



International Collaboration on Endocarditis

Endocardites infectieuses :
qu'avons-nous appris grâce à ICE ?

Bruno Hoen



ICE: History and Background

ICE-MD

- Merged dataset
 - 7 sites
 - IE cases from 1979-1999
-
- 2212 cases of IE
 - 13 published articles



ICE: History and Background

ICE-PCS

- Prospective cohort study
- 64 sites
- IE cases from 2000-2006
- 1 year follow-up
- Parallel projects: ICE Echo, ICE Micro
- 5595 cases of IE, 3857 with 1-year follow-up data
- 20 published manuscripts, more in the pipeline



ICE: History and Background

ICE Plus

- Focused prospective studies: Surgery & Daptomycin
- 30 sites
- September 2008 – present
- 6 month follow-up



ICE: 78 centers, 32 countries

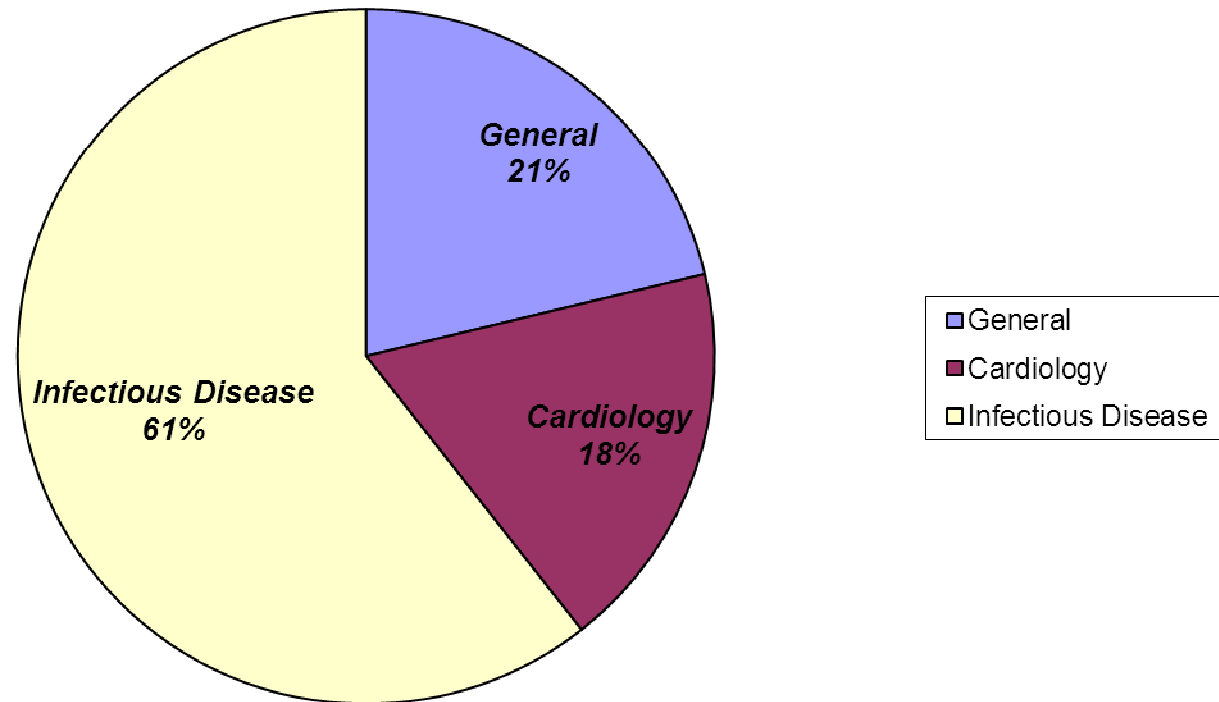
ARGENTINA	4	MEXICO	1
AUSTRALIA	10	NETHERLANDS	1
AUSTRIA	1	NEW ZEALAND	1
BRAZIL	6	ROMANIA	1
CANADA	1	RUSSIA	1
CHILE	2	SAUDI ARABIA	1
CROATIA	1	SINGAPORE	1
CZECH REPUBLIC	1	SLOVENIA	1
EGYPT	1	SOUTH AFRICA	1
FRANCE	6	SPAIN	5
GERMANY	2	SWEDEN	1
GREECE	2	THAILAND	1
INDIA	2	UNITED KINGDOM	2
IRELAND	1	USA	11
ISRAEL	2		
ITALY	4		
LEBANON	1		
MALAYSIA	1		



ICE: Journals by Therapeutic Area

Manuscripts: 35 (Merged: 13, PCS:22)

Published Manuscripts by Journal Therapeutic Area



Main objectives of ICE

- Capture a changing epidemiology in real time
 - Describe infrequent/selected conditions
 - Enterococcal, *S. bovis*, *Candida*, ...
 - Diabetes, hemodialysis
 - PV IE, IE with intracardiac abscess
 - Improve prognosis approach
 - Including "bedside prognosis" and propensity analysis as an aid to individual decision
 - Assess the impact of surgery on outcome and refine indications for surgery
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Main Results of the ICE project

- Changing epidemiology
 - Shift from streptococci to staphylococci
 - A growing proportion of healthcare-associated IE
 - Description of subgroups of IE
 - Enterococci
 - Coagulase-negative streptococci
 - HACEK and Gram-negative
 - Surgery in IE
 - The limits of analysis of observational data, even using sophisticated statistical methods
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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

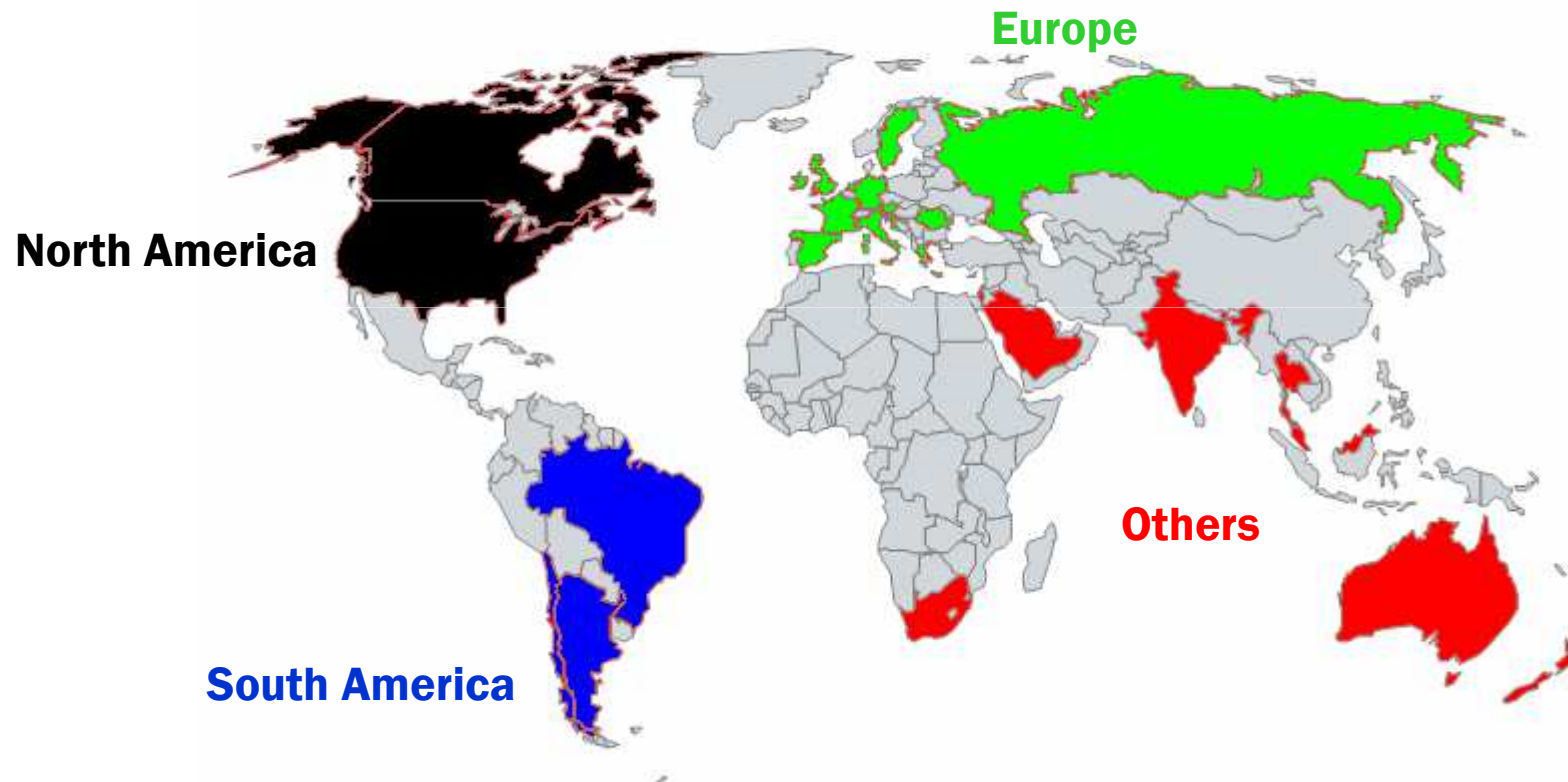


Table 2. Baseline Characteristics and Predisposing Conditions in 2781 Patients With Definite Endocarditis^a

	Total Cohort	Patients Admitted Directly to Study Sites Only ^b	Region				P Value for the Difference in Regions
			North America	South America	Europe	Other	
Baseline characteristics							
Age, median (IQR), y	57.9 (43.2-71.8)	59.8 (44.2-73.1)	52.9 (44.1-66.4)	56.8 (40.3-70.4)	61.4 (45.1-72.7)	58.0 (40.5-72.9)	<.001
Male	1889/2777 (68)	1045/1556 (67)	388/596 (65)	179/254 (70)	873/1212 (72)	449/715 (63)	<.001
First sign to admission <1 mo	2088/2711 (77)	1201/1529 (79)	496/582 (85)	166/244 (68)	896/1174 (76)	530/711 (75)	<.001
Hemodialysis	220/2777 (8)	130/1556 (8)	124/596 (21)	20/254 (8)	49/1210 (4)	27/717 (4)	<.001
Diabetes mellitus	447/2764 (16)	261/1550 (17)	158/592 (27)	25/253 (10)	169/1207 (14)	95/712 (13)	<.001
HIV positive	58/2748 (2)	41/1540 (3)	16/594 (3)	4/236 (2)	33/1211 (3)	5/707 (0.7)	.02
Cancer	230/2772 (8)	160/1553 (10)	52/596 (9)	15/251 (6)	101/1210 (8)	62/715 (9)	.56
IE type							.05
Native valve	1901/2636 (72)	1048/1471 (71)	411/573 (72)	167/246 (68)	860/1166 (74)	463/651 (71)	
Prosthetic valve	563/2636 (21)	321/1471 (22)	116/573 (20)	66/246 (27)	227/1166 (20)	154/651 (24)	
Pacemaker/ICD	172/2636 (7)	102/1471 (7)	46/573 (8)	13/246 (5)	79/1166 (7)	34/651 (5)	
Predisposing conditions							
Current IV drug use	268/2746 (10)	157/1540 (10)	93/587 (16)	1/249 (0.4)	113/1203 (9)	61/707 (9)	<.001
Previous IE	222/2780 (8)	138/1557 (9)	66/596 (11)	26/254 (10)	84/1213 (7)	46/717 (6)	.003
Invasive procedure within 60 d	690/2581 (27)	392/1463 (27)	162/508 (32)	64/247 (26)	289/1145 (25)	175/681 (26)	.03
Chronic IV access	244/2763 (9)	142/1548 (9)	148/595 (25)	12/251 (5)	56/1205 (5)	28/712 (4)	<.001
Endocavitary device							
Pacemaker	262/2752 (10)	146/1540 (9)	55/595 (9)	23/252 (9)	137/1191 (12)	47/714 (7)	.005
ICD	27/2720 (1)	15/1521 (1)	16/593 (3)	0/249 (0)	8/1172 (0.7)	3/706 (0.4)	<.001
Congenital heart disease	311/2656 (12)	167/1481 (11)	62/582 (11)	53/244 (22)	111/1156 (10)	85/674 (13)	<.001
Native valve predisposition	884/2761 (32)	538/1547 (35)	147/596 (25)	93/252 (37)	370/1201 (31)	274/712 (38)	<.001

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%

Table 4. Microbiologic Etiology by Region in 2781 Patients With Definite Endocarditis

Cause of Endocarditis	No. (%) of Patients ^a						P Value for the Difference Between Regions
	Total Cohort (N=2781)	Patients Admitted Directly to Study Sites Only ^b (n=1558)	Region				
			North America (n=597)	South America (n=254)	Europe (n=1213)	Other (n=717)	
<i>Staphylococcus aureus</i>	869 (31)	487 (31)	256 (43)	43 (17)	339 (28)	231 (32)	<.001
Coagulase-negative staphylococcus	304 (11)	161 (10)	69 (12)	18 (7)	156 (13)	61 (9)	.005
Viridans group streptococci	483 (17)	288 (19)	54 (9)	66 (26)	198 (16)	165 (23)	<.001
<i>Streptococcus bovis</i>	165 (6)	101 (7)	9 (2)	17 (7)	116 (10)	23 (3)	<.001
Other streptococci	162 (6)	101 (7)	38 (6)	16 (6)	66 (5)	42 (6)	.86
<i>Enterococcus</i> species	283 (10)	158 (10)	78 (13)	21 (8)	111 (9)	73 (10)	.05
HACEK	44 (2)	26 (2)	2 (0.3)	6 (2)	19 (2)	17 (2)	.02
Fungi/yeast	45 (2)	25 (2)	20 (3)	3 (1)	13 (1)	9 (1)	.002
Polymicrobial	28 (1)	23 (2)	8 (1)	1 (0.4)	13 (1)	6 (0.8)	.60
Negative culture findings	277 (10)	122 (8)	41 (7)	51 (20)	123 (10)	62 (9)	<.001
Other	121 (4)	66 (4)	22 (4)	12 (5)	59 (5)	28 (4)	.61

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%

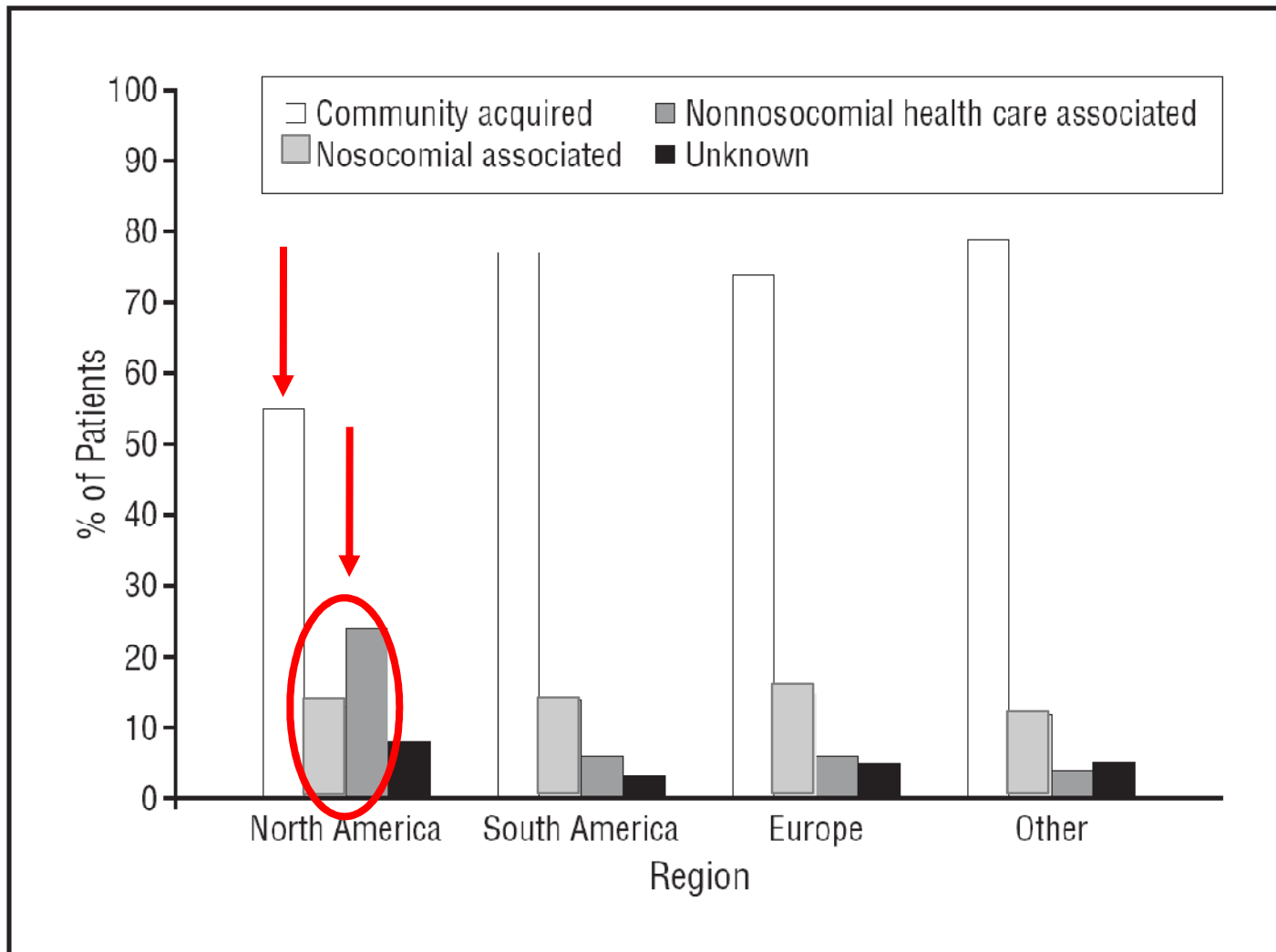


Figure. Geographic comparison of location of acquisition in 2781 patients with definite endocarditis.

Staphylococcus aureus endocarditis a consequence of medical progress

- ICE: 1779 definite IE cases collected prospectively between Jun '00 and Dec '03

	No. (%)
Staphylococcus	
<i>S aureus</i>	558 (31.6)
Coagulase-negative staphylococci	186 (10.5)
Streptococcus	
Viridans group streptococci	319 (18.0)
<i>Streptococcus bovis</i>	114 (6.5)
Other streptococci	91 (5.1)
Enterococci	188 (10.6)
HACEK	30 (1.7)
Non-HACEK gram-negative bacteria	38 (2.1)
Fungi	32 (1.8)
Polymicrobial	23 (1.3)
Other*	56 (3.1)
Culture negative	144 (8.1)

Staphylococcus aureus endocarditis a consequence of medical progress

- ICE: 1779 definite IE cases collected prospectively between Jun '00 and Dec '03

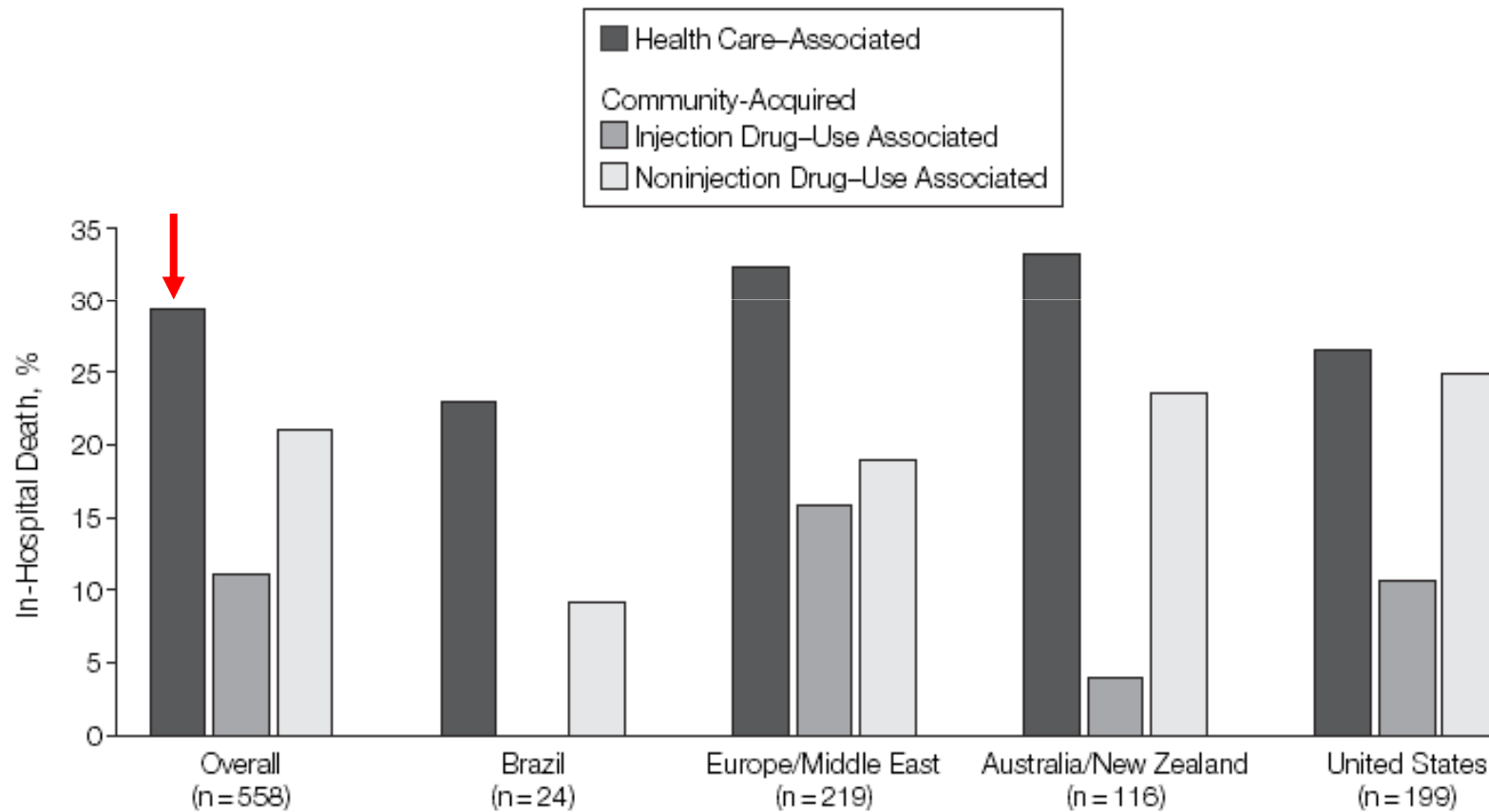
Characteristics	No. (%)		P Value
	Non- <i>S aureus</i> (n = 1221)	<i>S aureus</i> (n = 558)	
Male sex	868 (71.1)	341 (61.1)	<.001
Age, median (25th-75th percentiles), y	59.3 (45.2-72.2)	56.6 (41.1-70.5)	.007
Type of IE			
Prosthetic valve	276 (22.6)	86 (15.4)	23.7% <.001
Native valve	846 (69.3)	401 (71.9)	32.1% .27
Other and unknown	99 (8.1)	71 (12.7)	.002

Staphylococcus aureus endocarditis a consequence of medical progress

Clinical characteristics of Sa IE vs. Non Sa IE

	Non Sa IE N = 1221	Sa IE N = 558	Multivariate OR (95% CI)
1 st presentation < 1 mo from 1 st symptom	67.8%	92.7%	5.1 (3.2 – 8.2)
Diabetes mellitus	14.8%	19.7%	1.3 (1.1 – 1.8)
Intravascular device source	9.1%	28.4%	1.7 (1.2 – 2.6)
Health-care associated	17.3%	39.1%	2.9 (2.1 – 3.8)
IVDU associated	4.1%	21.0%	9.3 (6.3 – 13.7)

Staphylococcus aureus endocarditis a consequence of medical progress



Contemporary Clinical Profile and Outcome of Prosthetic Valve Endocarditis

- From 06/00 to 08/05, 3250 patients, 61 centers, 28 countries.
- PVE: 556 (20.1%) of 2670 patients with definite IE.

	PVE (n=556)	NVE (n=1895)	p value
Age, mean, years	65.0	56.3	<0.001
Hemodialysis dependent	25 (4.5)	173 (9.1)	<0.001
Current IVDU	10 (1.8)	235 (12.4)	<0.001
Previous IE	112 (20.1)	91 (4.8)	<0.001
Health-care associated infection	203 (36.5)	587 (31.0)	0.01
Echocardiographic findings			
- Vegetation	406 (73.0)	1703 (89.9)	<0.001
- New regurgitation	257 (46.2)	1346 (71.0)	<0.001
- Abscess	165 (29.7)	222 (11.7)	<0.001
Valve surgery during admission	272 (48.9)	879 (46.4)	0.30
In-hospital death	127 (22.8)	310 (16.4)	<0.001

Results are expressed as n (%)

A. Wang, JAMA. 2007;297:1354-1361

Contemporary Clinical Profile and Outcome of Prosthetic Valve Endocarditis

Causative organism (%)	PV IE n = 556	NV IE n = 1895	p
<i>Staphylococcus aureus</i>	23.0	32.9	<0.001
Coag-neg. staphylococci	16.9	8.3	<0.001

Causative Organism	Total, No. (%) (n = 556)	Early PVE, No. (%) (n = 53)	Late PVE, No. (%) (n = 331)
<i>Staphylococcus aureus</i>	128 (23.0)	19 (35.9)	61 (18.4)
Methicillin-sensitive <i>S aureus</i>	82 (14.7)	8 (15.1)	43 (13.0)
Methicillin-resistant <i>S aureus</i>	36 (6.5)	10 (18.9)	11 (3.3)
Coagulase-negative staphylococci	94 (16.9)	9 (17.0)	66 (19.9)
<i>Enterococcus</i> spp	71 (12.8)	4 (7.5)	42 (12.7)
<i>Viridans streptococci</i>	67 (12.1)	1 (1.9)	34 (10.3)
Culture negative	62 (11.2)	9 (17.0)	41 (12.4)
<i>Streptococcus bovis</i>	29 (5.2)	1 (1.9)	22 (6.7)
Fungal	23 (4.1)	5 (9.4)	11 (3.3)

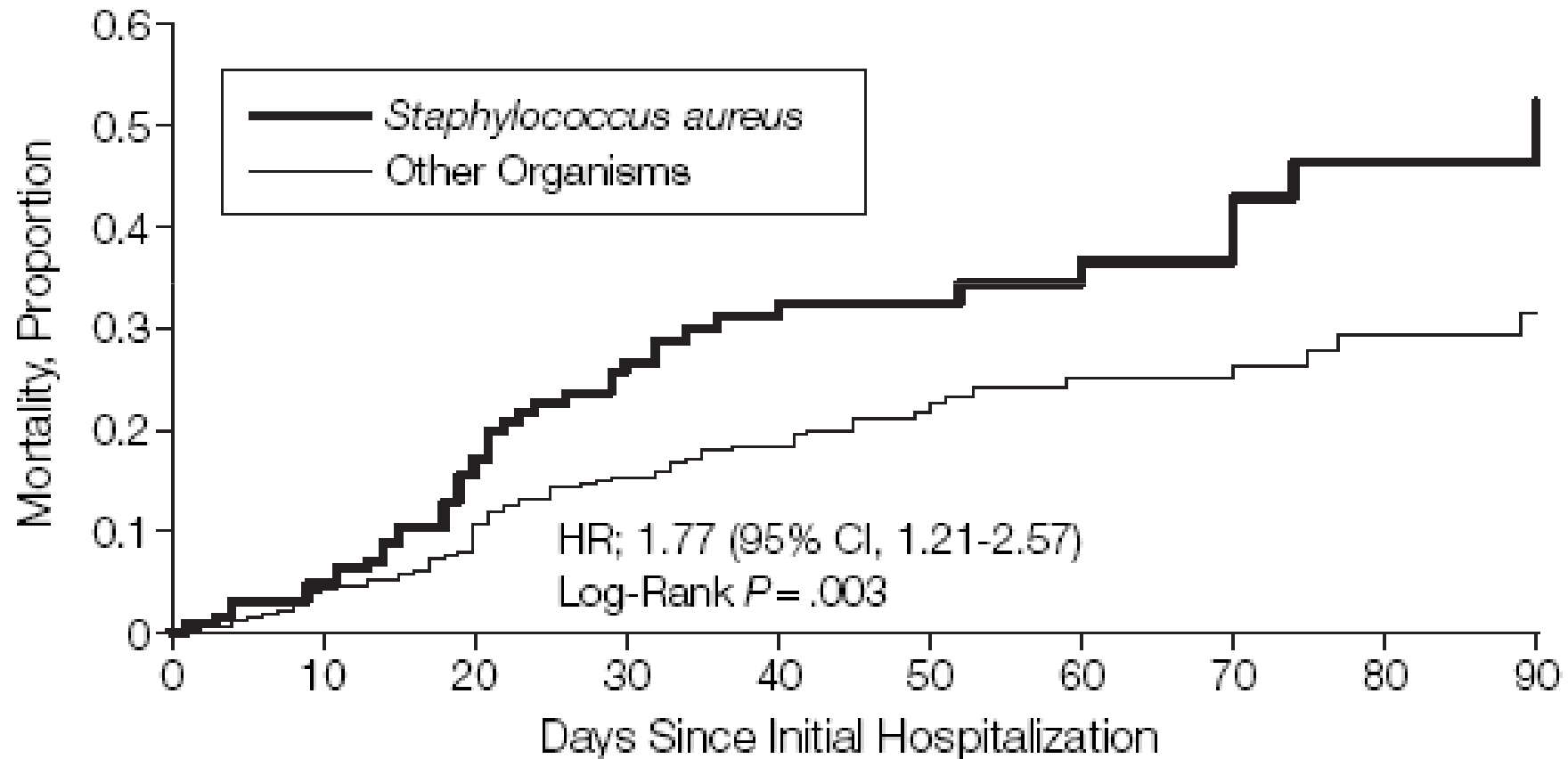
Contemporary Clinical Profile and Outcome of Prosthetic Valve Endocarditis

Prognostic factors (in-hospital mortality) of PVE

Variable	N	Mortality N (%)	Adjusted OR (95% CI)
Age (years)			
< 65	277	42 (15.2)	1 (reference)
65 – 75	151	38 (25.2)	1.82 (1.09 – 3.03)
> 75	128	47 (36.7)	3.73 (2.10 – 6.61)
Health-care associated	203	62 (30.5)	1.62 (1.08 – 2.44)
<i>S. aureus</i> IE	128	44 (34.4)	1.73 (1.01 – 2.95)
Persistent bacteremia	49	27 (55.1)	4.29 (1.99 – 9.22)
Congestive heart failure	183	60 (32.8)	2.33 (1.62 – 3.34)
Intracardiac abscess	144	47 (32.6)	1.86 (1.10 – 3.15)
Stroke	101	34 (33.7)	2.25 (1.25 – 4.03)

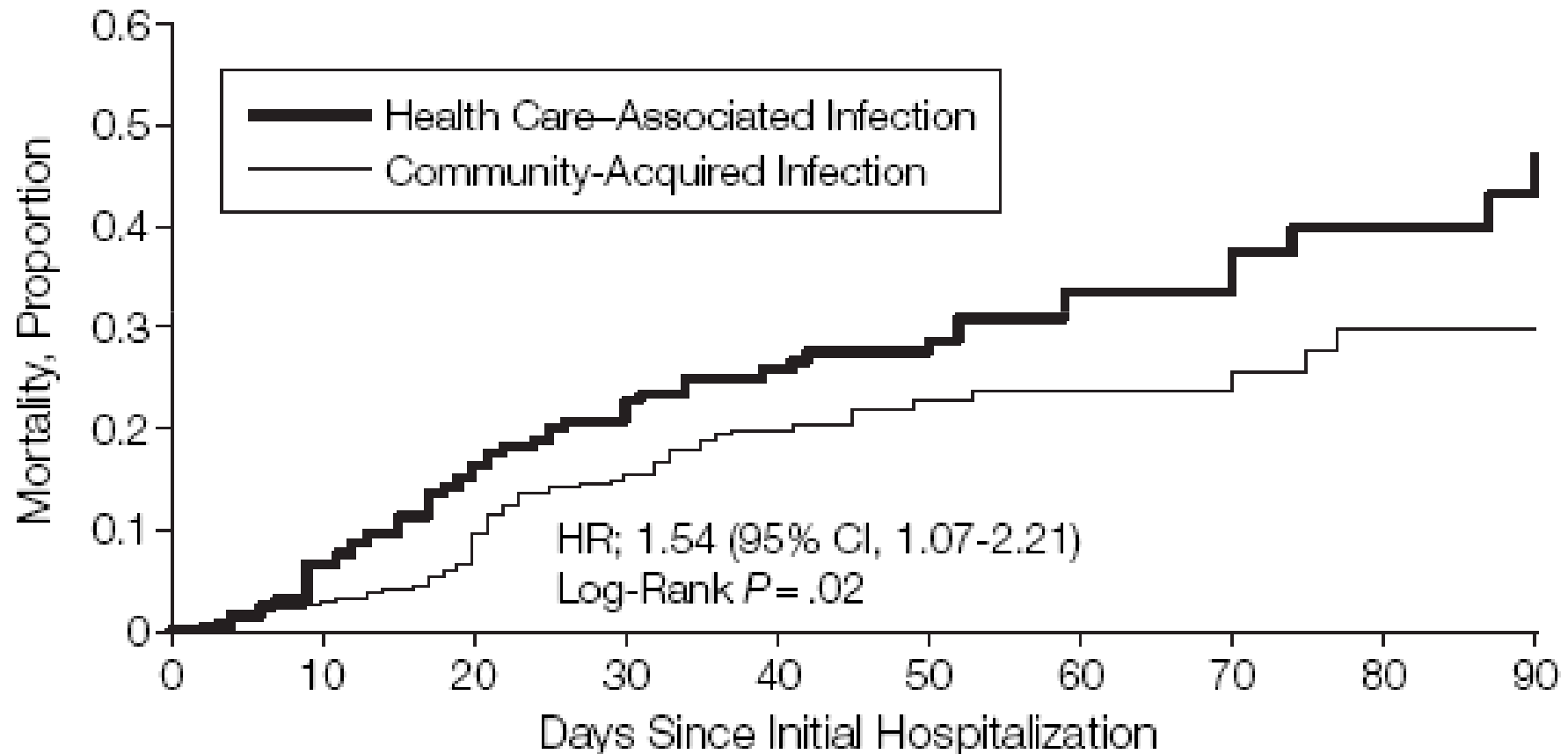
Contemporary Clinical Profile and Outcome of Prosthetic Valve Endocarditis

PVE Caused by *Staphylococcus aureus* or Other Organisms



Contemporary Clinical Profile and Outcome of Prosthetic Valve Endocarditis

Health Care–Associated or Community-Acquired PVE



Native Valve Endocarditis due to Coagulase-Negative Staphylococci: Report of 99 Episodes from the ICE Merged Database

6.6% of NVIE
22% of staph IE

Variable	Infecting organism			P value CoNS vs. <i>S. aureus</i>	P value CoNS vs. viridans group streptococci
	CoNS	<i>S. aureus</i>	Viridans group streptococci		
Total no. of patients	99	353	478		
Demographics					
Age, median years (25th–75th percentile)	68 (50–75)	63 (49–73)	59 (43–71)	.26	<.01
Male sex	76/99 (77)	223/353 (62)	329/476 (69)	<.01	.13
Place of acquisition					
Health care associated ^a	27/67 (40)	64/194 (33)	4/293 (1.36)	.36	<.001
Community	40/67 (60)	127/194 (65)	289/293 (99)	.36	<.001
Complications and outcome					
Heart failure	49/99 (49)	147/351 (42)	147/478 (31)	.18	<.001
Cardiac abscess	15/99 (15)	29/353 (8.2)	38/478 (8)	.04	.03
Surgery	53/99 (54)	123/353 (35)	167/478 (35)	<.001	<.001
In-hospital mortality	19/99 (19)	89/352 (25)	31/471 (6.6)	.21	<.001

Enterococcal endocarditis: 107 cases from the ICE merged database

8.3% of LS NV IE

Characteristic	Enterococcus (n = 107)	<i>S. aureus</i> (n = 314)	Streptococcus (n = 666)	P-value	
	Number (%) or Mean +/- SD			Enterococcus vs <i>S. aureus</i>	Enterococcus vs streptococcus
Age (years)	66.4 +/- 14	60.0 +/- 16	57.8 +/- 17	0.0003	<0.0001
Sex (men)	78 (73)	199 (63)	454 (68)	0.07	0.33
Community acquired	46 (74)	119 (63)	399 (98)	0.11	<0.0001
Nosocomial	9 (15)	36 (19)	2 (1)	0.48	<0.0001
Chronic catheter	2 (4)	24 (17)	2 (1)	0.02	0.06
Cancer	13 (21)	22 (13)	40 (11)	0.11	<0.0001
Diabetes	11 (18)	32 (19)	40 (11)	0.92	0.10
Chronic dialysis	4 (7)	20 (12)	6 (2)	0.26	0.02
Other chronic illness	12 (24)	50 (35)	65 (23)	0.13	0.98
Congenital heart disease	3 (4)	17 (8)	79 (17)	0.28	0.007
Mitral valve prolapse	1 (2)	7 (4)	43 (11)	0.42	0.03
Aortic valve vegetation	20 (44)	31 (23)	82 (29)	0.006	0.03
Mitral valve vegetation	10 (22)	59 (44)	103 (36)	0.009	0.07
Heart failure	49 (46)	136 (44)	234 (35)	0.69	0.03
Systemic embolization	28 (26)	155 (49)	198 (30)	<0.0001	0.45
Surgery this episode	33 (31)	114 (36)	246 (37)	0.31	0.22
Death this hospitalization	12 (11)	83 (27)	67 (10)	0.001	0.74

Enterococcal endocarditis in the beginning of the 21st century: Analysis from the ICE-PCS

	Enterococci N=500, 30.9%	Oral strep N=823, 51.0%	Gr. D strep N=293, 18.1%	P val.
Age (years), mean [SD]	65.5 [15.3]	54.7 [18.4]	65.2 [12.4]	<.0001
Male sex, N (%)	361 (72.6)	534 (71.0)	218 (74.7)	.46
Prior IE, N (%)	62 (12.5)	90 (10.5)	21 (7.2)	.07
Admission delay > 1 mo, N (%)	172 (36.8)	350 (44.9)	142 (51.4)	<.0001
Hemodialysis, N (%)	41 (8.4)	11 (1.4)	6 (2.1)	<.0001
Diabetes, N (%)	110 (22.4)	90 (11.1)	56 (19.3)	<.0001
Cancer, N (%)	55 (11.2)	67 (8.3)	34 (11.7)	.11
Charlson index, mean [SD]	1.7 [1.8]	1.0 [1.5]	1.3 [1.5]	<.0001
Place of acquisition, N (%)				
- community	352 (70.4)	758 (92.1)	280 (95.6)	<.0001
- healthcare, nosocomial	65 (13.0)	12 (1.5)	3 (1.0)	
- healthcare, non nosocomial	52 (10.4)	25 (3.0)	4 (1.4)	
- multiple, unknown, missing	31 (6.2)	28 (3.4)	6 (2.0)	

Enterococcal endocarditis in the beginning of the 21st century: Analysis from the ICE-PCS

	Enterococci N=500, 30.9%	Oral strep N=823, 51.0%	Gr. D strep N=293, 18.1%	P val
Intracardiac device, N (%)	61 (12.4)	31 (3.8)	21 (7.2)	<.0001
Type of IE, N (%)				
- Native valve	324 (66.4)	641 (80.9)	216 (75.8)	<.0001
- Prosthetic valve	142 (29.1)	130 (16.4)	62 (21.8)	
- Other	22 (4.5)	21 (2.7)	7 (2.5)	
Stroke, N (%)	78 (16.0)	118 (14.7)	38 (13.3)	.59
Embolic event, N (%)	94 (19.3)	147 (18.3)	70 (24.4)	.08
Heart failure	94 (18.8)	139 (16.9)	56 (19.1)	.90
Intracardiac abscess, N (%)	57 (11.8)	110 (13.6)	33 (11.5)	.51
Valve surgery w/in 60 days, N (%)	209 (42.1)	380 (46.5)	137 (47.2)	.22
In-hospital mortality, N (%)	88 (17.7)	68 (8.3)	28 (9.6)	<.0001
One-year mortality, N (%)	144 (28.9)	120 (14.6)	52 (17.8)	<.0001



Enterococcal endocarditis in the beginning of the 21st century: Analysis from the ICE-PCS

	Bivariate analysis		Multivariate analysis	
	OR	95% CI	OR	95% CI
Age, per 1-year increment	1.02	1.01-1.03	1.02	1.01-1.04
Sex, M vs. F	0.72	0.49-1.07		
Charlson index, per 1-unit increment	1.29	1.11-1.50		
Hemodialysis, yes vs. no	1.15	0.65-2.04		
Diabetes, yes vs. no	1.37	0.95-1.98		
Cancer, yes vs. no	1.62	1.04-2.53		
Stroke (time-dependent)	2.00	1.36-2.94	1.90	1.28-2.82
Heart failure, yes vs. no	2.47	1.75-3.50	2.43	1.71-3.45
Surgery (time-dependent)	1.04	0.74-1.46		



Enterococcal endocarditis in the beginning of the 21st century: Analysis from the ICE-PCS

	Bivariate analysis		Multivariate analysis	
	OR	95% CI	OR	95% CI
Age, per 1-year increment	1.02	1.02-1.04	1.02	1.01-1.03
Sex, M vs. F	0.95	0.74-1.22		
Charlson index, per 1-unit increment	1.42	1.27-1.57		
Hemodialysis, yes vs. no	1.91	1.20-3.03		
Diabetes, yes vs. no	1.63	1.25-2.12	1.47	1.09-1.88
Cancer, yes vs. no	1.94	1.44-2.62		
Stroke (time-dependent)	2.31	1.78-2.99	2.23	1.71-2.91
Heart failure, yes vs. no	2.88	2.29-3.63	2.77	2.15-3.57
Surgery, time-dependent	1.07	0.85-1.35		
Microorganism (ref = Enterococci)				
- oral streptococci	0.46	0.36-0.58	0.62	0.47-0.87
- group D streptococci	0.54	0.39-0.74	0.65	0.50-0.85



In conclusion: from facts to acts

▶ Facts

- ▶ > 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



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

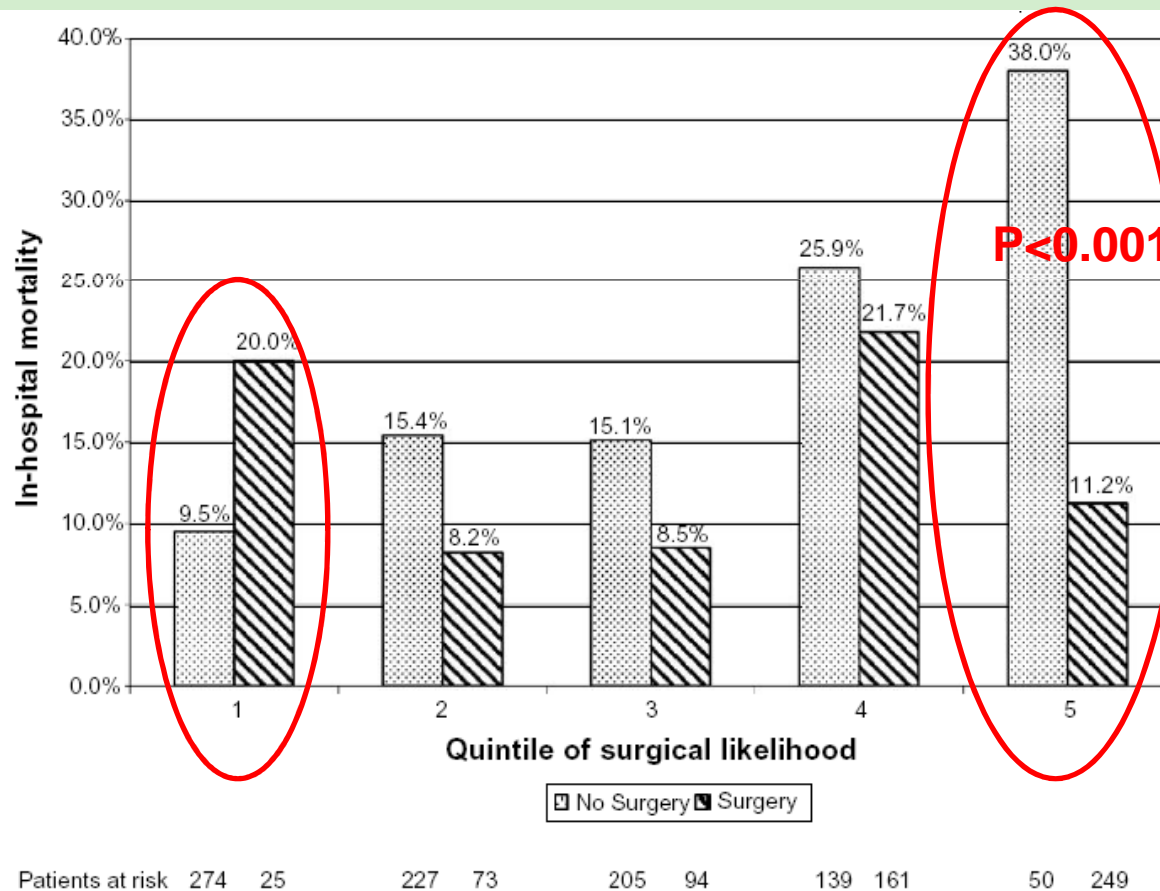
Surgery in patients with native valve IE: Results from the ICE-MD

- 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), $p=.14$



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

- No demonstration that surgical treatment of complicated PVIE reduces the in-hospital mortality rate compared to that of complicated PVIE treated with medical therapy alone.
- After adjustment for factors associated with the use of surgery, there was a trend toward a survival benefit of surgery.

Staphylococcus aureus native valve infective endocarditis: Report of 566 episodes from the ICE merged database

- Patients with *S. aureus* IE were more likely to
 - die (20% vs. 12%; $p < 0.001$)
 - experience an embolic event (60% vs. 31%; $p < 0.001$)
 - more likely to develop a CNS event (20% vs. 13%; $p < 0.001$)
 - NOT undergo valve surgery (26% vs. 39%; $p < 0.001$)

Prognostic factors – Multivariate analysis

	OR	95% CI
Age	1.4	1.1 – 1.7
Periannular abscess	2.4	1.1 – 5.6
Heart failure	3.9	2.3 – 6.7
No surgery	2.3	1.3 – 4.2



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



Does EVS improve outcome of SAPVIE?

	n	In-hospital mortality		p
		Ab + surgery	Ab alone	
Yu et <i>al.</i> , 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 <i>al.</i> , 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



Yu, Ann Thor Surg 1994 – Wolff, Chest 1995

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



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

Prognosis in 61 cases of SAPVIE from ICE-MD

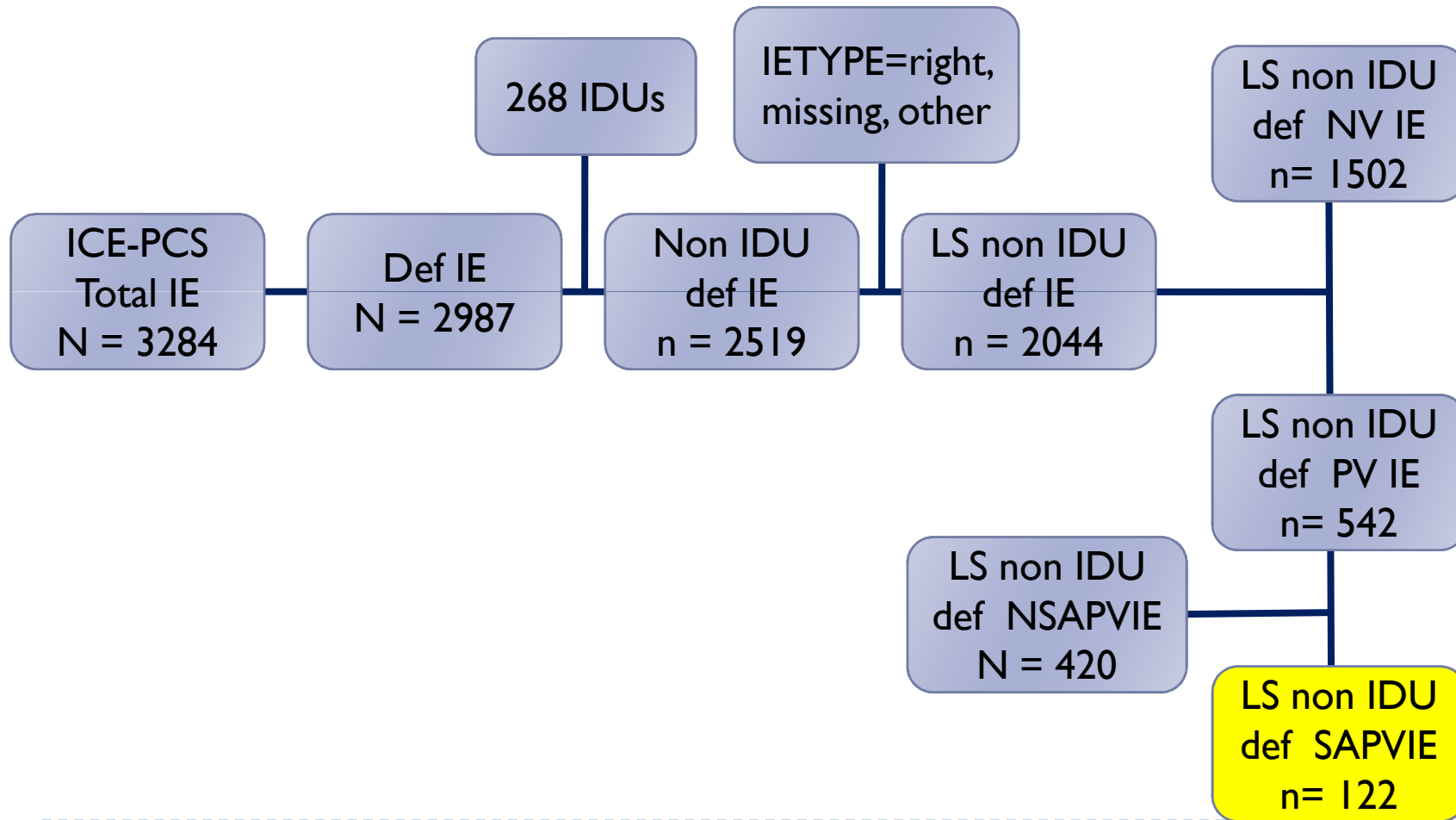
Mortality in 4 subgroups of patients, according to the presence of cardiac complication and the performance of an early valve replacement

Patient subgroup	Cardiac complication ^a	Early valve replacement	Mortality ^b	<i>P</i>
1	Yes	Yes	4/14 (28.6)	.09
2	Yes	No	8/15 (53.3)	
3	No	No	11/25 (44)	
4	No	Yes	6/7 (85.7)	

^a Cardiac complication is defined as congestive heart failure and/or intra-cardiac abscess.



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≥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], $p = 0.2865$



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 ^o 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	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)

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)



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
- ▶ **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
- ▶ **A randomized clinical trial should be conducted to optimally address this question**



Early Surgery versus Conventional Treatment for Infective Endocarditis

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

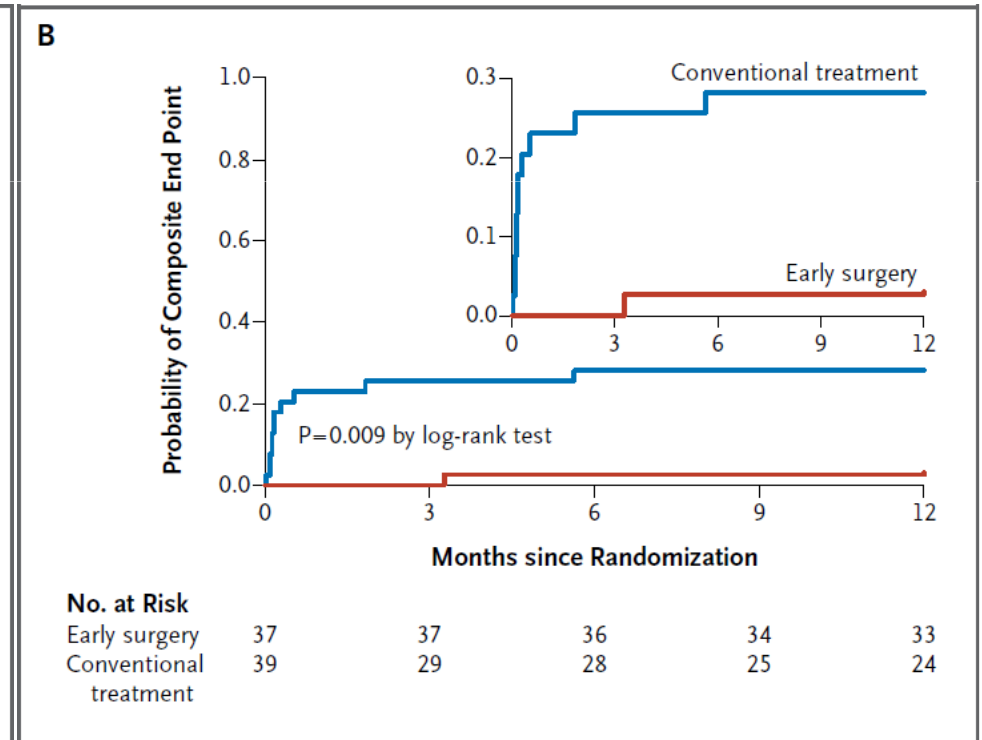
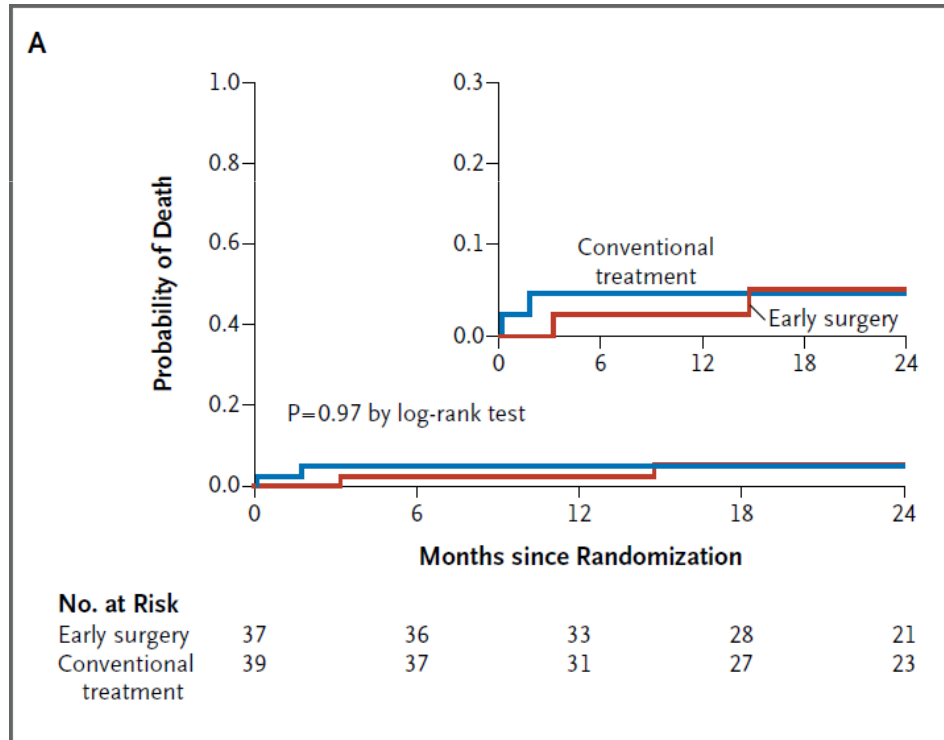
Outcome	Conventional Treatment (N=39)	Early Surgery (N=37)	P Value
Primary end point — no. (%)			
In-hospital death or embolic event at 6 wk	9 (23)	1 (3)	0.01
In-hospital death	1 (3)	1 (3)	1.00
Embolic event at 6 wk			
Any	8 (21)	0	0.005



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)



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