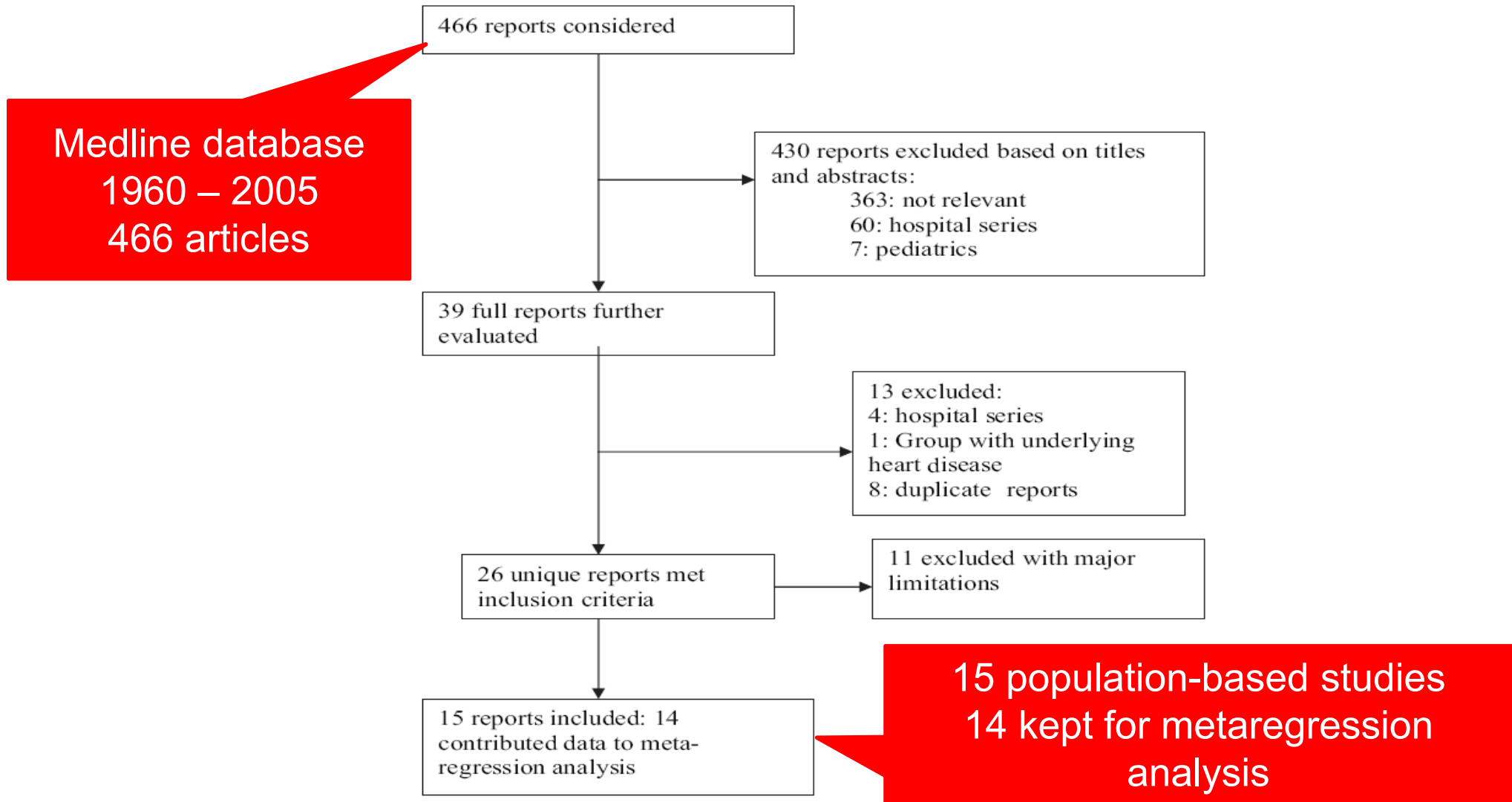


Medline : ≈ 500 articles/year with "endocarditis" in their title

Overall characteristics of endocarditis in low-income countries

- Rheumatic heart disease remains an important predisposing factor
- Prominence of streptococcal IE
- high prevalence of culture-negative IE
- Often younger population
- Overall, the characteristics of endocarditis in many regions of the world are similar to those described in Europe and North America 30+ years ago

A Systematic Review of Population-Based Studies of Infective Endocarditis



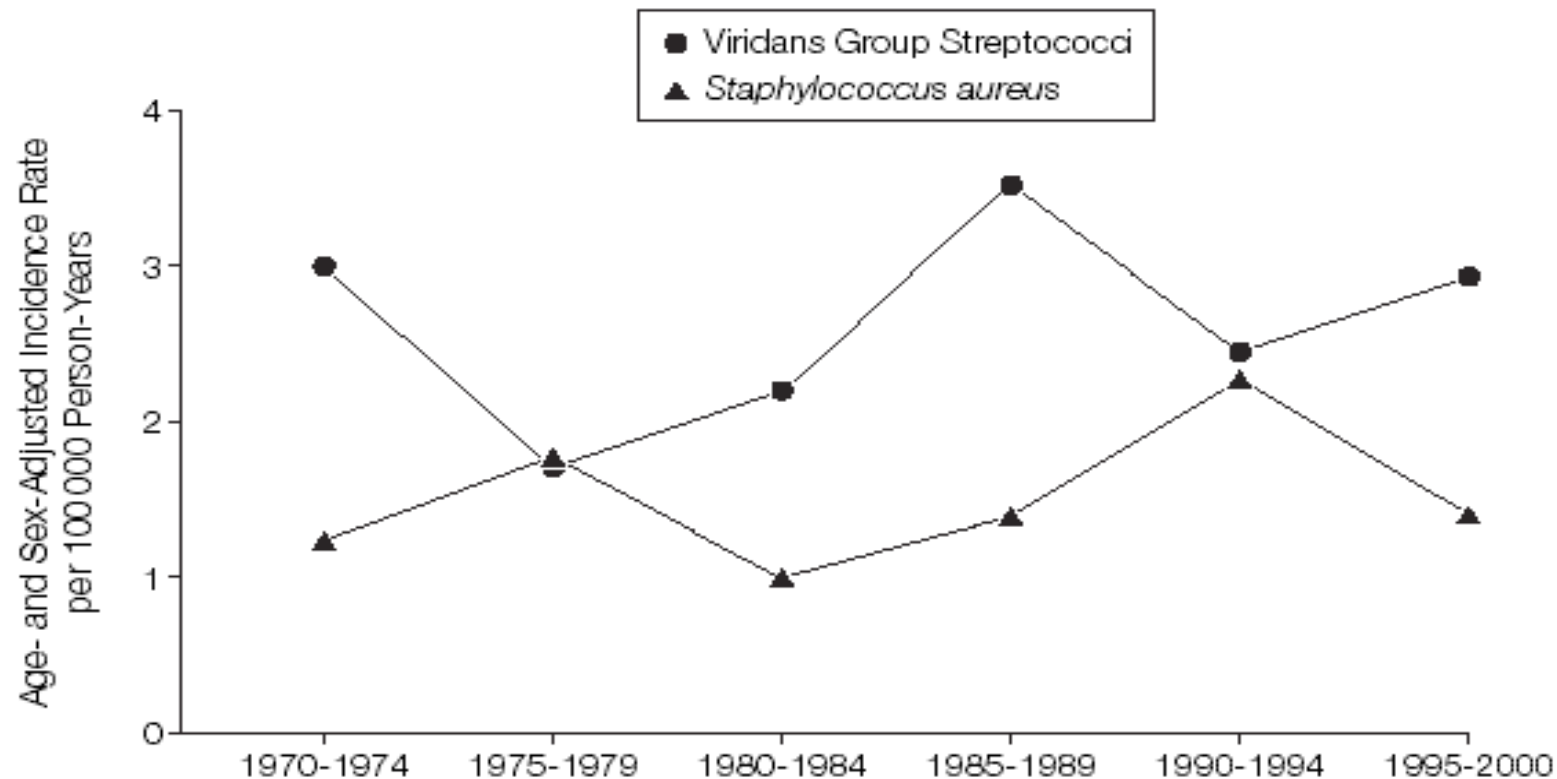
A Systematic Review of Population-Based Studies of Infective Endocarditis

- Decrease in IE cases with underlying RHD, in developed countries
- Increase in IE cases with prosthetic valve
- Increase in IE cases with mitral valve prolapse
- Increased proportion of patients undergoing valve surgery (7% per decade)
- **No significant temporal trend for causative microorganisms**

Temporal Trends in Infective Endocarditis

A Population-Based Study in Olmsted County, Minnesota

- Incidence of IE ranged from 5 to 7 cases per 10^5 person-years and did not change significantly over time ($P=.42$ for trend).



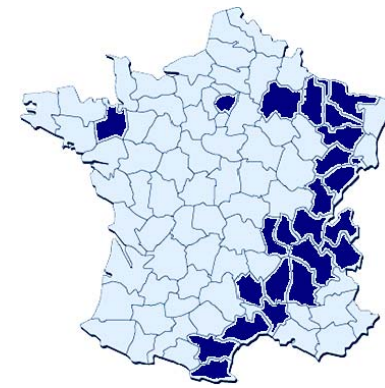


IE2008: third one-year population-based study on IE in France

French Study Group on Infective Endocarditis

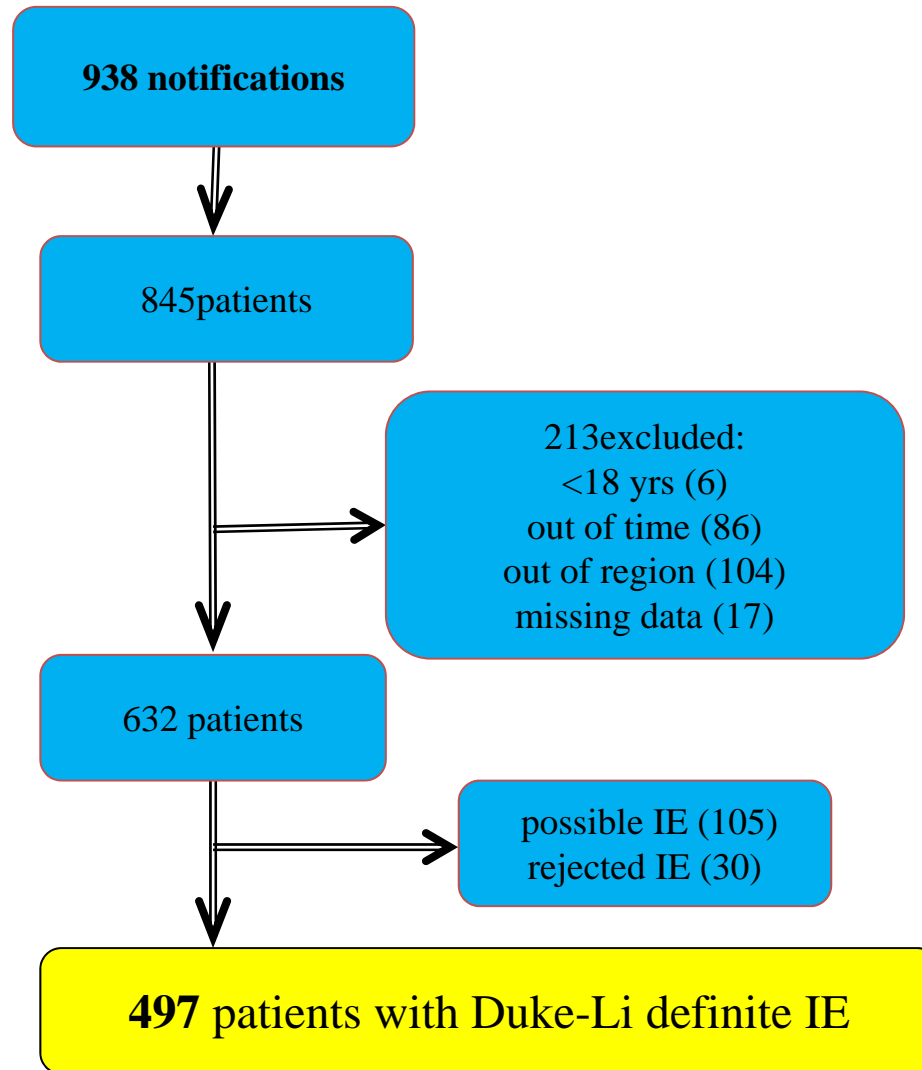


Methods



- Population-based prospective study conducted from Dec 1, 2007 to Mar 31, 2009 in 7 French regions
- Total population: **15 million** adults (32 % of the French population). Only pts whose first hospitalization date fell between Jan 1 and Dec 31, 2008 were retained in the analysis.
- Study publicized and recalled by mail to all hospital physicians falling into one of the following categories:
 - physicians likely to take care of patients with IE
 - echocardiographers
 - microbiologists
- Only Duke-Li definite cases of IE were kept in the study

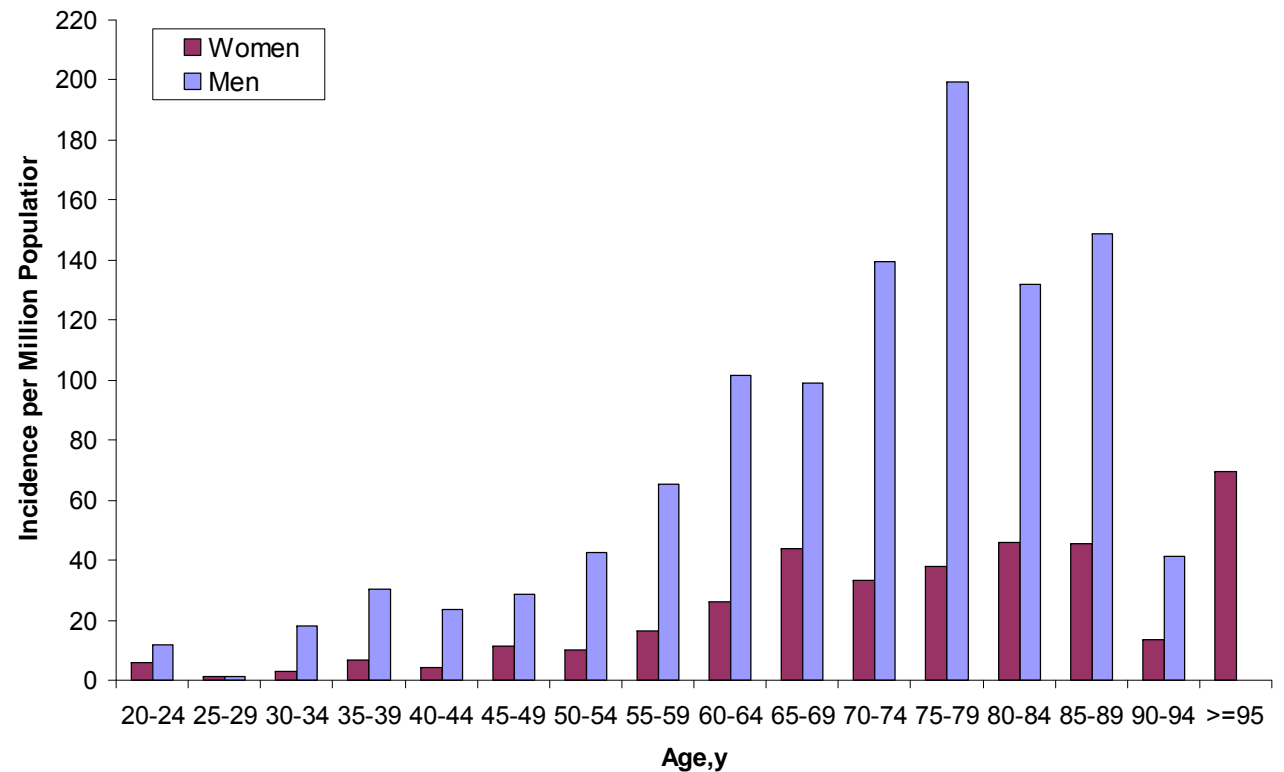
Flow diagram



Age, sex, and incidence

Incidence of IE by age and sex

- M/F :2.9
- Mean age
62 years (18-96)



- Overall annual incidence: 33.8 [30.8-36.9] cases/million

	Source of acquisition						
	Whole population		Community		Healthcare related		p
	N	%	N	%	N	%	
	497		335 (73.3%)		122 (26.7%)		
	N	%	N	%	N	%	p
Patients' characteristics							
Age, years (mean, SD)	62.3	15.9	62.9	15.4	67.4	12.4	0.0124
Male sex	369	74.2	260	77.6	78	63.9	0.0032
At least one comorbidity	237	47.7	145	43.3	73	59.8	0.0017
Charlson score (mean, SD)	1.9	2.2	1.7	2.0	2.9	2.5	<.0001
Cancer	89	17.9	55	16.4	32	26.2	0.018
Dialysis	11	2.2	0		10	8.2	<.0001
Intravenous drug users	29	5.8					
Cardiac history							
Underlying heart disease (HD)							0.5064
Prosthetic valve	104	20.9	69	20.6	30	24.6	
No previously known HD	262	52.7	168	50.1	62	50.8	
PKHD without prosthesis	131	26.4	98	29.3	30	24.6	
Intracardiac device	66	13.3	23	6.9	42	34.4	<.0001
Clinical and biological features							
Fever	424	86.0	284	85.3	101	84.2	0.7686
Septic shock	30	6.0	18	5.4	6	4.9	0.8470
Heart failure	168	33.8	114	34.0	41	33.6	0.9326
Cerebral emboli	102	20.5	79	23.6	12	9.8	0.0011
Cerebral haemorrhage	29	5.8	20	6.0	5	4.1	0.4363
Other emboli	164	33.0	109	32.5	29	23.8	0.0710
Extracardiac complication	288	57.9	198	59.1	55	45.1	0.0076
Serum creatinine > 180 µmol/l	141	28.9	80	24.2	43	36.1	0.0120

	Source of acquisition						
	Whole population		Community		Healthcare related		p
	497		335 (73.3%)		122 (26.7%)		
N	%	N	%	N	%		
Cardiac lesions of IE							
Positive echocardiogram	460	92.6	307	91.6	116	95.1	0.2151
Vegetation	435	87.5	289	86.3	110	90.2	0.2685
Prosthesis dehiscence	19	18.3	12	17.4	6	20.0	0.7571
Severe regurgitation	194	39.4	149	45.0	30	24.6	<.0001
Cardiac abscess	80	16.1	59	17.6	13	10.7	0.0710
Microorganisms							
Streptococcaceae	238	47.9	204	60.9	23	18.9	<.0001
Streptococci	177	35.6	161	48.1	8	6.6	<.0001
Oral streptococci	89	17.9	80	23.9	4	3.3	<.0001
Group D streptococci	63	12.7	58	17.3	4	3.3	0.0001
Pyogenic strep	25	5.0	23	6.9	.		0.0030
Enterococci	51	10.3	35	10.4	13	10.7	0.9489
Other strep	10	2.0	8	2.4	2	1.6	1.0000
Staphylococcaceae	180	36.2	83	24.8	72	59.0	<.0001
<i>Staphylococcus aureus</i>	134	27.0	70	20.9	41	33.6	0.0051
Coagulase-negative	46	9.3	13	3.9	31	25.4	<.0001
Other microorganisms	43	8.7	27	8.1	16	13.1	0.1015
Microorganisms > 1	10	2.0	3	0.9	4	3.3	0.0857
No microorganism identified	26	5.2	18	5.4	7	5.7	0.8795
Outcome							
Cardiac surgery	223	44.9	165	49.3	37	30.3	0.0003
In-hospital death	113	22.7	68	20.3	38	31.1	0.0151

Prognosis factors in the whole population

	Bivariate Cox regression			Multivariate Cox regression**		
	RR	95% CI*	p	RR	95% CI*	p
Age, years^o	1.03	1.01 - 1.04	0.0001	1.03	1.02 - 1.05	<0.0001
Sex			0.6224			
Women	1.11	0.74 - 1.67				
Men	1					
Underlying heart disease			0.4800			
No previously known heart disease	1.18	0.75 - 1.88				
Prosthetic valve	1.40	0.81 - 2.40				
Previously known heart disease	1					
Source of acquisition			0.1256			
Community	1.85	0.58 - 5.88				
Health-care related	2.56	0.79 - 8.32				
Intravenous drug users	1					
<i>Staphylococcus aureus</i>	2.57	1.78 - 3.72	<0.0001	2.69	1.85 - 3.89	<0.0001
Charlson score^o	1.08	1.01 - 1.16	0.0195			
Diabete			0.0511			
None	1.44	0.72 - 2.86				
With insulin requiring	2.33	1.08 - 5.04				
Without insulin requiring	1					
Dialysis	1.85	0.75 - 4.54	0.1820			
Cerebral complication	2.02	1.39 - 2.94	0.0002	2.12	1.45 - 3.10	<0.0001
Heart failure	1.37	0.94 - 1.99	0.0994	1.46	1.01 - 2.13	0.0464
Cardiac abscess	1.28	0.80 - 2.04	0.3048			
Cardiac surgery	0.63	0.43 - 0.92	0.0175			

Contemporary population-based profile of IE in Australia

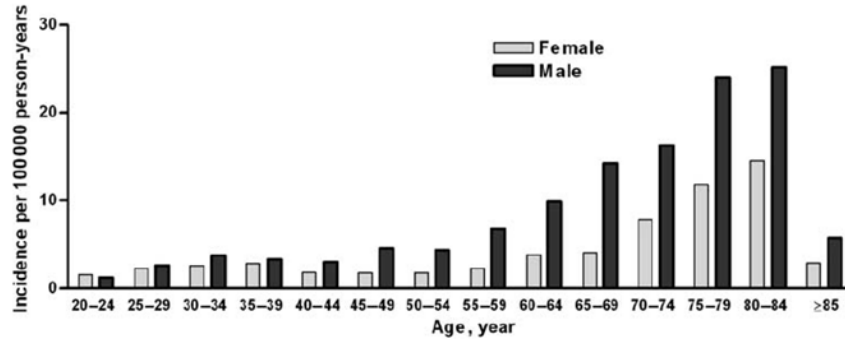


Figure 2 Incidence of endocarditis by age and sex in the study population.

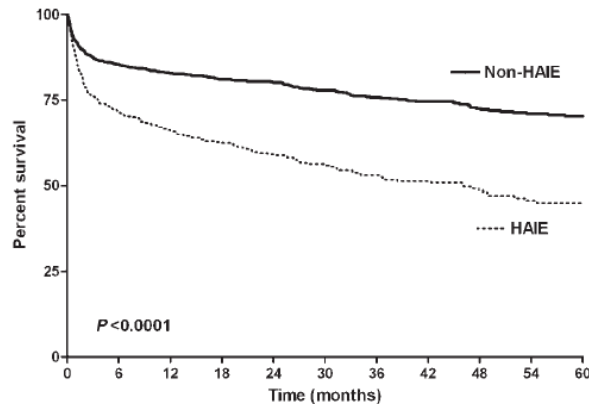


Figure 3 Kaplan–Meier analysis comparing survival in patients with health care-associated endocarditis (HAIE) and patients with non-HAIE. Log-rank *P*-value is provided.

Table 4 Multivariable Cox regression for all-cause mortality during follow-up

Variable	Hazard ratio (95% CI)	<i>P</i> -value
Age (per increase of 10 years)	1.45 (1.37–1.54)	<0.001
Male gender	0.91 (0.75–1.11)	0.36
Diabetes	1.14 (0.89–1.45)	0.30
Chronic renal failure	1.45 (1.13–1.86)	0.004
Health care-associated infection	1.62 (1.34–1.96)	<0.001
Prosthetic valve infection	1.05 (0.80–1.38)	0.71
<i>Staphylococcus aureus</i> infection	1.72 (1.37–2.15)	<0.001
Enterococcal infection	0.82 (0.60–1.13)	0.22
Streptococcal infection	0.75 (0.57–0.99)	0.046
Heart failure	1.89 (1.53–2.35)	<0.001
Severe embolic event	1.69 (1.28–2.22)	<0.001
Valvular surgery	0.67 (0.50–0.90)	0.008

Temporal trends 1991-2008

Selection of cases

1991	1999	2008
N=575	N = 925	N = 938
Definite, Probable and Possible (von Reyn classification) infective endocarditis cases by calendar year		
1991	1999	2008
N=323	N = 331	N = 339
Definite (Duke classification) Infective endocarditis cases by calendar year		
	1999	2008
	N = 323	N = 332

Standardized incidence per million

	1991 Survey	1999 Survey	2008 Survey
Overall			
Von Reyn (definite, probable, possible cases)	35.2 [31.5-39.2]	33.5 [30.0-37.4]	32.1 [28.8-35.7]
Von Reyn (definite and probable cases)	29.2 [25.8-32.9]	31.5 [28.1-35.2]	29.7 [26.5-33.1]
Duke (definite cases)	NA	31.2 [27.9-34.9]	31.4 [28.1-35]
Duke modified (definite cases)	NA	NA	32.0 [28.7-35.6]
No previously known underlying heart disease*	11.8 [9.7-14.2]	16.1 [13.8-18.8]	15.0 [12.8-17.5]
Previously known underlying heart disease*	23.4 [20.3-26.8]	17.4 [14.9-20.2]	17.1 [14.7-19.8]
Previously known native underlying heart disease*	18.8 [16.1-21.9]	11.4 [9.4-13.7]	7.1 [5.6-9.0]
IV drug addicts*	1.3 [0.8-2.1]	1.7 [1.0-2.6]	1.3 [0.8-2.2]

Standardized incidence per million

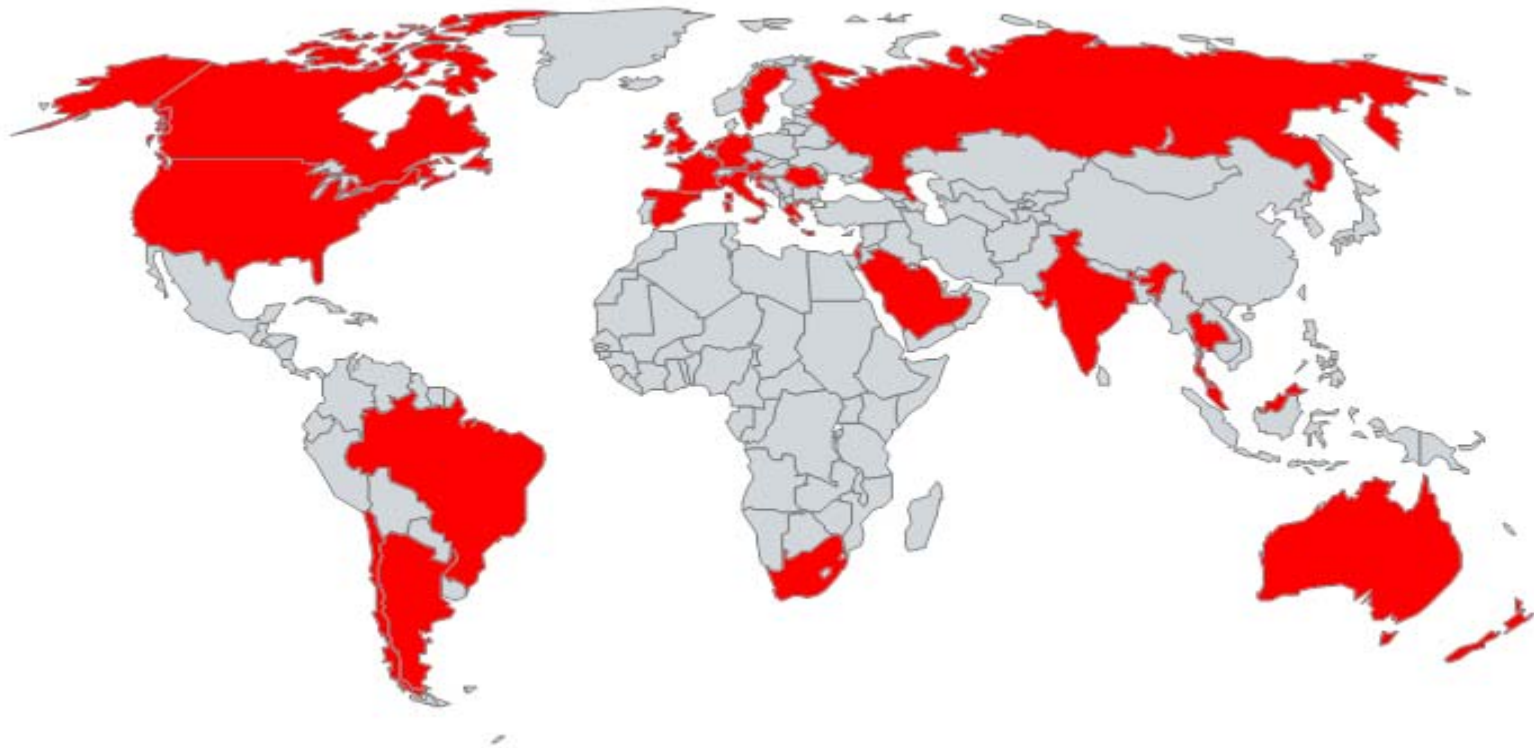
According to microorganisms	1991 Survey	1999 Survey	2008 Survey
Oral streptococci*			
Global population	8.1 [6.4–10.1]	6.3 [4.8-8.1]	6.3 [4.9-8.0]
Previously known native underlying heart disease	4.6 [3.3-6.1]	3.4 [2.3-4.7]	1.8 [1.1-2.9]
Prosthetic valve disease	0.7 [0.3-1.5]	1.2 [0.6-2.1]	1.2 [0.6-2.1]
Group D streptococci*			
Global population	6.4 [4.8-8.3]	8.5 [6.8 –10.6]	3.9 [2.8 – 5.3]
Previously known native underlying heart disease ^H	2.9 [1.9-4.3]	1.9 [1.1-2.9]	0.6 [0.2-1.3]
Prosthetic valve disease	0.7 [0.3-1.5]	0.9 [0.4-1.8]	1.1 [0.5-2.0]

Standardized incidence per million

According to microorganisms	1991 Survey	1999 Survey	2008 Survey
<i>Staphylococcus aureus</i>*			
Global population	5.2 [3.9-6.8]	6.8 [5.3-8.6]	8.3 [6.6-10.2]
Previously known native underlying heart disease	2.3 [1.4-3.5]	1.6 [0.9-2.7]	1.6 [0.9-2.5]
Prosthetic valve disease	1.6 [0.9-2.6]	0.8 [0.4-1.6]	1.6 [0.9-2.6]
Coagulase negative Staphylococci*			
Global population	1.5 [0.8-2.6]	2.1 [1.3-3.3]	3.4 [2.3-4.7]
Previously known native underlying heart disease	1.0 [0.4-1.8]	0.6 [0.2-1.3]	0.4 [0.1-1]
Prosthetic valve disease	0.3 [0.1-0.9]	0.8 [0.3-1.7]	1.5 [0.9-2.5]

Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century

The International Collaboration on Endocarditis–Prospective Cohort Study



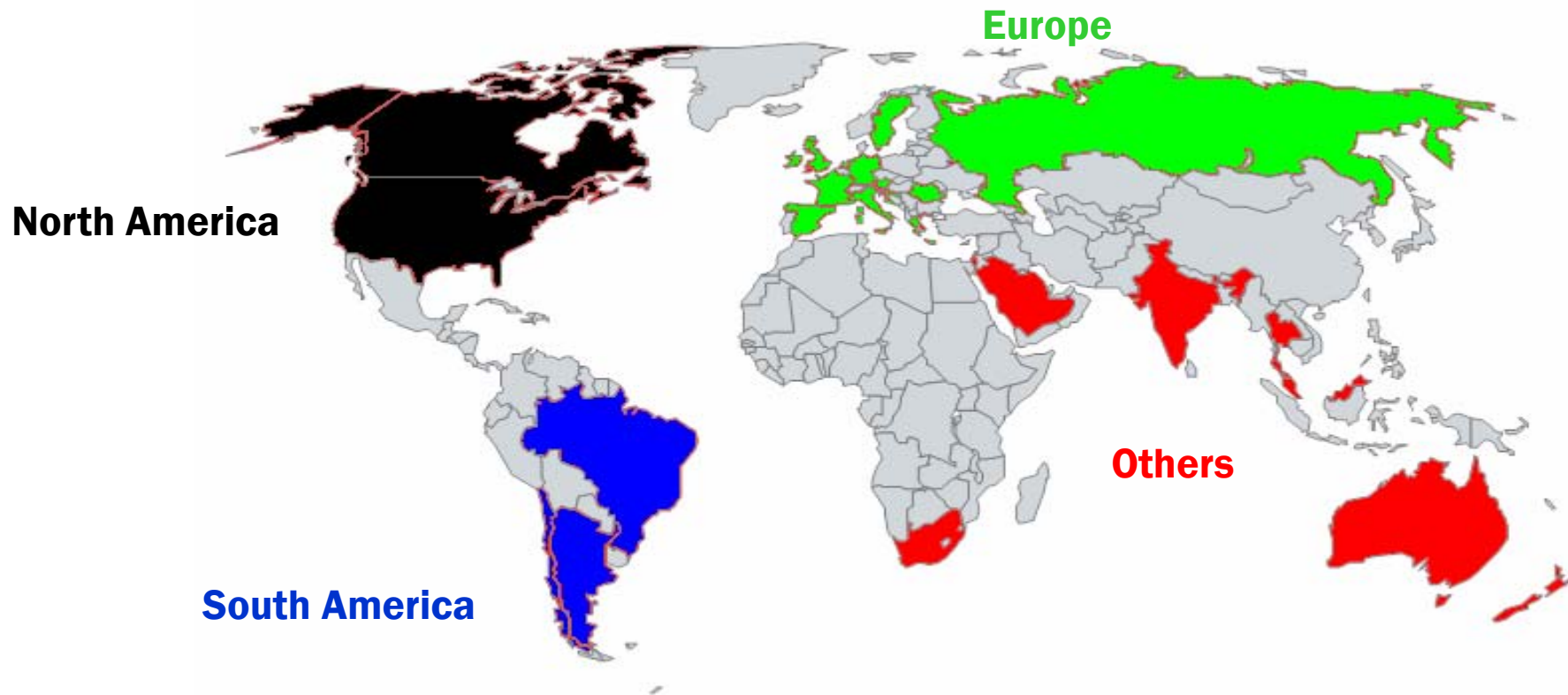
Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century

The International Collaboration on Endocarditis–Prospective Cohort Study

- 2781 adults with definite infective endocarditis admitted to 58 hospitals in 25 countries during 2000-2005
- Divided into 4 regions:
 - North America
 - South America
 - Europe
 - Others

Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century

The International Collaboration on Endocarditis–Prospective Cohort Study



Baseline Characteristics and Predisposing Conditions

	North America	South America	Europe	Other
Haemodialysis	21%	8%	4%	4%
Diabetes	27%	10%	14%	13%
Current IV drug use	16%	0.4%	9%	9%
Chronic IV access	25%	5%	5%	4%
Congenital heart disease	11%	22%	10%	13%

Causative microorganisms by region

	North America	South America	Europe	Other
<i>Staphylococcus aureus</i>	43%	17%	28%	32%
Viridans streptococci	9%	26%	16%	23%
Group D streptococci	2%	7%	10%	3%
HACEK bacteria	0.3%	2%	2%	2%
Negative blood cultures	7%	20%	10%	9%

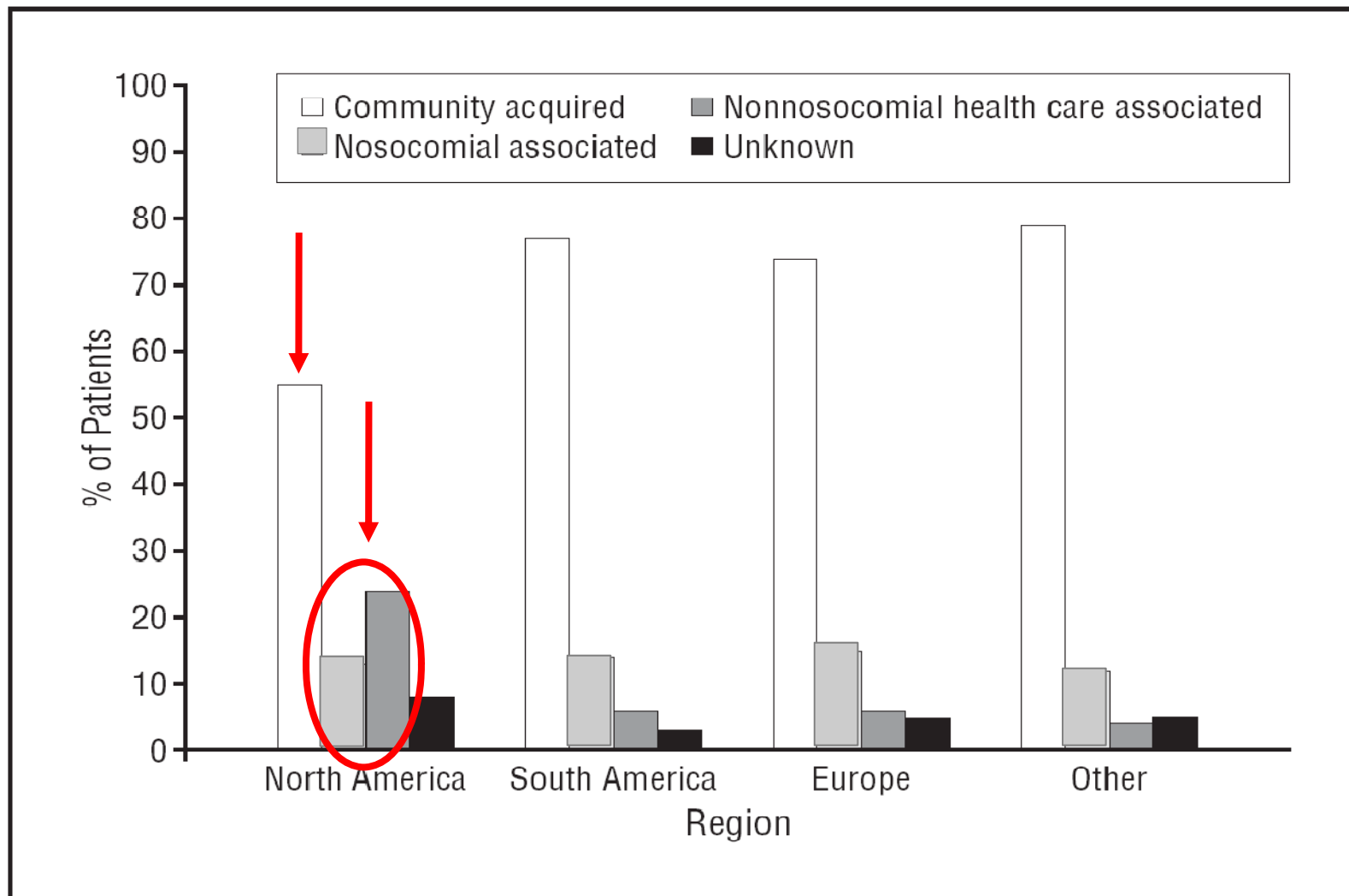


Figure. Geographic comparison of location of acquisition in 2781 patients with definite endocarditis.

In conclusion: from knowledge to acts

■ Facts (in industrialized countries)

- ❑ > 30% of IE are SA IE
- ❑ > 30% of SA IE are healthcare associated
- ❑ > 30% of PV IE are healthcare associated
- ❑ > 30% of HCA SA IE die

■ Consequences: public health and prophylaxis

- ❑ We **MUST** shift **NOW** from an outdated dental paradigm to an emergent "healthcare associated" paradigm.
-

Impact de la chirurgie valvulaire précoce sur
le pronostic de l'endocardite infectieuse :

Analyse critique de la méthodologie des
études observationnelles



Indications for surgery in IE

- Well-defined indications for surgery in IE
 - Congestive heart failure
 - Refractory infection
 - Severe anatomical/functional valve damages
- Major uncertain indication of surgery in IE
 - Prevention of embolic complication
- Benefits of surgery in IE are supported by clinical experience, not evidence-based
 - Absence of randomized trials
 - Unavoidable biases of observational studies
 - Overall, sicker patients are selected for surgery
 - The sickest patients are not operated on.

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%	

Does EVS improve outcome of SAPVIE?

	n	In-hospital mortality		p
		Ab + surgery	Ab alone	
Yu et al., 1994				
Any pathogens	64	5/22, 23%	29/52, 56%	0.01
<i>S. aureus</i>	15	0/4	9/11, 82%	0.01
Wolff et al., 1995				
Any pathogens	122	16/65, 25%	27/57, 47%	0,0001
<i>S. aureus</i>	40	11/20, 55%	20/20, 100%	<0.0001

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
 - Altered mental status 1.98
 - Comorbidity 1.76
 - Heart failure 1.91
 - Pathogen \neq viridans strep 4.87
 - No surgery 2.45

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

Analyse de propension (*propensity analysis*)

- ▶ Dans une étude observationnelle, une différence observée sous différents traitements peut ne pas être liée au choix du traitement mais aux raisons de ce choix (biais d'indication)



Analyse de propension (*propensity analysis*)

- ▶ Dans une étude observationnelle, une différence observée sous différents traitements peut ne pas être liée au choix du traitement mais aux raisons de ce choix (biais d'indication)
 - ▶ L'analyse de propension consiste à tenir compte, dans l'analyse de la relation entre l'exposition à un traitement et l'évolution, de la probabilité pour un patient d'avoir reçu une des options thérapeutiques en fonction de ses propres caractéristiques (facteurs de confusion)
-



Analyse de propension (*propensity analysis*)

- ▶ Un score de propension d'un sujet est défini comme sa probabilité conditionnelle d'être soumis à une exposition plutôt qu'à une autre (*opéré ou pas*), tenant compte des facteurs de confusion (*âge, comorbidités, ...*)
- ▶ On modélise ce score de propension à l'aide d'une régression logistique où la variable expliquée est l'exposition (*être opéré*) et les variables indépendantes sont les facteurs de confusion potentiels. Le modèle peut être "grossier" et inclure de nombreuses covariables, les interactions, des termes non linéaires...
- ▶ 2 patients avec le même score de propension ont la même probabilité d'exposition (*d'avoir été opéré*). Si l'un a été exposé (*opéré*) et l'autre pas, la répartition de l'exposition (*avoir été opéré ou pas*) peut être considérée comme "résultant du hasard" et conditionnelle aux facteurs de confusion
- ▶ Et donc, après ajustement (voire appariement) sur le score de propension, les facteurs de confusion sont équilibrés entre les patients exposés et non exposés (*opérés et non opérés*), "un peu comme" dans un essai thérapeutique...



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)

Surgical therapy for prosthetic valve IE:

A propensity analysis of a multicenter, international cohort

	Surgery (n = 148)	No surgery (n = 207)	P
CHF	53.4 (79/148)	28.0 (58/207)	<.001
Systemic embolization	25.0 (37/148)	29.0 (60/207)	.406
Brain embolization	19.4 (27/139)	18.5 (34/184)	.830
Intracardiac abscess	35.1 (52/148)	8.2 (17/207)	<.001
Inhospital death	25.0 (36/144)	23.4 (47/201)	.729

Variable	Wald χ^2	P
Intracardiac abscess	33.95	<.001
CHF	20.45	<.001
Age	18.06	<.001
Coagulase-negative staphylococci	7.88	.005
Year of diagnosis	6.14	.013
<i>S aureus</i> infection	3.92	.048
Mitral valve vegetation	3.06	.080

Surgical therapy for prosthetic valve IE:

A propensity analysis of a multicenter, international cohort

Logistic regression analysis of variables independently associated with in-hospital mortality in patients with PVIE, matched propensity for surgical treatment

Variable	OR	95% CI	P
<i>S aureus</i> infection	3.67	1.39-9.74	.009
Brain embolization	11.12	4.16-29.73	<.001
Surgery	0.56	0.23-1.36	.198

- After adjustment for factors associated with the use of surgery, this study shows no clear survival benefit attributable to surgery.

Surgery in patients with native valve IE: Results from the ICE-MD

	Surgery (n=610)	No Surgery (n=906)	p-value
Age, years	54.7 ± 15.2	61.1 ± 17.4	<0.001
Male	73.9%	63.7%	<0.001
<i>S. aureus</i> , %(n)	20.8%	25.4%	0.04
Staph coag neg	9.0%	5.2%	0.004
Strep, viridans gr.	24.6%	30.7%	0.001
Aortic v. alone	33.3%	23.3%	<0.001
Mitral v. valve	29.6%	37.1%	0.007
CHF	55.9%	26.2%	<0.001
Death, hosp	13.6%	16.4%	0.14

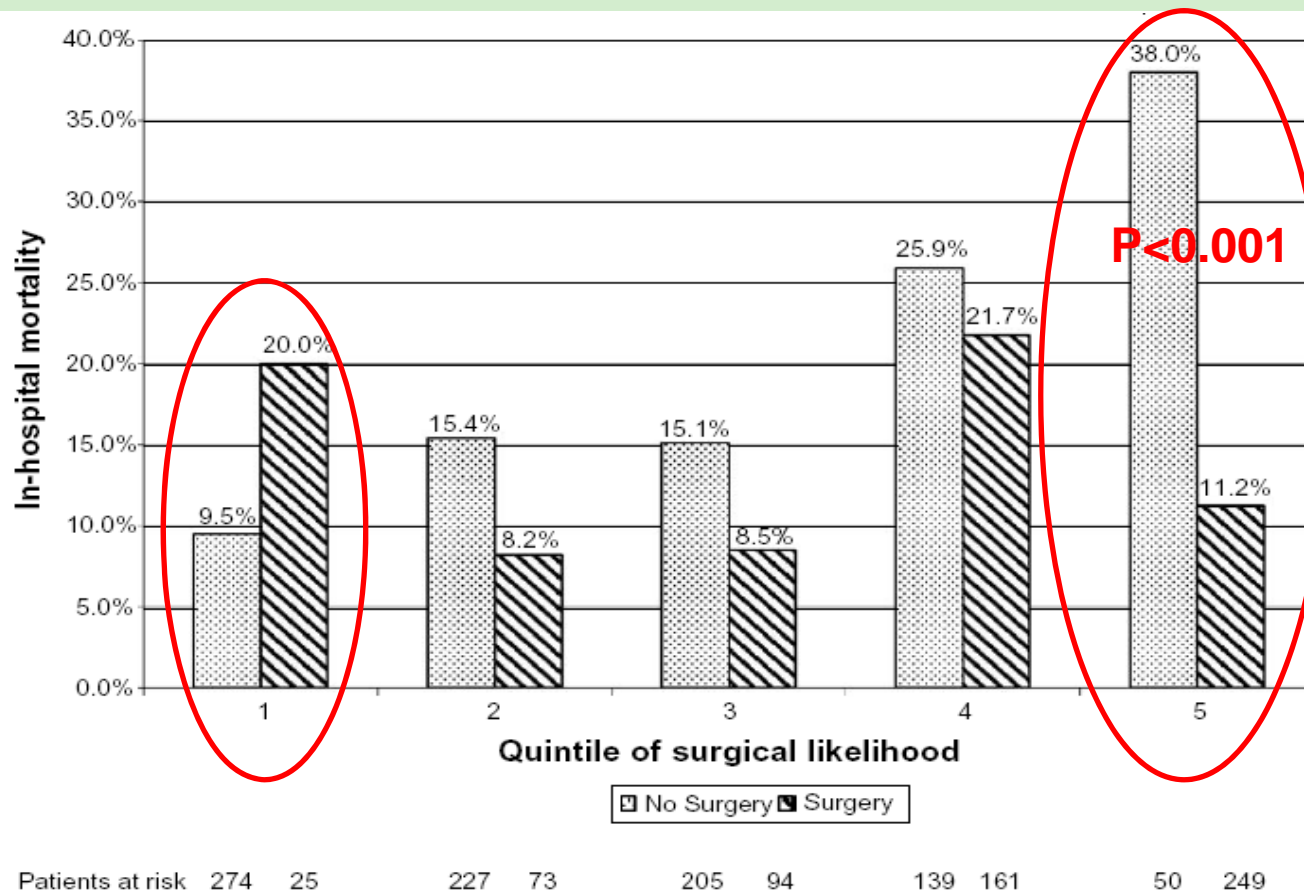
Surgery in patients with native valve IE: Results from the ICE-MD

- Variables included in the propensity model
 - age, sex, year of diagnosis, site of enrollment,
 - *S. aureus*, coag-neg staphylococci, viridans streptococci,
 - vegetation location, intracardiac abscess, CHF, systemic embolization, and cerebral embolization.

	Propensity group				
	1 (n = 299)	2 (n = 300)	3 (n = 299)	4 (n = 300)	5 (n = 299)
Female	47.5	33.7	35.5	25.0	20.1
<i>S aureus</i>	31.4	20.0	27.1	24.3	16.1
Coagulase-negative staphylococci	2.7	5.0	5.0	9.0	12.4
Viridans group streptococci	39.1	34.3	23.1	21.0	23.4
AV vegetation	10.0	20.0	26.8	31.7	52.2
MV vegetation	32.4	33.0	38.5	37.0	26.8
TV vegetation	10.4	5.0	5.7	4.3	1.7
CHF	0.7	12.0	36.5	68.0	73.6
Abscess	0.0	0.0	0.0	6.0	43.1
Embolization, systemic	31.8	31.3	37.5	36.3	30.1

Surgery in patients with native valve IE: Results from the ICE-MD

Mortality rates: 13.6% (S) vs 16.4% (No S), $p=.14$



Early Valve Surgery in Patients with IE: A Propensity Score Analysis

- **Methods** : Propensity analysis (control for bias in Rx assignment)
 - Observational cohort study (1996–2002) : 333 pts with LS IE
 - 78 (23%) underwent valve surgery
 - 255 (77%) received medical therapy alone
 - 51 patients in each group were propensity-matched
 - Endpoint: 5-year mortality
- **Results**

Characteristic	χ^2 test score	Hazard ratio (95% CI)
Surgery	13.01	0.27 (0.13–0.55)
Diabetes mellitus	19.80	4.81 (2.41–9.62)
Chronic indwelling central catheter	7.43	2.65 (1.31–5.33)
Paravalvular complications	4.43	2.16 (1.06–4.44)

The impact of valve surgery on 6-month mortality in left-sided IE

■ Methods : Propensity analysis

- Observational cohort study (1980–1998) : 546 pts with LS IE
 - 129 (23.6%) underwent valve surgery
 - 417 (76.4%) received medical therapy alone
 - 91 patients in each group were propensity-matched
- Endpoint: 6-month mortality

■ Results

Analysis	Unadjusted	Adjusted for Logit (Propensity)	Adjusted for Logit (Propensity) and Individual Covariates*
Matched cohort 93 pairs, total (n=186)	1.6 (0.8 to 2.9)	1.7 (0.9 to 3.2)	1.3 (0.5 to 3.1)
<i>P</i>	0.16	0.12	0.56
Time-dependent covariate without lag (n=546)	2.1 (1.4 to 3.4)	2.3 (1.4 to 3.8)	1.9 (1.1 to 3.2)
<i>P</i>	0.001	0.001	0.02
Time-dependent covariate with 3-day lag (n=546)	1.8 (1.2 to 2.8)	1.9 (1.2 to 3.0)	1.5 (0.9 to 2.6)
<i>P</i>	0.005	0.009	0.11

Synthèse des 5 analyses de propension sur chirurgie précoce et pronostic de l'EI

	Vikram 2003	Wang 2005	Cabell 2005	Aksoy 2007	Tleyjeh 2007
N	513	367	1516	426	546
Valve	N–G	P–G/D	N–G/D	N/P–G/D	N/P–G
Format Chir	Binaire	Binaire	Binaire	Binaire	Dep. Tps
Échéance	6 mois	Hospit	Hospit	5 ans	6 mois
Mortalité	↓	↔	↔	↓	↑

Overview of the 5 propensity analyses of the relation between early valve surgery and outcome of IE

Vikram *Jama* 2003

0.40 (0.18-0.91)

Wang *Am Heart J* 2005

0.56 (0.23-1.36)

Cabell *Am Heart J* 2005

NS

Aksoy *Clin Infect dis* 2007

0.27 (0.13-0.55)

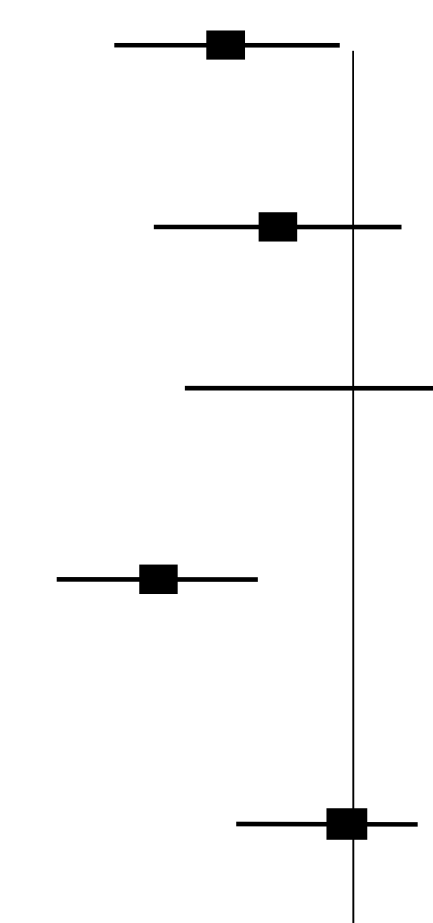
Tleyjeh *Circulation* 2007

6.21 (2.72-14.18)

0.92 (0.48-1.76)

RR of death

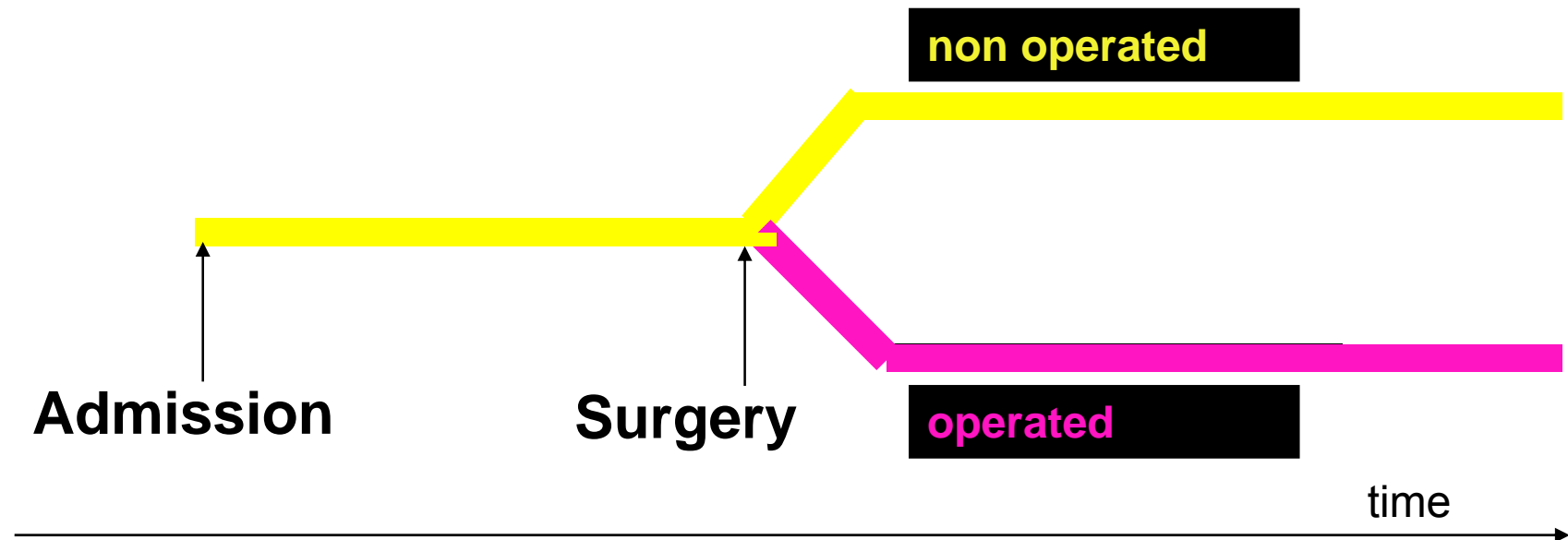
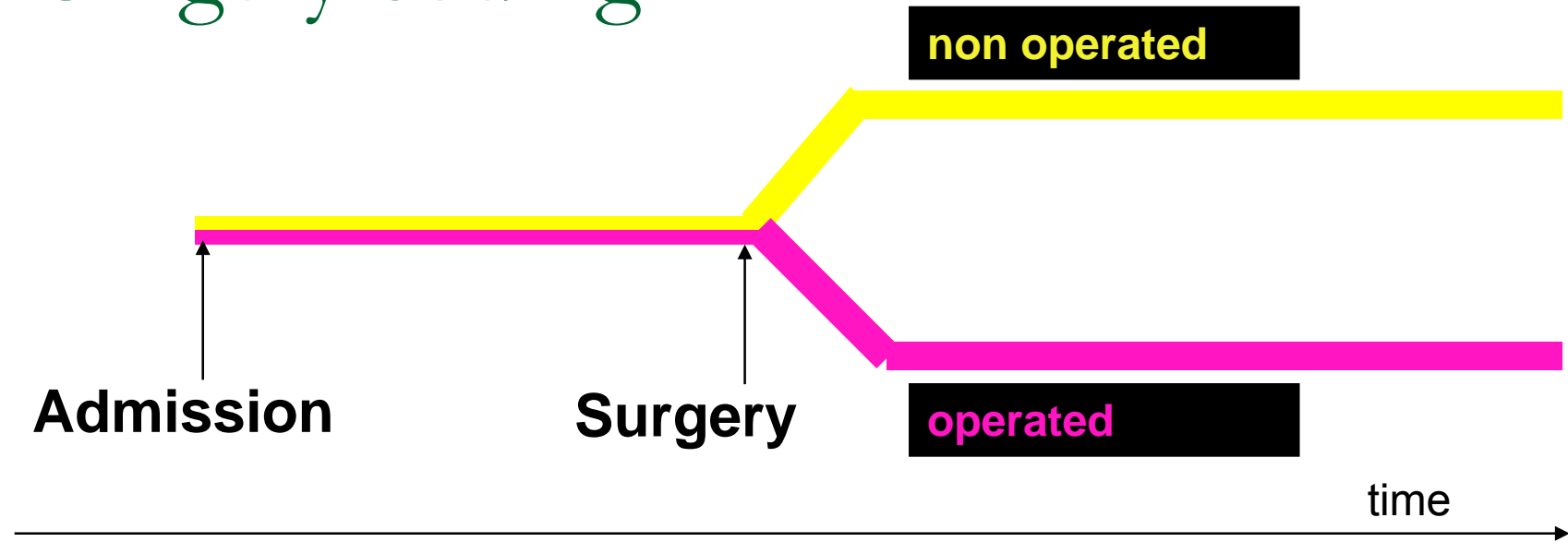
0,1 0,2 0,5 1 2 5 10 100



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
-

1. Surgery coding



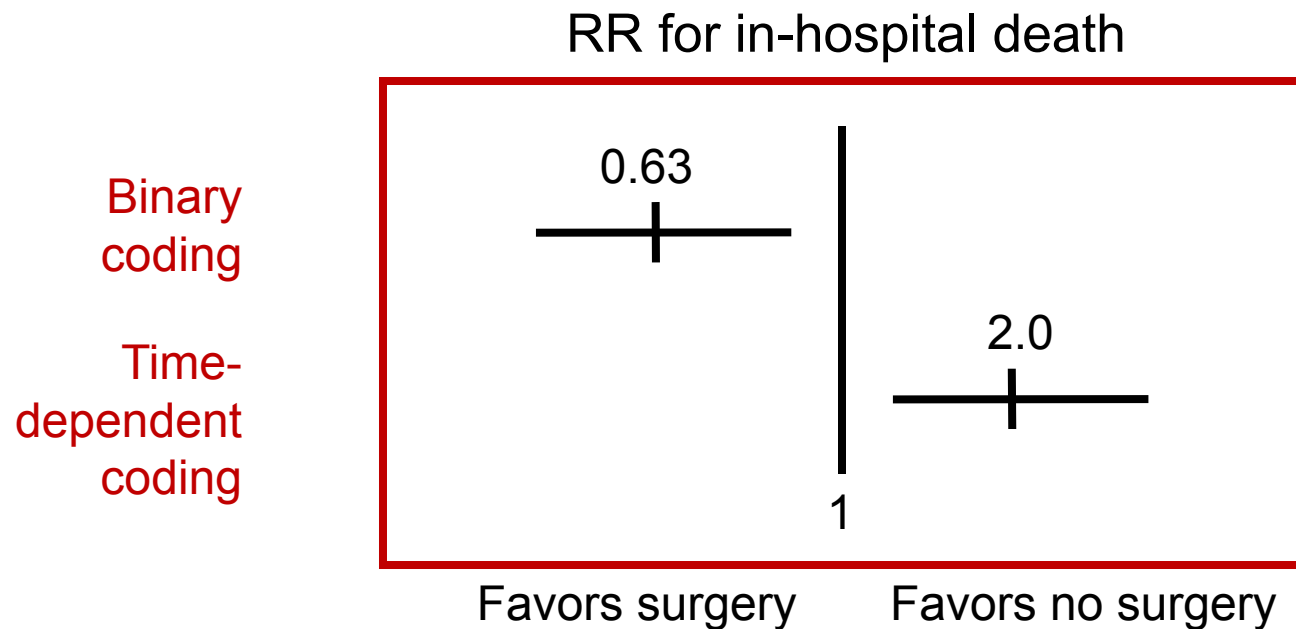
1. Surgery coding

- Valve surgery occurs at some time in the course of follow-up. An analysis in which surgery is coded as a binary variable ignores this fact
- Patients who live longer are more likely to receive any treatment than patients who die early. As a result of this bias, one can mistakenly interpret the correlation of longer survival with use of a particular treatment as evidence that treatment improves survival.
- This leads to a "survivor treatment selection bias", which can make ineffective treatments appear to be beneficial, and therefore lead to erroneous conclusions!
- One way to control this bias is to use a time-dependent coding for surgery
- A time-dependent variable is a variable whose value may change over time: patients who undergo surgery remain in the non-surgical group until the date of surgery

1. Surgery coding

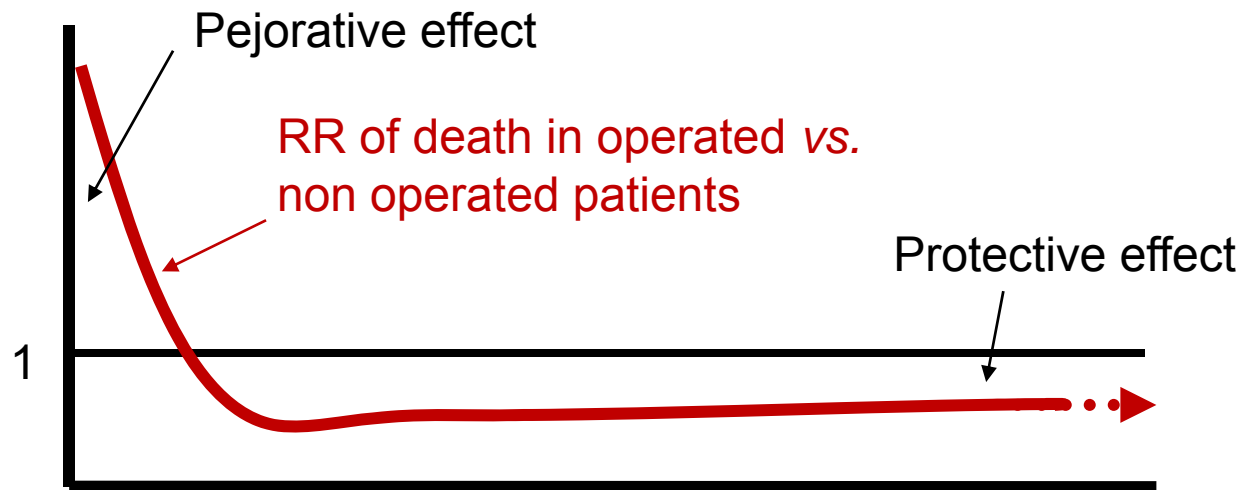
- La chirurgie valvulaire est réalisée à des moments variables de l'évolution. Si on code la variable chirurgie de façon binaire, on ignore cet effet du moment de la chirurgie
- Les patients qui vivent plus longtemps ont une probabilité plus élevée de recevoir un traitement (quel qu'il soit) que ceux qui meurent précocement. Du fait de ce biais, on peut faire l'erreur de raisonnement d'interpréter le lien entre survie plus longue et recours à un traitement particulier comme la preuve que ce traitement améliore la survie !
- Ce "survivor treatment selection bias" peut faire apparaître efficace un traitement n'ayant aucune efficacité réelle...
- Une façon de contrôler ce biais est de coder la chirurgie comme une variable dépendant du temps. Une variable dépendant du temps change de valeur au cours du temps (0 jusqu'à la chirurgie, 1 à partir de la chirurgie)

1. Surgery coding



2. Follow-up duration

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

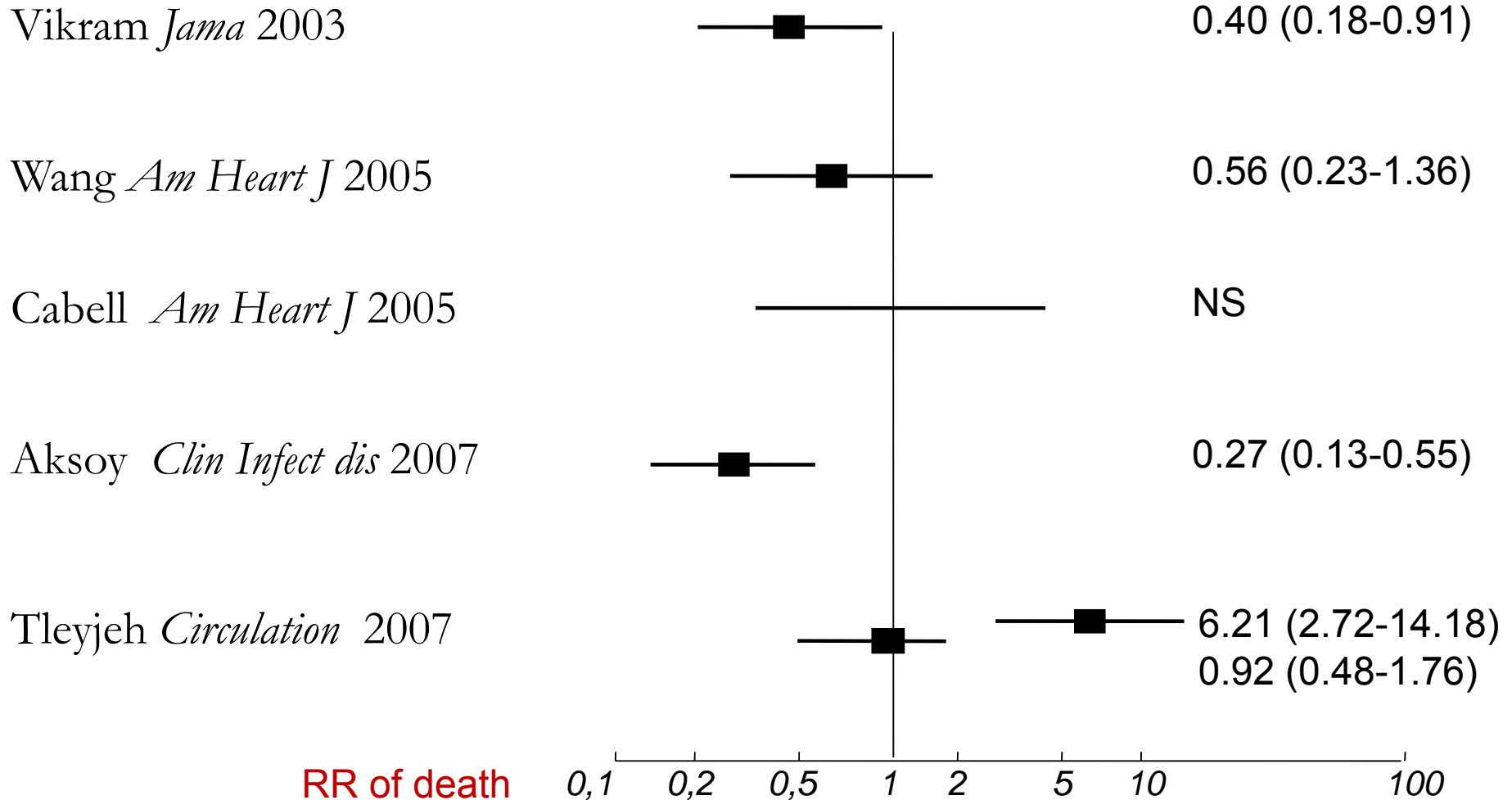


- Two RRs must be calculated (a short-term and a long-term RR)
- Follow-up duration must be long enough for the high early post-operative risk be offset by the long-term protective effect of surgery

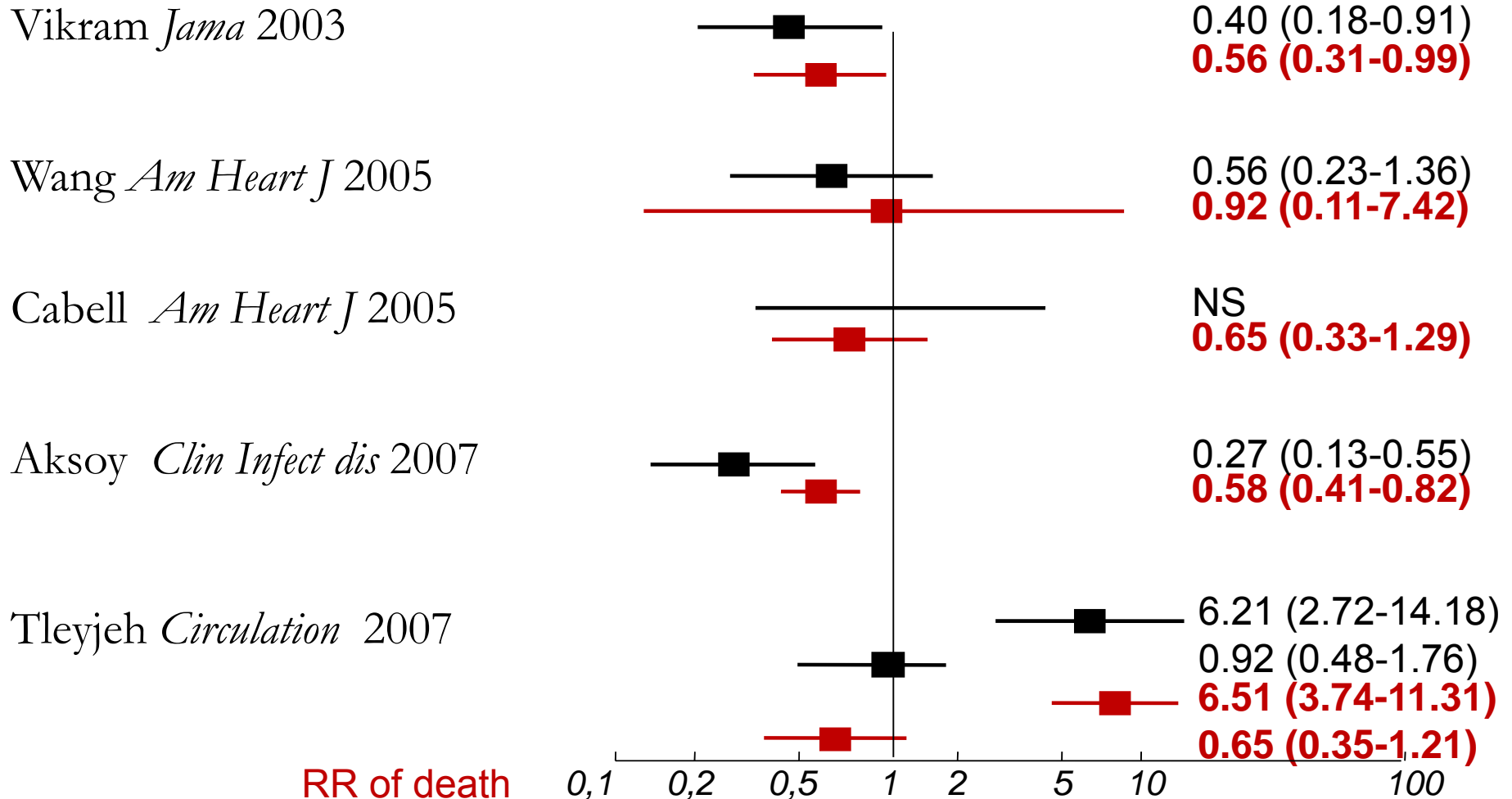
Objective and methods

- **Objective:** to evaluate whether conflicting results reported by previous studies could be explained by differences in their methodological approaches.
- **Methods**
 - Population: 559 IE patients from the French nationwide 1999 study, followed up for 5 years
 - Statistical analysis: we re-analyzed the relationship between valve surgery and mortality in our database, using each of the methods used in the five previous studies (i.e. inclusion criteria, follow-up duration, statistical model, surgery coding)

Results



Results



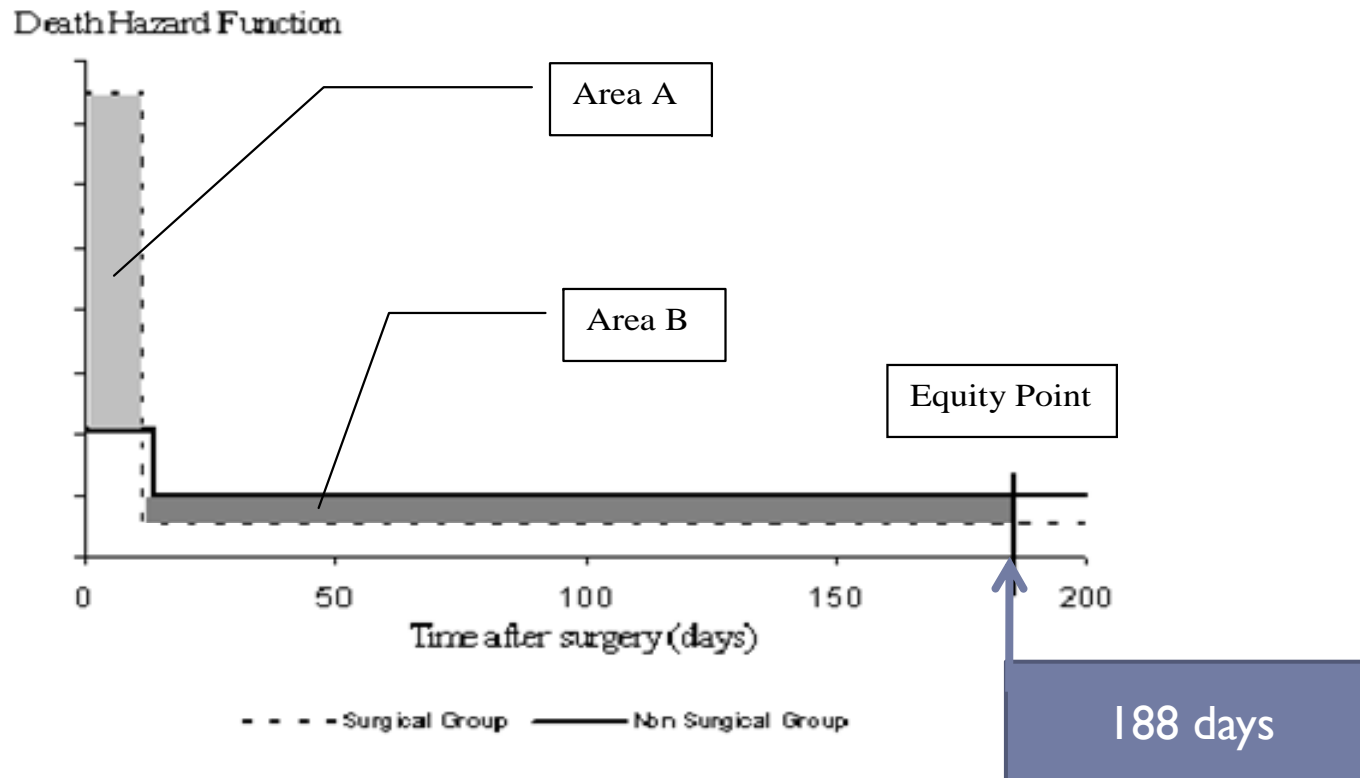
Relationship between early valve surgery and mortality (left-sided valve IE)

	Adjusted RR
Post-operative surgery risk (0-14 days)	3.69 (2.17-6.25)
Long-term surgery risk (15 days-5 years)	0.55 (0.35-0.87)

Equity point
=
188 Days

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)



Conclusion 1

- Les discordances observées entre les études sont très probablement attribuables à leurs méthodes d'analyse différentes.
 - Ces méthodes sont inadéquates pour plusieurs d'entre elles:
 - Non prise en compte du biais de survie (4/5)
 - Suivi trop court pour observer l'effet bénéfique à long terme de la chirurgie (4/5)
 - Variable chirurgie non dépendante du temps (4/5)
-

Conclusion 2

- Si méthodologie appropriée
 - Modèle multivarié dépendant du temps (Cox)
 - Variable expliquée dépendante du temps
 - Ajustement sur score de propension et variables pronostiques
 - Prise en compte du biais de survie

 - la chirurgie valvulaire précoce est associée
 - à un sur-risque de décès à court terme (jusqu'à 6 mois)
 - à un effet protecteur à long terme.
-

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)





Presentation Number: K-3757

Tuesday, Oct 28, 2008, session 265: Breaking your heart with infection

Does Early Valve Surgery (EVS) Improve the Outcome of *Staphylococcus aureus* (SA) Prosthetic Valve Infective Endocarditis (PVIE)?

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On behalf of the ICE-PCS study group



EVS and outcome in IE

- ▶ Absence of randomized trials
- ▶ In observational studies, biases are almost unavoidable
 - ▶ Overall, sicker patients are selected for surgery
 - ▶ The sickest patients are not operated on
- ▶ Multivariate, propensity-adjusted prognosis models did help but did not completely solve the problem



Does EVS improve outcome of SAPVIE?

	n	In-hospital mortality		p
		Ab + surgery	Ab alone	
Yu et al., 1994				
Any pathogens	64	5/22, 23%	29/52, 56%	0.01
<i>S. aureus</i>	15	0/4	9/11, 82%	0.01
Wolff et al., 1995				
Any pathogens	122	16/65, 25%	27/57, 47%	0,0001
<i>S. aureus</i>	40	11/20, 55%	20/20, 100%	<0.0001

S. aureus prosthetic valve endocarditis: optimal management and risk factors for death

Risk factor	N, % dead	Multivariate log. regression		Multivariate Cox model	
		OR (IC95)	p	RR (IC95)	p
Cardiac complication	Y: 12/22, 55 N: 2/11, 18	13.7 (1.4–131)	0.02	6.1 (1,3–28,2)	0.02
Early valve replacement	Y: 2/14, 14 N: 12/19, 63	0.05 (0.005–0.4)	0,004	0.18 (0.04–0.89)	0.04

S. aureus prosthetic valve endocarditis: optimal management and risk factors for death

- ▶ 33 cases of SAPVIE collected from 1975 to 1995
 - ▶ 20 M/13 F, 22 mechanical valves, 11 bioprosthetic valves
- ▶ Risk factors analyzed
 - ▶ Age, sex
 - ▶ Prosthetic valve-related
 - ▶ Year of IE: 1975-84 / 1985-95
 - ▶ Delay of onset after valve insertion: ≤ 12 mois / > 12 mois
 - ▶ type : mechanical / bioprosthetic
 - ▶ Location: aortic valve / mitral valve
 - ▶ Complications
 - ▶ cardiac : yes/no
 - ▶ neurologic : yes/no
 - ▶ systemic : yes/no
 - ▶ Valve replacement during antibiotic Rx: yes/no

Prognosis in 61 cases of SAPVIE from ICE-MD

- ▶ No prognostic impact of age, sex, comorbidity, intracardiac abscess

Potential prognostic characteristic	No. of patients who died/ no. of patients with indicated characteristic (%)	Analysis			
		Univariate		Multivariate	
		OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Cardiac complication					
No	17/32 (53)	1
Yes	12/29 (41)	0.62 (0.2–1.8)	.36
Any embolic complication					
No	16/36 (44)	1
Yes	13/25 (52)	1.4 (0.5–3.9)	.56
Stroke					
No	20/47 (43)	1	...	1	...
Yes	9/14 (64)	2.4 (0.7–8.6)	.15	3.04 (0.8–11.6)	.09
Early valve replacement					
No	19/40 (48)	1
Yes	10/21 (48)	1.0 (0.34–3.0)	.99

Objectives and Methods

▶ Objectives

- ▶ Update the data obtained on ICE-MD, using ICE-PCS data
- ▶ Re-assess the role of EVS as a "protective factor", i.e. likely to significantly improve outcome

▶ Methods

▶ Definitions

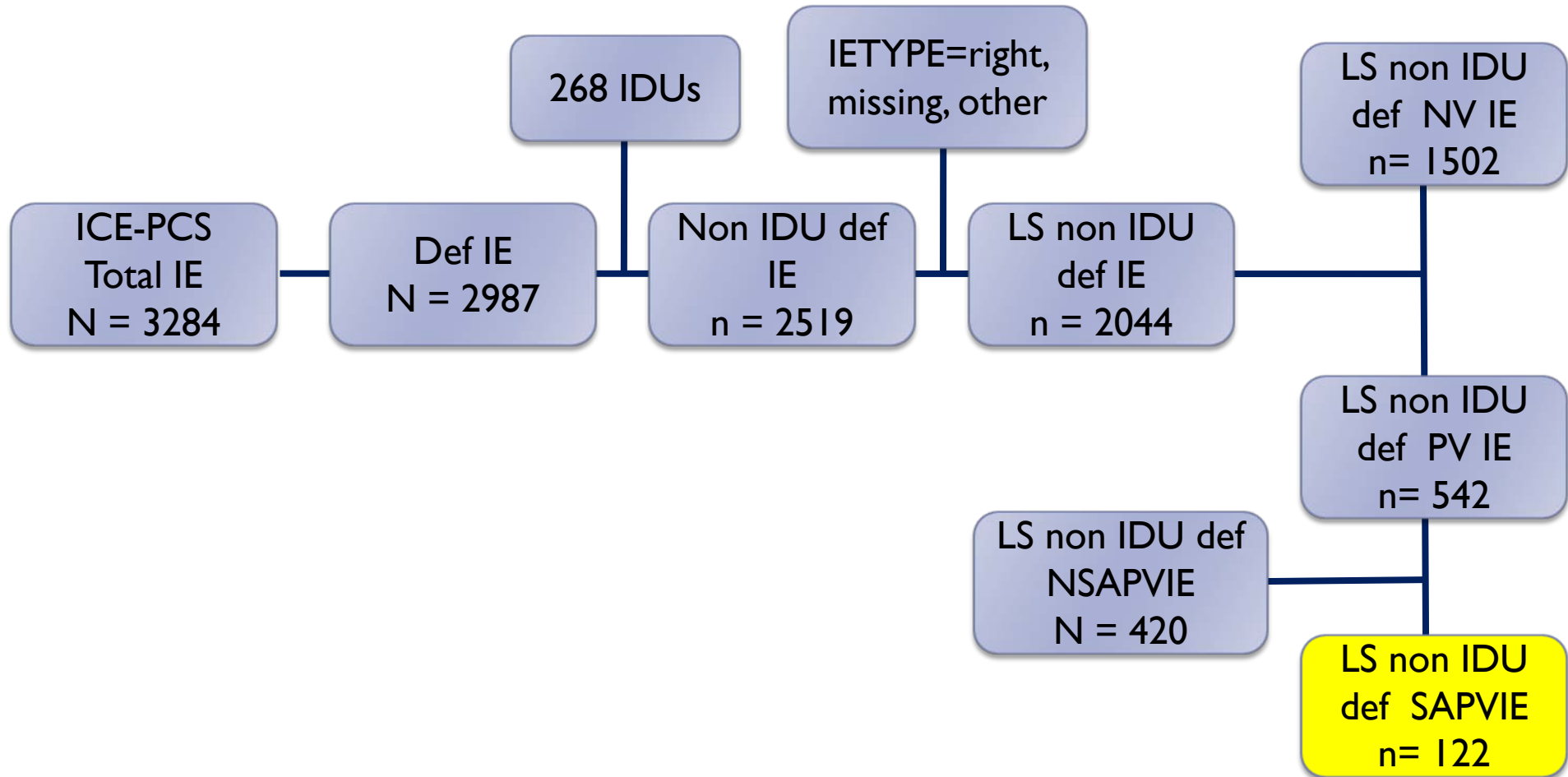
- ▶ EVS: valve surgery performed during the course of antibiotic therapy
- ▶ Outcome: mortality at the end of hospitalization

▶ Multivariate prognosis model

- ▶ Age, sex, center, comorbidities
 - ▶ Echo findings: vegetations, abscess, PV dehiscence
 - ▶ Stroke (time-dependent), embolic events, CHF, cardiac complications
 - ▶ EVS (binary: Y/N within 60 d, and time-dependent)
-



Selection of cases



SA PVIE vs. non-SA PVIE

	nonSA PVIE N = 420	SA PVIE N = 122	P-val
Sex, % males	66	64	NS
Age, years (mean)	61	62	NS
Surgery within 60 d, %	50	43	NS
Death within 60 d, %	20	32	0.005



Prognostic factors on SAPVIE

▶ Independent predictors of death (adjusted Cox model)

Prognosis factors	RR [95% CI]	P value
Age, per one year increment	1.05 [1.02 – 1.08]	0.004
Stroke (time-dependent)	3.33 [1.52 – 7.28]	0.003
CHF (NYHA \geq 3)	3.61 [1.65 – 7.91]	0.004
Female gender	2.14 [1.02 – 4.51]	0.04

▶ Weight of EVS as a prognostic factor, according to the format of the variable

▶ Binary: RR 0.392 [0.176-0.872]; p = 0.0217

▶ Time-dependent : RR 0.789 [0.349-1.779]; p = 0.5671



Surgery and prognosis of SAPVIE

- ▶ Lethality rate in SAPVIE and EVS (within 60 d).
 - ▶ Operated: 15% Non-operated: 45%
 - ▶ RR 0.34 [0.17-0.67], $p < 0.0005$ (unadjusted)
- ▶ Re-calculation of RR when taking into account timing of surgery, i.e. encoding the 'surgery' variable into a partitioned time-dependent variable
 - ▶ RR 0.63 [0.29-1.41], $p = 0.26$ (unadjusted)
 - ▶ RR 0.79 [0.35-1.78], $p = 0.57$ (adjusted)
- ▶ RR for short-term mortality (death within 14 days post-op)
 - ▶ RR 1.51 [0.60-3.81], $p = 0.38$
- ▶ RR for mid-term mortality (14 days-2 months)
 - ▶ RR 0.324 [0.041-2.573], $p = 0.2865$



Does EVS improve outcome of SAPVIE?

- ▶ Yes, probably, BUT
 - ▶ It is NOT that EASY to demonstrate it, even using sophisticated analytic methods
 - ▶ It is IMPOSSIBLE to evidence the benefit as early as at the end of initial hospitalization
- ▶ More certainty will hopefully come from re-analysis of ICE-PCS after inclusion of one-year follow-up data
- ▶ EVS does not mean SASAP (surgery as soon as possible)
 - ▶ If current results tend to show an advantage for EVS, they give no indication on how early surgery should be performed
 - ▶ Let's always keep in mind to
 - ▶ be humble
 - ▶ do no harm

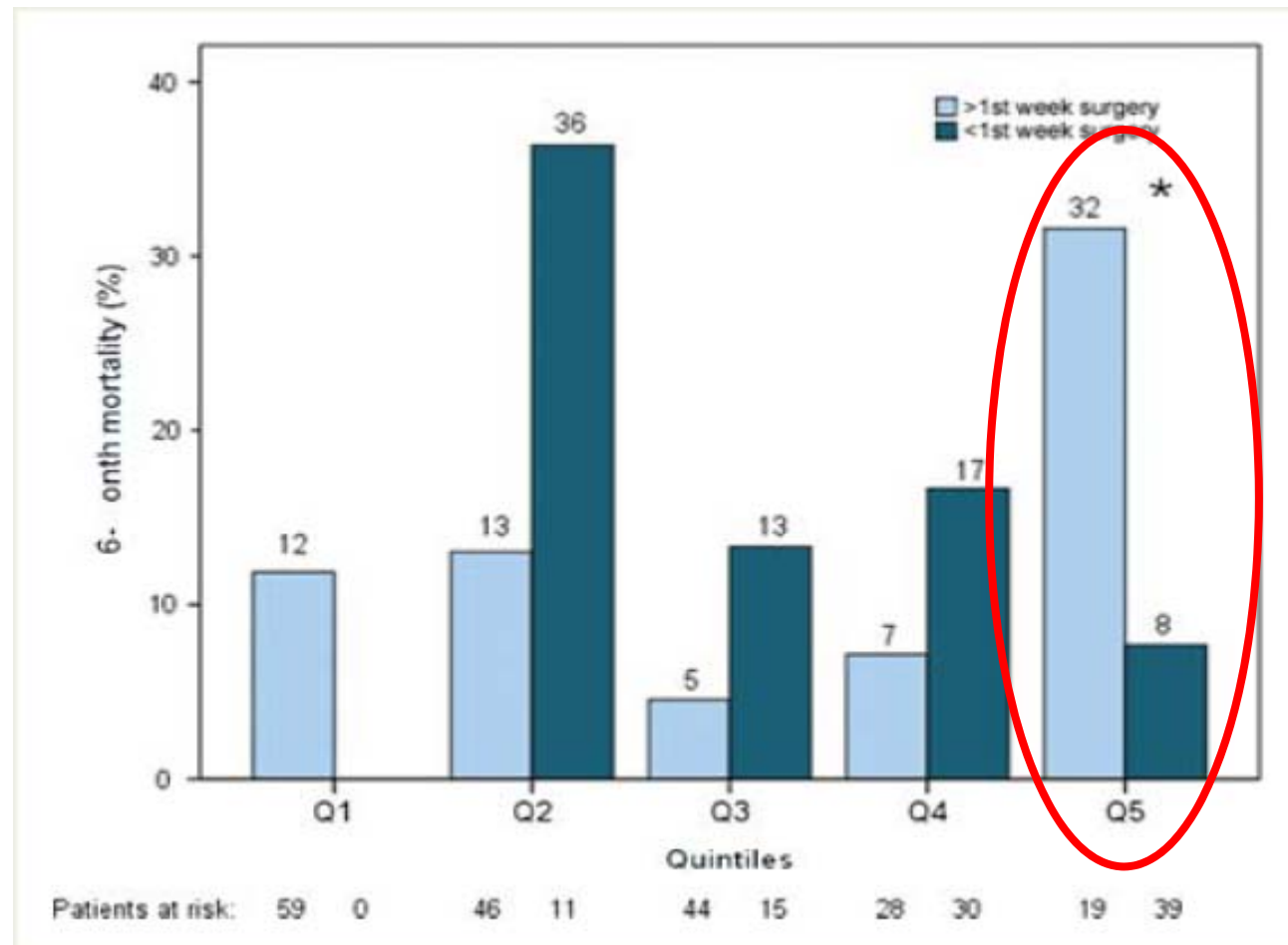


The timing of surgery influences mortality and morbidity in adults with severe complicated IE: a propensity analysis

	≤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

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

- Patients of the 5th quintile
 - were younger
 - were more likely to have
 - Sa IE
 - CHF
 - larger vegetations

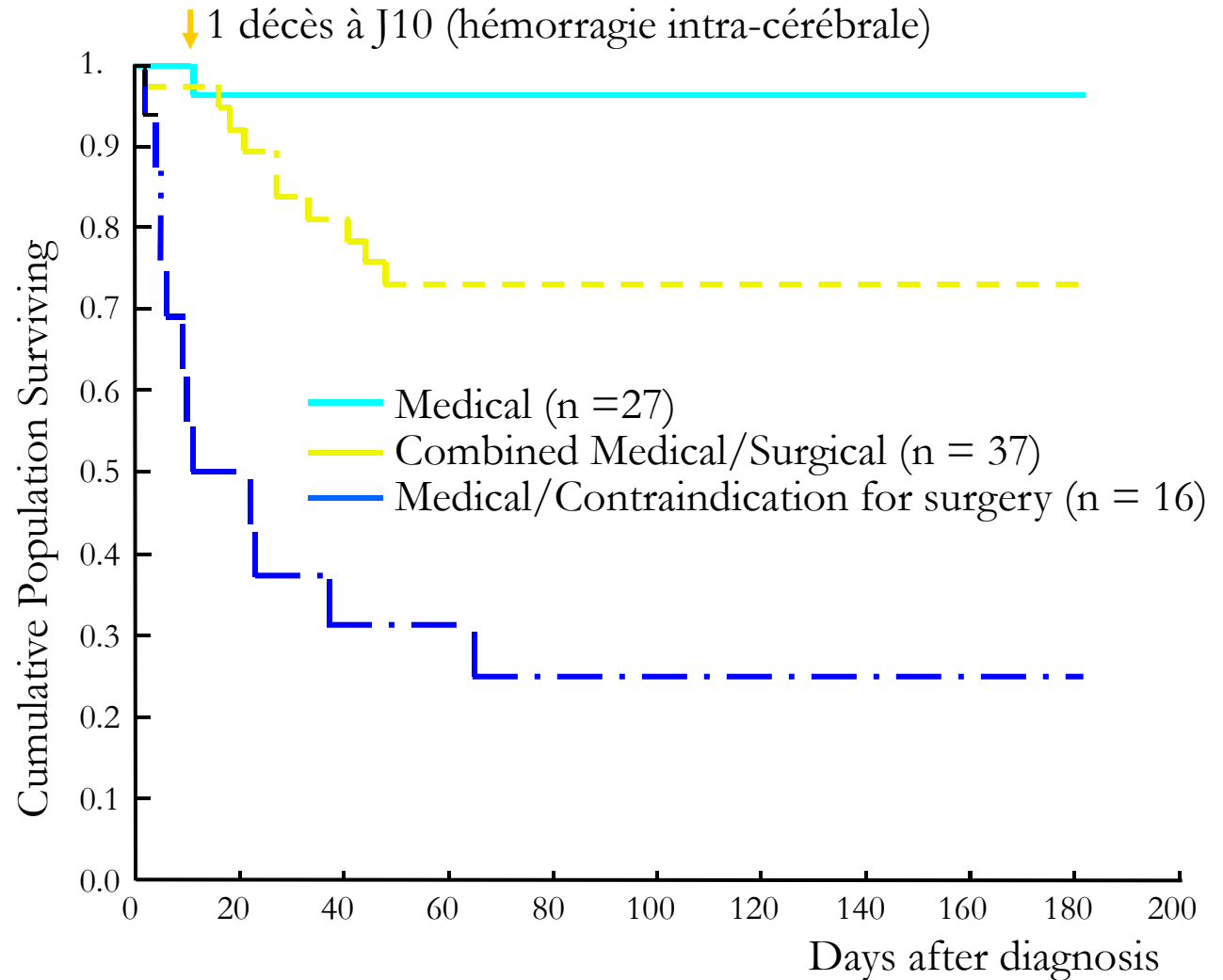


Management of prosthetic valve infective endocarditis

- Décrire et comparer les caractéristiques cliniques et la mortalité à 6 mois des EI/PV opérées *vs.* EI/PV non opérées (cohorte observationnelle – 2000 à 2006)
- 80 EI sur prothèse valvulaire (mécanique ou biologique)
 - traitement médico-chirurgical, n = 37
 - traitement médical choisi, n = 27
 - traitement médical "forcé", n = 16
- Délai médian entre le diagnostic et la chirurgie :
 - tous germes confondus : 9 jours
 - *S. aureus* : 3,5 jours

Management of prosthetic valve infective endocarditis

Taux de mortalité à 6 mois :
23/80 (29%)



Survie à 6 mois (courbe de Kaplan-Meier)

How to move forward?

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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Study objectives and inclusion criteria

- ▶ to compare the 30-day mortality rate in high-risk patients with active infective endocarditis between
 - ▶ an early surgical approach (surgery within the first 48 hours after inclusion or 5 days after initial diagnosis)
 - ▶ and the state-of-the-art treatment in this disease (medical treatment followed by elective surgery)

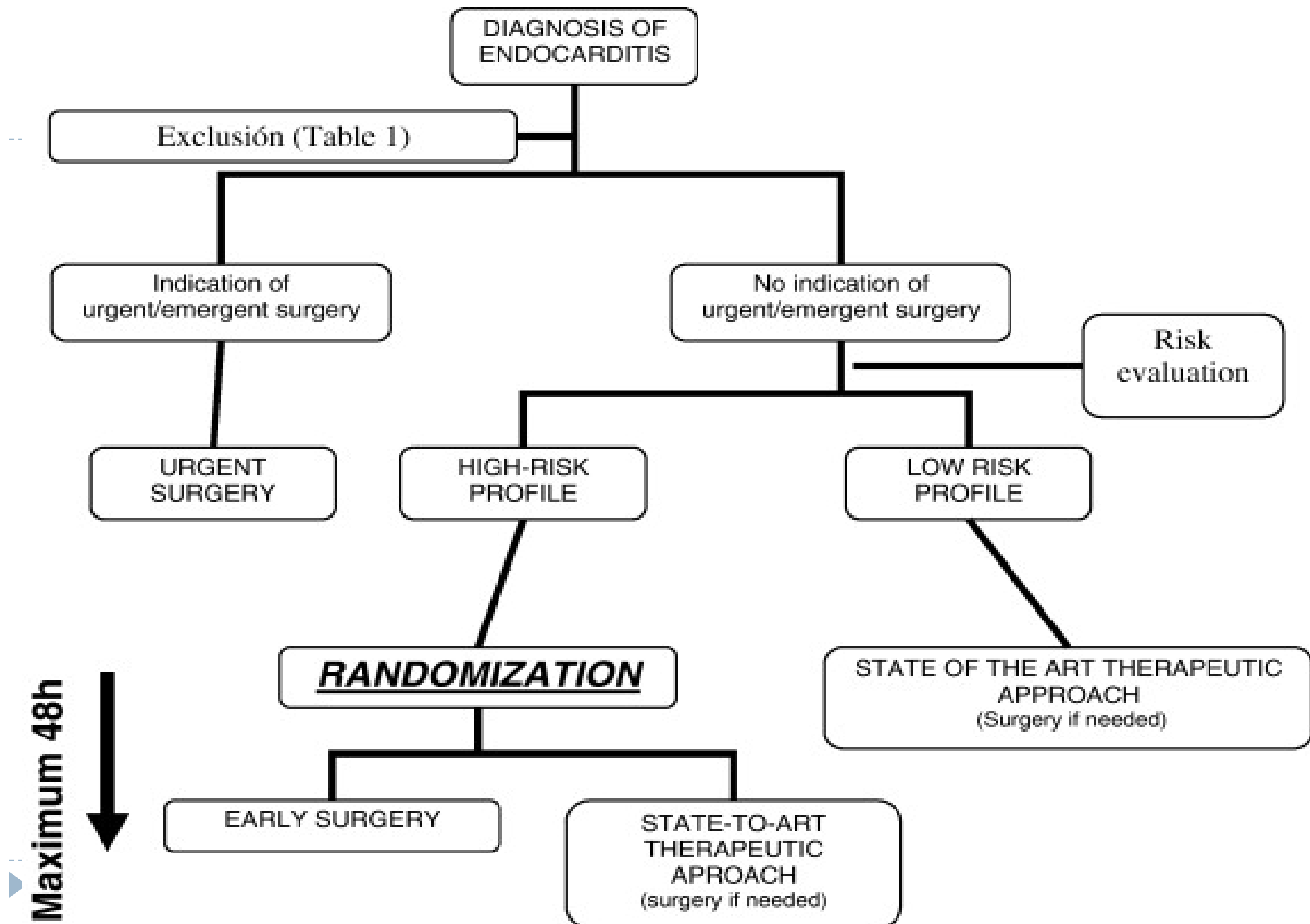
▶ Inclusion criteria

- ▶ Patients > 18 years old.
- ▶ Duke definite IE
- ▶ At least one of the following risk factors:
 - ▶ Periannular complications
 - ▶ New onset auriculo-ventricular block
 - ▶ New onset severe valvular insufficiency
 - ▶ Early-onset prosthetic valve endocarditis
 - ▶ *Staphylococcus aureus* endocarditis

Exclusion criteria

- Urgent indication for surgery
- Patients referred for surgery





Comments

- ▶ Well-targeted population and relevant selection procedures
- ▶ Endpoint at 30 days!
- ▶ Endpoint does not include relapses
- ▶ Optimistic assumptions for risk differences and accrual

	ENDOVAL	EI 1999 France
30-day mortality Control group (standard of care)	30%	6%-10%
30-day mortality Early surgery group (<5 jours)	13%	0%
Accrual previsions	248 3 years 6 centers	71/390 could be enrolled 1 year 19 centers



Conclusion : restons pragmatique

- ▶ Il n'y a pas de données justifiant la réalisation d'une chirurgie précoce systématique, même dans les EI sur prothèse, à Sa
- ▶ Les analyses/scores de propension ne permettent pas de dire que la chirurgie améliore le pronostic mais peuvent aider à sélectionner les malades qui vont bénéficier de la chirurgie
- ▶ Lorsque l'indication chirurgicale est posée, le pronostic est meilleur si la chirurgie est réalisée
- ▶ La chirurgie ultra-précoce ne peut être justifiée actuellement que par la gravité de l'état hémodynamique. Elle est associée à
 - ▶ une amélioration du pronostic vital
 - ▶ une augmentation du risque de rechute et de désinsertion
- ▶ Reste le difficile problème de la chirurgie valvulaire pour prévenir le risque embolique...

