

**Epidemiological Changes and Improvement in Outcomes of Infective Endocarditis in Europe in the 21<sup>st</sup> century: An International Collaboration on Endocarditis (ICE) prospective cohort study (2000–2012).**

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**Key words:** Infective endocarditis, Europe, Epidemiology, Cardiac Surgery, Mortality.

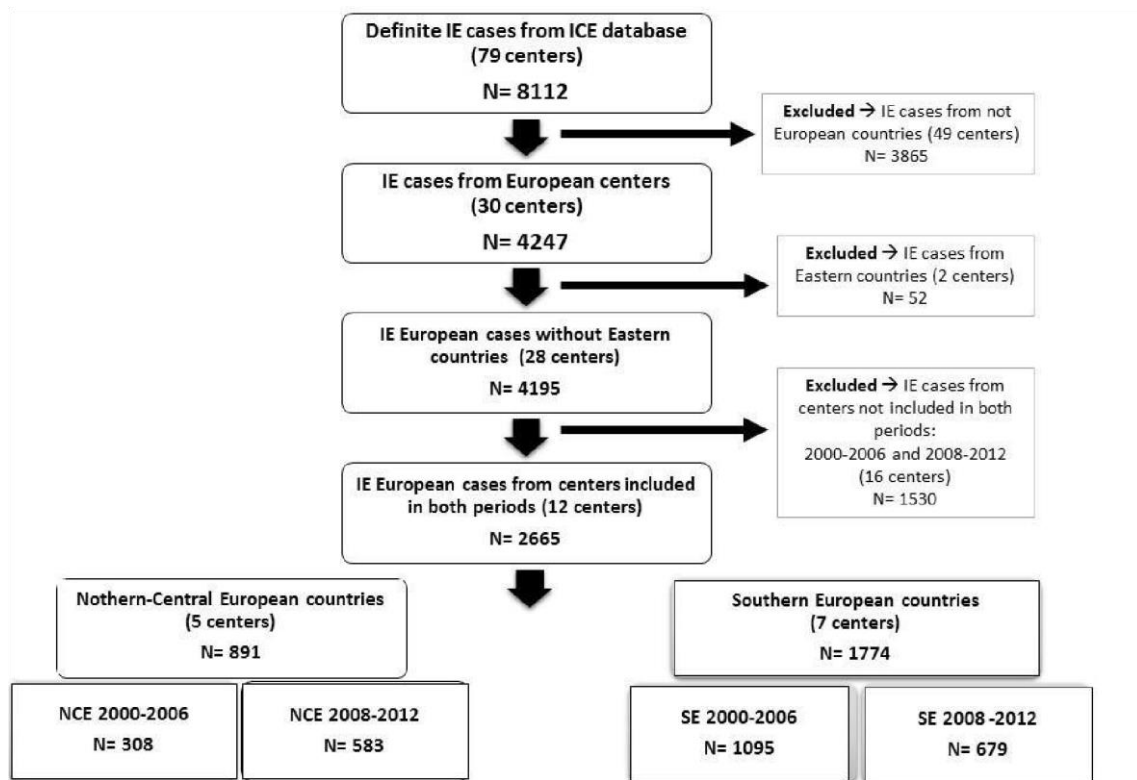
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**Supplementary Figure 1.** Patient flowchart for the specific sub-analysis performed only with centers reporting cases in both periods (N=2665 cases, from 12 centers)



**Supplementary table 1.** Baseline characteristics and predisposing conditions of all cases from the centers included in both periods.

	Total N= 2665	NCE N= 891	SE N=1774	p	Early period (2000-2006) N= 1403	Later period (2008-2012) N= 1262	p
Baseline characteristics							
Age (years, median IQR) (N=2665)		63 (50 – 74)	63.6 (48-74)	0.18	62.8 (47-73)	63.7 (51-74)	0.02
Male gender (N=2662)	1861 (69.9%)	636 (71.5%)	1225 (69.1%)	0.21	978 (69.8%)	883 (70.1%)	0.86
First sign to admission < 1 month (N=2467)	2048 (83%)	683 (84.6%)	1365 (82.2%)	0.13	974 (76.9%)	1074 (89.5%)	<0.01
Hemodialysis (N= 1879)	119 (6.3%)	24 (4.7%)	95 (6.9%)	0.06	64 (4.6%)	55 (11.5%)	<0.01
Diabetes (N= 2632)	523 (19.9%)	160 (18.4%)	363 (20.6%)	0.17	239 (17.1%)	284 (23%)	<0.01
Cancer (N= 2641)	261 (9.9%)	124 (10%)	137 (7.8%)	<0.01	140 (10%)	121 (9.7%)	0.78
HIV positive (N= 2631)	60 (2.3%)	5 (0.6%)	55 (3.1%)	<0.01	43 (3.1%)	17 (1.4%)	<0.01
Predisposing conditions							
Previous IE (N=2649)	192 (7.2%)	36 (4.1%)	156 (8.8%)	<0.01	108 (7.7%)	84 (6.7%)	0.32
Native valve predisposition* (N= 2563)	714 (27.9%)	257 (30%)	457 (26.8%)	0.10	412 (29.9%)	302 (25.5%)	0.01
Congenital heart disease (N= 2587)	243 (9.4%)	102 (11.8%)	141 (8.2%)	<0.01	105 (7.7%)	138 (11.2%)	<0.01
CIED (N= 2077)	322 (15.5%)	74 (10.8%)	248 (17.9%)	<0.01	167 (19.3%)	155 (12.8%)	<0.01
Intravenous drug use (N= 2647)	178 (6.7%)	37 (4.2%)	141 (8%)	<0.01	115 (8.2%)	63 (5%)	<0.01
IE Type							
CA-IE (N=2665)	1899 (75.5%)	678 (86.3%)	1221 (70.6%)	<0.01	1046 (77.3%)	853 (73.5%)	0.02
N-IE (N=2665)	471 (18.7%)	80 (10.2%)	391 (22.6%)	<0.01	234 (17.3%)	237 (20.4%)	0.04
HA-IE (N=2665)	144 (5.8%)	28 (3.5%)	116 (6.8%)	<0.01	74 (5.4%)	70 (6.1%)	0.55
Native (N= 2614)	1769 (67.7%)	622 (70.8%)	1147 (66.1%)	0.02	961 (70.5%)	808 (64.6%)	<0.01
Prosthetic (N= 2614)	626 (19.5%)	219 (24.9%)	407 (23.5%)	0.41	299 (21.9%)	327 (26.1%)	0.01
CIED endocarditis (N= 2614)	219 (8.4%)	38 (4.3%)	181 (10.4%)	<0.01	103 (7.6%)	116 (9.3%)	<0.01

\*Including aortic regurgitation, aortic stenosis, mitral regurgitation and mitral stenosis.

Abbreviations: NCE: Northern and Central European countries; SE: Southern European countries; HIV: human immunodeficiency virus; IE: infective endocarditis; CA: community-acquired; N: nosocomial, HA: healthcare-associated CIED: cardiovascular implantable electronic devices.

**Supplementary table 2.** Microbiologic etiology comparative analyses between the two predefined regions and two periods of all cases from the centers included in both periods.

	Total N=2665	NCE N= 891	SE N=1774	P	Early period (2000-2006) N= 1403	Later period (2008-2012) N= 1262	p
<i>Staphylococcus aureus</i> (N= 2493)	669 (26.8%)	210 (26.2%)	459 (27.2%)	0.59	370 (27.2%)	299 (26.3)	0.61
<i>Viridans group Streptococci</i> (N= 2493)	435 (17.4%)	128 (15.9%)	307 (18.2%)	0.16	245 (18%)	190 (16.7)	0.39
<i>Coagulase negative Staphylococcus</i> (N= 2493)	338 (13.6%)	87 (10.8%)	251 (14.9%)	<0.01	170 (12.5%)	168 (14.8)	0.10
<i>Enterococcus</i> spp. (N= 2493)	263 (10.5%)	81 (10.1%)	182 (10.8%)	0.60	121 (8.9%)	142 (12.5%)	<0.01
<i>Streptococcus gallolyticus</i> (N= 2493)	222 (9%)	99 (12.3%)	123 (7.3%)	<0.01	120 (8.8%)	102 (9%)	0.90
<i>Other streptococci</i> * (N= 2493)	179 (7.2%)	81 (10.1%)	98 (5.8%)	<0.01	87 (6.4%)	92 (8.1%)	0.11
<i>Gram negative</i> (not HACEK**) (N= 2493)	97 (4%)	33 (4.1%)	64 (3.8%)	0.70	53 (3.9%)	44 (3.9%)	0.97
Polymicrobial (N= 2493)	41 (1.6%)	21 (2.6%)	20 (1.2%)	0.02	7 (0.5%)	34 (3.9%)	<0.01
HACEK*** (N= 2493)	31 (1.2%)	12 (1.5%)	19 (1.1%)	0.46	18 (1.3%)	13 (1.1%)	0.68
<i>Fungi</i> (N= 2493)	31 (1.2%)	10 (1.2%)	21 (1.2%)	0.99	17 (1.3%)	14 (1.2%)	0.97
Negative culture (N= 2493)	121 (4.9%)	21 (2.6%)	100 (5.9%)	<0.01	109 (8%)	12 (1.1%)	<0.01
Other (N= 2493)	66 (2.6%)	20 (2.5%)	46 (2.7%)	0.73	41 (3%)	25 (2.2%)	0.20

\*Other streptococci includes: *Streptococcus pneumoniae*. betahemolytic group streptococci. etc.

\*\*HACEK group includes: *Haemophilus* species. *Aggregatibacter actinomycetemcomitans*. *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus* and *Haemophilus paraphrophilus*). *Cardiobacterium hominis*. *Eikenella corrodens* and *Kingella* species.

Abbreviations: NCE: Northern and Central European countries; SE: Southern European countries.

**Supplementary table 3.** Echo findings, complications, treatment and outcome of all cases from centers included in both periods.

	Total N=2665	NCE N= 891	SE N=1774	P	Early period (2000-2006) N= 1403	Later period (2008-2012) N= 1262	p
Vegetation findings							
Intracardiac vegetation (N= 2634)	2241 (85%)	720 (81.7%)	1521 (86.8%)	<0.01	1210 (87.1%)	1031 (82.8%)	<0.01

Aortic valve (N=2623)	1062 (40.5%)	362 (41.1%)	700 (40.2%)	0.63	562 (40.8%)	500 (40.2%)	0.75
Mitral valve (N=2622)	989 (37.7%)	352 (40%)	637 (36.5%)	0.08	528 (38.4%)	461 (37%)	0.45
Tricuspid valve (N=2618)	222 (8.5%)	59 (6.7%)	163 (9.4%)	0.02	132 (9.6%)	90 (7.2%)	0.11
Pulmonary valve (N=2614)	27 (1%)	9 (1%)	18 (1%)	0.99	10 (0.7%)	17 (1.4%)	0.11
Complications							
Stroke (N=2635)	500 (19%)	202 (23.1%)	298 (16.9%)	<0.01	255 (18.4%)	245 (19.6%)	0.42
Embolization non-stroke (N=2632)	830 (31.5%)	316 (36.1%)	514 (29.3%)	<0.01	387 (27.9%)	443 (35.6)	<0.01
CHF (N= 2628)	921 (35%)	319 (36.6%)	602 (34.3%)	0.24	470 (33.8%)	451 (36.4%)	0.17
Persistent positive blood culture* (N=2571)	215 (8.4%)	73 (8.4%)	142 (8.4%)	0.98	111 (8%)	104 (8.7%)	0.53
Intracardiac abscess (N=2629)	515 (19.6%)	238 (27.2%)	277 (15.8%)	<0.01	228 (16.4%)	287 (23.1%)	<0.01
Treatment/outcome							
Surgical therapy (N=2641)	1385 (52.4%)	564 (63.6%)	821 (46.8%)	<0.01	676 (48.5%)	709 (56.9%)	<0.01
In-hospital death (N=2651)	516 (19.5%)	141 (15.9%)	375 (21.2%)	<0.01	295 (21.1%)	221 (17.7%)	0.03
One-year follow up							
One-year mortality (N=2201)	681 (30.9%)	191 (25.2%)	490 (33.9%)	<0.01	401 (29.6%)	280 (33.1%)	0.09
Relapses (N= 1365)	79 (5.8%)	25 (4.1%)	54 (7.2%)	0.01	42 (5.6%)	37 (6.1%)	0.70

\*Persistent blood cultures were defined as blood cultures that remained positive after 7 days of effective therapy.

Abbreviations: NCE: Northern and Central European countries; SE: Southern European countries; CHF: congestive heart failure

**Supplementary table 4.** Multivariable analysis of factors associated with in-hospital mortality and one-year mortality of all cases from centers included in both periods.

	In-hospital mortality			One-year mortality		
	MULTIVARIATE OR	CI 95%	p	MULTIVARIATE OR	CI 95%	p
Charlson	1.31	(1.18, 1.45)	<0.01	1.33	(1.18, 1.50)	<0.01
Prosthetic valve IE	1.40	(0.97, 1.29)	0.07	1.41	(0.98, 1.97)	0.08
<i>Staphylococcus aureus</i> *	1.68	(1.34, 2.10)	<0.01	1.73	(1.25, 2.40)	<0.01
<i>ConS</i> *	1.41	(0.91, 2.20)	0.12	1.55	(1.03, 2.35)	0.04
Viridans group <i>Streptococci</i> *	0.59	(0.47, 0.74)	<0.01	0.63	(0.41, 0.95)	0.03
Intracardiac vegetation	2.11	(1.33, 3.38)	<0.01	1.35	(0.89, 2.07)	0.16
Stroke	2.72	(1.98, 3.72)	<0.01	1.86	(1.35, 2.56)	<0.01
CHF	3.12	(2.35, 4.14)	<0.01	2.48	(1.88, 3.27)	<0.01
Persistent positive blood culture	2.66	(1.76, 4.04)	<0.01	2.24	(1.45, 3.47)	<0.01
Paravalvular complications	2.69	(1.91, 3.78)	<0.01	1.87	(1.38, 2.54)	<0.01
N IE and HA IE vs CA IE	1.64	(1.31, 2.08)	<0.01	1.15	(0.82, 1.43)	0.42
In-hospital surgery	0.59	(0.44, 0.88)	<0.01	0.55	(0.41, 0.74)	<0.01
European region (NCE vs SE)	0.63	(0.44, 0.88)	<0.01	0.72	(0.52, 1.02)	0.06
Period (2008-2012 vs 2000-2006)	0.63	(0.44, 0.88)	0.01	0.97	80.66, 1.44)	0.90

\*The reference group is the rest of the etiological microorganisms. Abbreviations: NCE: Northern and Central European countries; SE: Southern European countries; IE: infective endocarditis; CHF: congestive heart failure; CA: community acquired; N: nosocomial; HA: health-care associated; IE: infective endocarditis.

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