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on behalf of the Group for the Study of Cardiovascular Infections of the Andalusian Society of Infectious Diseases (SAEI) and the Spanish Network for Research in Infectious Diseases (REIPI)

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Neurological Complications of Infective Endocarditis

Risk Factors, Outcome, and Impact of Cardiac Surgery: A Multicenter Observational Study

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Background—The purpose of this study was to assess the incidence of neurological complications in patients with infective endocarditis, the risk factors for their development, their influence on the clinical outcome, and the impact of cardiac surgery.

Methods and Results—This was a retrospective analysis of prospectively collected data on a multicenter cohort of 1345 consecutive episodes of left-sided infective endocarditis from 8 centers in Spain. Cox regression models were developed to analyze variables predictive of neurological complications and associated mortality. Three hundred forty patients (25%) experienced such complications: 192 patients (14%) had ischemic events, 86 (6%) had encephalopathy/meningitis, 60 (4%) had hemorrhages, and 2 (1%) had brain abscesses. Independent risk factors associated with all neurological complications were vegetation size ≥3 cm (hazard ratio [HR] 1.91), *Staphylococcus aureus* as a cause (HR 2.47), mitral valve involvement (HR 1.29), and anticoagulant therapy (HR 1.31). This last variable was particularly related to a greater incidence of hemorrhagic events (HR 2.71). Overall mortality was 30%, and neurological complications had a negative impact on outcome (45% of deaths versus 24% in patients without these complications; $P<0.01$), although only moderate to severe ischemic stroke (HR 1.63) and brain hemorrhage (HR 1.73) were significantly associated with a poorer prognosis. Antimicrobial treatment reduced (by 33% to 75%) the risk of neurological complications. In patients with hemorrhage, mortality was higher when surgery was performed within 4 weeks of the hemorrhagic event (75% versus 40% in later surgery).

Conclusions—Moderate to severe ischemic stroke and brain hemorrhage were found to have a significant negative impact on the outcome of infective endocarditis. Early appropriate antimicrobial treatment is critical, and transitory discontinuation of anticoagulant therapy should be considered. **(*Circulation*. 2013;127:2272-2284.)**

Key Words: endocardium ■ infection ■ nervous system ■ complications

Infective endocarditis (IE) remains a major clinical problem, with mortality rates of 20% to 40%.[1–3] During the active course of IE, neurological complications occur in 20% to 40% of patients[1,4,5] and have been linked to a poorer outcome.[1,2,5,6] In several of the related reports, however, *neurological complication* is a generic term referring to a broad spectrum of complications ranging from nonspecific manifestations, such as nonfocal encephalopathy, seizures, or headache, to stroke or severe cerebral hemorrhage.[4,7] This all-inclusive approach can lead to confusion when investigating the true effect of brain involvement on the outcome of IE or the relationships between brain injury and certain characteristics

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of IE (eg, vegetation size or affected valve). Another debated point requiring clarification is whether brain damage may worsen after valve surgery in patients experiencing these complications. Several of the previous studies investigating these and other issues have the limitations of retrospective data collection,[8,9] referral center bias,[8,10] or analysis of too few events to obtain valid conclusions.[4,8]

Clinical Perspective on p 2284

The objectives of the present study were to assess the incidence of neurological complications in IE patients, the risk factors for their development, the associated risk of death, and the influence of valve surgery in this situation on patient outcome.

Methods

Study Design and Patients

The study included patients consecutively diagnosed with IE in 7 hospitals in Andalusia (southern Spain) and registered in a dedicated database from January 1984 to December 2009. Five of the participating centers are tertiary referral hospitals for cardiac surgery, and 2 are community hospitals, where patients at higher risk are transferred to the referral centers for assessment for surgery. The information in this database was merged with data from the Vall d'Hebron Hospital database for IE. Vall d'Hebron is a 1000-bed teaching hospital in Barcelona, Spain, and a referral center for cardiac surgery, with a prospective IE cohort registered from January 2000 to December 2009. The specific variables included in both registries and analyzed for the present study were the date of IE diagnosis; patient age and sex; type of endocarditis (native or prosthetic); location and size of vegetations on echocardiography; infecting microorganism; date, type, and extent of neurological complications; anticoagulant therapy given; date of the start of antimicrobial treatment; date of surgery (if performed); and outcome.

Possible and definite IE were defined with the modified Duke criteria,[11] and episodes recorded before 1994 were evaluated retrospectively according to these criteria. Right-sided IE cases and patients with pacemaker infection were excluded, unless there was concomitant left-sided infection. Prosthetic valve endocarditis was considered early if it occurred within 1 year after valve implantation and late if it occurred thereafter.

Over the period studied, predisposing IE factors, comorbidities, complications during hospitalization, therapeutic interventions, and follow-up data were collected by the same principal investigator in each center. All participating investigators were experienced clinicians in IE and were, additionally, the attending physicians in most episodes. The study was approved by the ethics and research committees of all the participating hospitals. Because no interventions outside of the established hospital treatment protocols and follow-up for these patients were performed, the informed consent requirement was waived by the committees.

Echocardiography

Transthoracic echocardiography was performed in all patients. Vegetations were measured in 2 orthogonal dimensions at the point in the cardiac cycle when the oscillating mass appeared the largest, with the greatest diameter obtained recorded. Transesophageal echocardiography has been available in our centers since 1995 and was performed in the following situations: (1) When strong clinical suspicion remained after a nondiagnostic transthoracic echocardiography and (2) to better evaluate the valve complications.

Microbiology

Microbiological information was obtained from culture of blood and intraoperative heart tissue specimens, as well as from serological studies. Blood cultures were always performed serially (minimum of 2 separate samples) and processed by the automated methods used at each center.

Definitions

Neurological complications were classified into the following categories: Meningitis-encephalopathy, ischemic complications, cerebral hemorrhage, and brain abscess. Encephalitis was defined as mental changes or stupor, with no focal neurological signs and no abnormal computed tomography (CT) findings. The diagnosis of meningitis required cerebrospinal fluid pleocytosis, with or without isolation of the causal microorganism on culture. The diagnosis of ischemic and hemorrhagic complications was based on clinical and radiological data. Ischemic complications were divided into 2 groups according to CT imaging and clinical findings: small ischemic complication, which included transient ischemic attack or minor infarction (embolism affecting <30% of 1 brain lobe), and moderate-severe ischemic complication, which was defined as multiple cerebral embolisms or a single embolism affecting ≥30% of a brain lobe. Hemorrhagic complication included primary intracerebral hemorrhage, hemorrhagic infarction, and subarachnoid hemorrhage. CT scanning of the brain was performed based on clinical suspicion. The diagnosis of mycotic aneurysm was always supported by cerebral arteriography. Patients with brain abscesses, diagnosed by CT, were included in the overall group of neurological complications for the analyses.

Comorbidity and Other Complications

The Charlson Index score[12] was determined at hospital admission to evaluate the type and severity of the patient's underlying comorbidity. The additive EuroSCORE (European System for Cardiac Operative Risk Evaluation) index[13] was calculated in each case to determine the cardiac operative risk. Heart failure was defined according to the Framingham criteria[14] and was evaluated at admission and over the patient's clinical course. Septic shock was defined by standard criteria.[15] Acute renal failure was established on the basis of a creatinine concentration >1.5 mg/dL in patients with normal renal function previously or a decrease of >25% of the previous creatinine clearance in patients with chronic renal insufficiency.

Hospital-Acquired IE

IE manifesting >48 hours after hospital admission or acquired in association with an invasive procedure performed within 6 months before the diagnosis[16,17] was considered hospital-acquired infective endocarditis.

Anticoagulant Therapy

Patients given dicoumarol or heparin on the day of the neurological event were considered to be receiving anticoagulant therapy, and those in whom anticoagulant therapy was stopped on the day of the IE diagnosis with no clinical or radiological evidence of a neurological complication were recorded as having no anticoagulant therapy.

Antimicrobial Therapy

The start of antimicrobial therapy was established as the first day of appropriate bactericidal treatment decided by the principal investigator according to the universally accepted guidelines or consensus documents in effect at the time of the diagnosis. The timing of the neurological event was established relative to the time point antimicrobial treatment was started.

Indication for Surgery

The indication for cardiac surgery during hospitalization was initially determined by the principal investigator in each center, and the final decision was made in agreement with the center's cardiologists and cardiac surgeons. The time to surgery was the interval between the diagnosis of IE and the date of surgery. The indications for surgery

and the reasons for not performing surgery when it was indicated are described in the online-only Data Supplement.

Mortality and Follow-Up

Early mortality was defined as a death that occurred during hospitalization regardless of cause or within 1 month of discharge if it was related to the IE episode. If the cause of death during this period was unknown (eg, sudden death after discharge with no autopsy or insufficient information on cause), it was also considered IE-related. Deferred mortality was defined as death that occurred during the follow-up period after the first month and that resulted from the consequences of endocarditis, such as late ventricular failure or neurological injury.

Clinical follow-up continued for 1 year, with scheduled visits at 1, 3, 6, and 12 months. At least 1 echocardiographic examination was performed during this period to evaluate the need for deferred surgery. Follow-up blood cultures were performed 2 months after completion of antimicrobial treatment to ensure definite microbiological cure. Cases with insufficient follow-up (<1 month after discharge) were excluded.

Because of recent advances in the diagnosis (microbiological procedures, magnetic resonance imaging, and transesophageal echocardiography), medical treatment, and cardiac surgery, the data were divided into 2 time periods and analyzed separately: 1984 to 1995 and 1996 to 2009.

Statistical Analysis

Continuous variables were not adjusted on normal distribution and were compared with the Mann-Whitney *U* test. Results are expressed as the median and interquartile range. Univariate associations for proportions were performed with a 2-sided Pearson correlation coefficient. The χ^2 test or Fisher exact test were used for statistical inference, and the Bonferroni correction was applied for multiple comparisons.

To evaluate the effect of antimicrobial treatment in reducing neurological complications, the standardized risk difference was calculated: The residual risk that remained after 1 week of appropriate antimicrobial treatment was subtracted from the risk obtained during the first week of treatment, and the result was divided by the risk during the first week.

To determine the independent effect of the variables on early mortality and the association of risk factors with the various neurological complications, multivariable Cox regression models were performed. Variables showing a significance of <0.05 in the univariate analysis were included, and forward stepwise Cox regression was performed, adjusted by the Wald statistic. We used the default level of significance of 0.05 for entry and 0.10 for removal of variables from the analysis. Adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated for each variable. Model goodness of fit was assessed by the Atkinson R^2 coefficient.[18] The risk factor analysis was performed only for early mortality. Deferred mortality is presented as descriptive data. Statistical significance was set at $P<0.05$. Data were analyzed with SPSS version 18.0 (Chicago, IL) software. All reported probability values were based on 2-tailed tests.

Results

Demographic Features

Seventy-three cases were excluded because of missing data (n=46) or insufficient follow-up (n=27). A total of 1345 episodes of left-sided IE were ultimately included: 1247 (93%) definite IE and 98 (7%) possible IE. Among the 1018 patients from Andalusia, 833 (82%) were first attended in the referral hospitals, whereas 185 (18%) were transferred from hospitals without cardiac surgery departments (76 from the 2 participating community hospitals and 109 from other centers). Vall d'Hebron Hospital in Barcelona recorded 327 cases, and 34% of them were transferred patients. There were no significant differences between the patients registered in the 2 databases (online-only Data Supplement), and the percentage of neurological complications occurring in transferred patients was not significantly different from that of patients initially seen in the referral hospitals (23% versus 27%; $P=0.1$).

The epidemiological and microbiological characteristics of the patients studied, divided into 2 time periods, are summarized in Table 1. On comparison of patients in the 2 periods analyzed, the median age, comorbidities, healthcare origin, and cases caused by *S aureus,* enterococci, and *Streptococcus bovis* were higher in the second period. The cardiac surgery and mortality rates were also higher in the second period.

Neurological Complications

Three hundred forty patients (25.3%) experienced ≥1 neurological event during the IE episode. Ischemic events were the most frequent neurological complication, occurring in 192 (56%) of 340 patients. Within this subgroup, small embolic complications were diagnosed in 138 (72%) of 192 patients, including 54 cases of transient ischemic attack (39%). Moderate-severe embolic complications occurred in 54 patients (28%); 31 of these cases (57%) were multiple embolisms with bilateral involvement. Sixty patients (18%) had cerebral hemorrhage, including 43 primary hemorrhages, 9 secondary to embolic events, and 8 attributable to ruptured mycotic aneurysms. Encephalopathy occurred in 69 patients, meningitis in 17, and brain abscesses in 2. *S aureus* was the most commonly implicated causal microorganism of IE in all patients with neurological complications: Embolic (52/192, 27%), hemorrhagic (18/60, 30%), encephalopathy (33/69, 48%), and meningitis (8/17, 47%). Overall, 114 (43.3%) of 263 patients in whom *S aureus* was the causal pathogen experienced ≥1 neurological complication, that is, twice the percentage observed in IE cases caused by other microorganisms (eg, *viridans group* streptococci [19%], coagulase-negative staphylococci [21%], or enterococci [20%]).

Predictors of Neurological Complications

The risk factors associated with the development of all neurological complications were vegetation size ≥3 cm (HR, 1.91; 95% CI, 1.07–3.43; $P=0.029$), *S aureus* as the cause of IE (HR, 2.47; 95% CI, 1.94–3.15; $P<0.001$), anticoagulant therapy at IE diagnosis (HR, 1.31; 95% CI, 1.00–1.72; $P=0.048$), and mitral valve involvement (HR, 1.29; 95% CI, 1.02–1.61; $P=0.03$). Further analysis showed that elderly patients (≥70 years) had lower complication rates than younger ones, and only hemorrhagic events showed statistical significance (HR, 0.36; 95% CI, 0.16–0.83; $P=0.014$). Anticoagulant treatment was particularly associated with cerebral hemorrhage (HR, 2.71; 95% CI, 1.54–4.76; $P=0.001$; Tables 2 and 3).

The distribution of each neurological complication relative to the time point antibiotics were started is illustrated in Figure 1. The neurological event was the first sign of IE in 100 patients (7% of the total IE cohort), occurring before the start of antimicrobial treatment, and in 192 patients (14%) the complication occurred during the first week of treatment. Thus, in 292 of the 340 affected patients (86%), the neurological complication was observed before or during the first week

Table 1. Characteristics of Patients With IE

Demographic Data	1984–1995 Period (n=208)	1996–2009 Period (n=1137)	Total (n=1345)
Male sex	153 (74)	758 (67)*	911 (68)
Age, median (IQR), y	49 (30)	62 (30)†	61 (24)
Elderly (≥70 y)	29 (14)	389 (34)†	418 (31)
Charlson Index, median (range)	0 (0–10)	2 (0–11)†	1 (0–11)
Type of infective endocarditis			
Native valve IE	165 (79)	855 (75)	1020 (76)
Early prosthetic valve IE	14 (7)	114 (10)	128 (9)
Late prosthetic valve IE	29 (14)	168 (15)	197 (15)
Hospital-acquired	40 (19)	263 (23)	303 (22)
Affected valve			
Aortic	94 (45)	534 (47)	628 (47)
Mitral	88 (42)	471 (41)	559 (42)
Aortic and mitral	26 (13)	132 (12)	158 (11)
Causal agents			
VGS	52 (25)	229 (20)	281 (21)
Staphylococcus aureus	29 (14)‡	234 (21)§	263 (19)‖
CNS	26 (12)	153 (13)	179 (13)
Enterococcus spp	18 (9)	150 (13)	168 (12)
Streptococcus bovis	1 (1)	62 (6)	63 (5)
Streptococcus agalactiae	3 (2)	34 (3)	37 (3)
Other streptococci	11 (5)	31 (3)	42 (3)
Gram-negative bacilli¶	5 (2)	25 (2)	30 (2)
Coxiella burnetii	10 (5)	16 (2)	26 (2)
Brucella spp	9 (4)	3 (0.3)	12 (1)
Fungi	3 (1.5)	14 (1)	17 (1)
HACEK group#	2 (1.0)	15 (1)	17 (1)
Others	7 (3)	43 (4)	50 (4)
Polymicrobial	9 (4)	21 (2)	30 (2)
Unknown cause	23 (11)	107 (9)	130 (10)
Neurological complications	59 (28)	282 (25)	340 (25)
Ischemic complications	32 (15)	160 (14)	192 (14)
Moderate-severe complication	10 (5)	44 (4)	54 (4)
Small complication	22 (11)	116 (10)	138 (10)
Cerebral hemorrhage	15 (7)*	45 (4)	60 (5)
Encephalopathy	9 (4)	60 (7)	69 (5)
Meningitis	2 (1)	15 (1)	17 (1)
Brain abscesses	1	1	2
Cardiac surgery	66 (32)	457 (40)*	523 (39)
Early mortality	50 (24)	351 (31)*	401 (30)
One-year related mortality**	57 (31)	381 (34)	438 (32)

All values are n (%), unless otherwise specified. CNS indicates coagulase-negative staphylococci; HACEK, *Haemophilus* (*Haemophilus parainfluenzae*), *Aggregatibacter* (*Aggregatibacter actinomycetemcomitans*, *Aggregatibacter aphrophilus*), *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* (*Kingella kingae*); IE, infective endocarditis; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; and VGS, *viridans* group streptococci.

*$P<0.05$ when the 2 periods were compared.

†$P<0.001$ when the 2 periods were compared.

‡MRSA 19 (7.7%).

§MRSA 1 (3.4%)

‖MRSA 18 (8.3%).

¶Gram-negative bacilli other than HACEK group.

#HACEK group included.

**Forty patients did not complete 1 year of follow-up: 17 (8%) patients in the first period and 23 (2%) in the second period.

Table 2. Univariate Analysis of Risk Factors for Neurological Complications in Patients With Infective Endocarditis

	Total Cohort (n=1345)	Neurological Complications (n=340)	Encephalopathy Meningitis (n=86)	Ischemic Complication (n=192)	Small Ischemic Complication (n=138)	Moderate-Severe Ischemic Complication (n=54)	Cerebral Hemorrhage (n=60)
Period							
1984–1995	208 (15)	59 (28)	11 (5)	32 (15)	22 (11)	10 (5)	15 (7)
1996–2009	1137 (85)	281 (25)	75 (7)	160 (14)	116 (10)	44 (4)	45 (4)*
Sex							
Male	911 (67)	234 (26)	57 (6)	137 (15)	92 (10)	45 (5)*	39 (4)
Female	434 (33)	106 (24)	29 (7)	55 (12)	46 (10)	9 (2)	21 (5)
Age, y							
<70	927 (69)	251 (27)	60 (7)	138 (15)	97 (11)	41 (4)	51 (5)
≥70	418 (31)	89 (21)*	26 (6)	54 (13)	41 (10)	13 (3)	9 (2)†
Charlson index, median (range)	2 (0–11)	2 (0–11)	2 (0–9)	1 (0–9)	2 (0–11)	0 (0–8)	1.5 (0–6)
Valve							
Native valve	1020 (76)	261 (26)	71 (7)	145 (14)	102 (10)	43 (4)	43 (4)
Prosthetic valve	325 (24)	79 (24)	15 (5)	47 (14)	36 (11)	11 (3)	17 (5)
Mechanical	230 (17)	63 (27)*	10 (4)	38 (16)	29 (13)	9 (4)	15 (6)
Biological	95 (7)	16 (17)	5 (5)	9 (9)	7 (7)	2 (2)	2 (2)
Affected valve							
Mitral	559 (41)	166 (30)†	39 (7)	94 (17)*	66 (12)	28 (5)*	33 (6)*
Aortic	628 (47)	136 (22)	39 (6)	75 (12)	57 (9)	18 (3)	20 (3)
Aortic and mitral	158 (12)	38 (24)	8 (5)	23 (15)	15 (9)	8 (5)	7 (4)
Causal agent							
VGS	280 (21)	53 (19)	6 (2)	35 (13)	30 (11)	5 (2)	13 (5)
Staphylococcus aureus	263 (20)	114 (43)†	42 (16)†	52 (20)†	33 (12)	19 (7)†	18 (7)*
CNS	179 (13)	38 (21)	6 (3)	27 (15)	19 (11)	8 (4)	5 (3)
Enterococcus spp	168 (12)	33 (20)	6 (4)	18 (11)	15 (9)	3 (2)	9 (6)
Anticoagulant therapy							
Yes	241 (18)	77 (32)†	11 (5)	44 (18)	29 (12)	15 (6)	22 (9)†
No	1104 (82)	263 (24)	75 (7)	148 (13)	109 (10)	39 (3)	38 (3)
Vegetation size, mm‡							
No vegetation	352 (26)	79 (22)	18 (5)	43 (12)	33 (8)	10 (3)	18 (5)
<10	669 (50)	160 (19)	41 (6)	89 (13)	61 (9)	28 (4)	30 (4)
≥10	447 (33)	121 (27)	26 (6)	74 (17)	51 (11)	23 (5)	19 (4)
≥20	133 (10)	36 (27)	10 (7)	19 (14)	10 (7)	9 (7)	5 (4)
≥30	24 (2)	12 (50)†	1 (4)	7 (30)*	5 (21)	2 (8)	3 (12)*
Cardiac surgery							
Yes	523 (39)	109 (21)†	23 (5)*	71 (14)	54 (10)	17 (4)	15 (3)†
No	822 (61)	231 (28)	63 (8)	121 (15)	84 (10)	37 (5)	45 (5)

All values are n (%), unless otherwise specified. CNS indicates coagulase-negative staphylococci; and VSG, *viridans* group streptococci.

*$P<0.05$, †$P<0.001$.

‡Median mitral valve vegetation size: 1 cm (25th percentile, 1; 75th percentile, 2). Median aortic valve vegetation size: 1 cm (25th percentile, 0; 75th percentile, 2); $P<0.001$. When mitral valve was affected, 204 (41%) of 497 vegetations measured >1 cm vs 176 (31.7%) of 573 with aortic valve involvement ($P<0.001$).

of treatment, with a subsequent gradual decrease during the following weeks: 32 episodes in the second week, 9 in the third, and only 5 episodes after 4 weeks of treatment. After 1 week of appropriate antimicrobial treatment, the incidence of neurological complications showed a marked decrease (4% of the total cohort), although this reduction was lower for hemorrhagic events (Figure 1A). The decrease was similar in IE caused by streptococci and staphylococci, but was less evident in cases caused by enterococci or unknown causes (Table 4). Vegetations >1 cm were also associated with a less

Table 3. Unadjusted and Adjusted Multivariable Analysis of HR of Risk Factors Associated With Neurological Complications in Patients With Infective Endocarditis

Neurological Complications	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Global neurological complications				
Elderly (age ≥70 y)	0.87 (0.68–1.11)	0.22		
Aortic valve	1		1	
Mitral valve	1.16 (0.90–1.48)	0.25	1.29 (1.02–1.61)	0.03
Aortic and mitral valve	0.94 (0.61–1.42)	0.94	1.00 (0.70–1.44)	0.99
Staphylococcus aureus	2.43 (1.94–3.05)	<0.001	2.47 (1.94–3.15)	<0.001
Anticoagulant therapy	1.19 (0.92–1.54)	0.184	1.31 (1.00–1.72)	0.048
Vegetation ≥30 mm	2.29 (1.28–4.07)	0.005	1.91 (1.07–3.43)	0.029
Encephalopathy/meningitis				
Staphylococcus aureus	4.50 (2.94–6.88)	<0.001	4.34 (2.84–6.64)	<0.001
Ischemic complications				
Aortic valve	1			
Mitral valve	1.33 (0.98–1.80)	0.069		
Aortic and mitral valve	1.13 (0.71–1.81)	0.604		
Staphylococcus aureus	1.81 (1.32–2.49)	<0.001	1.77 (1.27–2.48)	0.001
Vegetation ≥30 mm	2.25 (1.05–4.79)	0.036	2.02 (1.09–4.30)	0.007
Cerebral hemorrhage				
Period 1996–2009	0.71 (0.39–1.28)	0.253	0.55 (0.27–1.07)	0.079
Elderly (age ≥70 y)	0.45 (0.22–0.91)	0.026	0.36 (0.16–0.83)	0.014
Aortic valve	1			
Mitral valve	1.73 (0.99–3.02)	0.054		
Aortic and mitral valve	1.24 (0.52–2.95)	0.62		
Anticoagulant therapy	2.26 (1.33–3.84)	0.002	2.71 (1.54–4.76)	0.001
Staphylococcus aureus	2.27 (1.22–4.25)	0.01	2.35 (1.30–4.23)	0.005
Vegetation ≥30 mm	3.49 (0.97–12.64)	0.056	2.93 (0.91–9.49)	0.073

CI indicates confidence interval; and HR, hazard ratio.

pronounced risk decrease after treatment, and in those with diameters ≥3 cm, the incidence of embolic events after the first week of treatment remained very high (20%). In patients whose anticoagulant therapy was maintained, the risk reduction was also less marked because of the greater number of hemorrhagic events (10/19 versus 9/31; *P*=0.06), with no reduction in the rate of ischemic events.

Risk Factors for Mortality

Early mortality in the cohort was 30% (n=401); no differences were observed between patients who underwent surgery (31%) and those receiving medical treatment (29%) alone. The causes of death were ventricular failure (n=179; 45%), sepsis (n=93; 23%), vascular neurological event (n=40; 10%), and others (n=89; 22%), mostly related to complications in the postoperative period (n=42; 47%).

Neurological complications had a negative impact on the outcome. In patients who experienced a neurological event, early mortality was 45% compared with 24% in patients who did not have this complication (HR, 1.58; 95% CI, 1.23–2.02; *P*<0.001). Nonetheless, only cerebral hemorrhage and moderate-severe ischemic events were independently associated with mortality in the adjusted multivariable analysis (Table 5). The other independent risk factors associated with early mortality were septic shock (HR, 2.24; 95% CI, 1.69–2.95), heart failure (HR, 2.35; 95% CI, 1.80–3.07), *S aureus* (HR, 2.25; 95% CI, 1.72–2.94) or coagulase-negative staphylococcus as the cause of IE (HR, 2.05; 95% CI, 1.50–2.60), early prosthetic valve IE (HR, 1.58; 95% CI, 1.16–2.15), acute renal failure (HR, 1.65; 95% CI, 1.30–2.10), age ≥70 years (HR, 1.57; 95% CI, 1.23–2.01), late prosthetic valve IE (HR, 1.49; 95% CI, 1.07–2.08), and Charlson comorbidity index score (HR, 1.06; 95% CI, 1.01–1.12).

Forty patients (3%) were lost to late follow-up. Death because of late complications related to the IE episode occurred in 37 patients (26 with left ventricular failure, 8 deferred cardiac surgery, and 3 neurological sequelae), 36 patients died of causes unrelated to IE (10 neoplasms, 14 advanced chronic diseases, 7 other infections, 1 upper gastrointestinal tract hemorrhage, and 1 road traffic accident), and in 3 patients, the cause was unknown.

Surgery and Neurological Complications

Surgery was indicated in 710 patients (53%) but was performed in only 523 patients (39%). A smaller percentage of patients with neurological complications underwent surgery

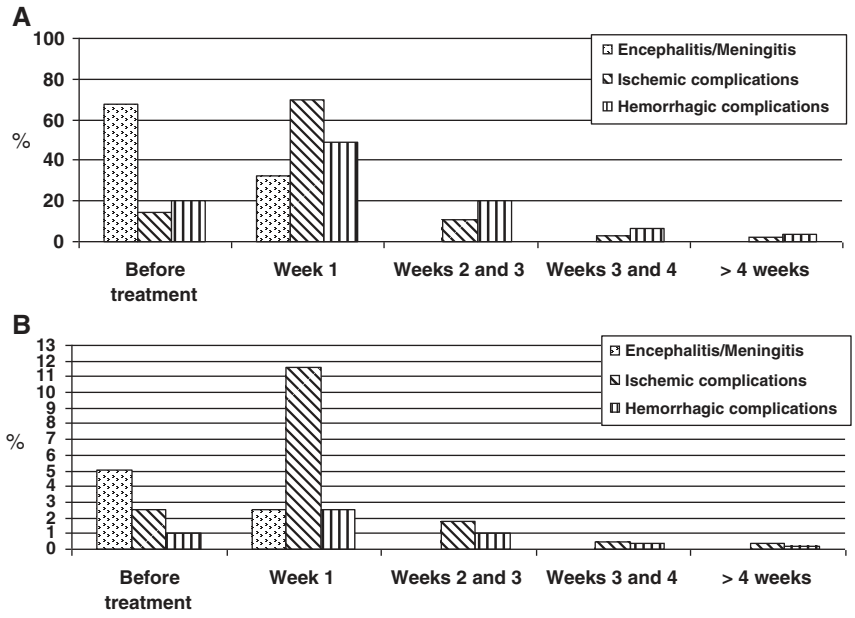

Figure 1. A, Percentage of each neurological complication occurring in patients with these events (n=340) relative to the start of antibiotic treatment. **B**, Percentage of each neurological complication in the total cohort (n=1345) of patients with infective endocarditis relative to the start of antibiotic treatment.

(109/340, 32%) than patients without these complications (414/1005, 41%; $P<0.01$). Sixty-two patients with neurological complications (18%) had an indication for surgery but were not operated on because of deteriorated neurological status or unacceptable operative risk versus 114 patients without these complications (11%; $P<0.01$).

Only 12 (20%) of 60 patients with cerebral hemorrhage underwent surgery, and mortality was high when the procedure was performed within the first 2 weeks (3 of 4 cases), in the third week (2 of 3 cases), and 21 days after the neurological event (2 of 5 cases). Of note, 4 of these 7 deaths were related to new severe bleeding after cardiac surgery. The percentage of new bleeds postoperatively was 50% (2 of 4 cases) in surgery performed in the first 2 weeks, 33% (1 of 3 cases) in surgery in the third week, and 20% (1 of 5 cases) in surgery performed 21 after days of the neurological event (Figure 2; Table 6).

Fifteen (28%) of 54 patients with moderate-severe ischemic lesions also underwent surgery, 5 of them within 2 weeks of the neurological event (2 deaths) and 10 after 2 weeks (2 deaths). Two of these 4 deaths were related to new cerebral bleeding. Thirty-eight patients (70%) who had small ischemic complications and underwent surgery in the first 2 weeks showed higher mortality than those with no neurological events (18/38 [47%] versus 77/257 [30%]; $P=0.032$), but higher mortality was also observed when surgery was performed after 2 weeks (8/16 [50% mortality]; Figure 2B). The percentage of bleeding events and exacerbation of neurological symptoms in this group was 11% in the first week, 10% in the second, and 27% in the third week; there were no cases after 21 days (Table 6). Of note, 8 (2%) of 393 patients who underwent surgery with no apparent neurological complications experienced a cranial hemorrhage in the postoperative period; 6 of them had been operated on within 14 days after the diagnosis.

Discussion

This observational study describes the incidence of neurological complications in a large, well-defined multicenter cohort of left-sided IE patients, analyzes the risk factors for developing these complications, and describes the effect on them of antimicrobial treatment and anticoagulant therapy. In addition, the outcome of early surgery in these patients was investigated to assess the risk of new time-dependent neurological damage. The traditional therapy for IE concentrates on bacteriological cure of the infected heart valve and surgical correction of hemodynamic decompensation. Neurological complications are a common and often salient feature of IE,[1–5] and the advent of CT and magnetic resonance imaging enables a more reliable clinical assessment of stroke syndromes. However, there are few available data about the risk of recurrent stroke, the best approach with regard to anticoagulant therapy, or the consequences of early surgery.

The overall frequency of neurological complications in the present study cohort was 25%, and 19% were vascular events, in keeping with the results from other large cohorts.[8,19] In the present series, the majority of cases were first attended in referral centers, but patients transferred from other institutions were also included. The percentage of complicated cases may have been somewhat overrepresented, with patients from community hospitals accounting for 23% of the total. Nonetheless, other multicenter studies only include cases from referral centers; hence, it is likely that the present series better reflects the overall clinical reality of this patient population.

We found that the percentage of neurological complications did not change substantially between the 2 periods studied except for hemorrhagic complications, which showed a decrease in more recent years, which contrasted with the increase in patient age. Older patients in the present study had lower rates of these events, as has been reported previously,[8,20] but the cause of this reduction is not fully understood. Use of antiplatelet therapy[21,22] (often prescribed in elderly patients), a hypothetical decline in hemostatic function, and smaller size of vegetations in this population are some of the proposed reasons,[3] but it is also possible that these events are simply

Table 4. Changes in the Frequency of Vascular Neurological Complications Over Time in Patients With Infective Endocarditis

	Antibiotic Therapy ≤7 d (n=162)*	Antibiotic Therapy >7 d (n=49)†	Standardized Risk Differences (95% CI), %‡
Type of neurological complication			
Ischemic	133/1216 (10.9)	30/1083 (2.8)	−74.7 (−75.7, −73.7)
Hemorrhagic	29/1216 (2.4)	19/1187 (1.6)	−32.9 (−33.6, −32.2)
Valve affected			
Mitral	76/499 (15.2)	30/423 (7.1)	−53.4 (−55.9, −51.0)
Aortic	69/574 (12.2)	13/495 (2.6)	−78.5 (−80.0, −77.1)
Aortic and mitral	17/143 (19.0)	6/126 (4.8)	−59.9 (−63.7, −56.2)
Causal agent			
VGS	30/263 (11.4)	6/233 (2.6)	−77.4 (−79.5, −75.4)
Staphylococcus aureus	53/221 (25.0)	10/159 (6.3)	−74.8 (−78.7, −71.0)
CNS	21/167 (12.6)	5/146 (3.4)	−72.8 (−75.8, −69.7)
Enterococcus spp	14/159 (8.8)	10/145 (6.9)	−21.7 (−25.8, −17.5)
Others	33/295 (11.2)	10/262 (3.8)	−65.9 (−67.0, −64.2)
Unknown cause	11/120 (9.2)	8/109 (7.3)	−19.9 (−24.9, −15.0)
Anticoagulant treatment			
Yes	40/241 (16.5)	18/202 (8.9)	−43.1 (−47.2, −39.0)
No	122/974 (12.5)	31/852 (3.6)	−71.9 (−73.1, −70.6)
Vegetation size, mm			
No vegetation	37/321 (11.5)	11/284 (3.9)	−66.4 (−68.7, −64.1)
<10	82/611 (13.4)	20/529 (3.8)	−71.8 (−73.5, −70.2)
≥10	53/404 (13.1)	25/351 (7.1)	−45.7 (−48.4, −43.0)
≥20	15/118 (12.7)	6/103 (5.8)	−54.2 (−58.8, −49.6)
≥30	7/22 (31.8)	3/15 (20.0)	−37.1 (−58.4, −15.9)

Values are n/N (%), except for standardized risk differences. CI indicates confidence interval; CNS, coagulase-negative staphylococci; NC, neurological complications; and VSG, *viridans* group streptococci.

*Patients with meningitis, encephalitis, and brain abscesses were excluded. Patients with NC before admission or during the first week of antimicrobial treatment were excluded.

†Patients who developed NC after 1 week of appropriate antimicrobial treatment.

‡Standardized risk differences=(risk of NC with 1 week of appropriate antibiotic treatment minus risk of NC during the first 1 week of appropriate antibiotic treatment)/risk of NC during the first 1 week of appropriate antibiotic treatment.

underdiagnosed in this population because of mild clinical signs and symptoms.

Mitral valve involvement and vegetation size have been considered important predictors of stroke in several studies,[3,8,10,23–26] whereas others have not confirmed this observation.[27–30] Some authors have emphasized the importance of vegetations only when other factors are present, such as large size, mitral valve location, and *S aureus* as the cause of IE.[27,30] In the present cohort, mitral endocarditis was a mild risk factor for a greater rate of ischemic complications, and vegetation size showed a significant association, but only in relation to larger diameters. Therefore, we believe that the real prognostic influence of vegetation size and location on the development of embolic events may be outweighed by other factors that appear to be more important, such as the causal microorganism. *Staphylococcus aureus* as the causal microorganism was the most important risk factor for all neurological complications in the present study, and its impact was 2 to 3 times higher than that of other causative agents.

Appropriate antimicrobial treatment considerably decreased the embolism rate after 1 week, and this effect was observed with all the microorganisms implicated, as has been reported previously.[10,31] The comparatively smaller reduction seen in the present study in relation to enterococci or unknown causes likely reflects the difficulty to obtain a bactericidal activity with the antimicrobial treatment used in these 2 scenarios. Nonetheless, even in the best microbiological context, in patients with very large vegetations (≥3 cm diameter), the risk of developing a neurological complication after 1 week of medical therapy remained very high. This fact should be borne in mind when making important clinical decisions, such as the need for an early surgical intervention. Prompt surgery to prevent embolic events based on a vegetation size >1 cm was proposed in early echocardiographic studies,[32] but greater percentages of relapse and prosthesis dehiscence after surgery when antimicrobial treatment has not been completed remain a concern. In this regard, 2 recent studies have demonstrated that early surgery effectively decreases systemic embolism without increasing the IE relapse rate or prosthetic valve–related problems compared with conventional treatment.[33,34]

Not all neurological complications had a negative impact on the outcome, and this could explain in part the contradictory

Table 5. Unadjusted and Adjusted Multivariable Analyses of Risk Factors Related to Early Mortality

	Total Cohort (n=1345)	Survivors (n=944)	Nonsurvivors (n=401)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Period					
1984–1995	208 (15)	158 (76)	50 (24)	1	1
1996–2007	1137 (85)	786 (69)	351 (31)*	1.42 (1.05–1.91)*	1.01 (0.73–1.41)
Sex					
Male	911 (67)	649 (71)	262 (29)	1	
Female	434 (33)	295 (68)	139 (32)	1.16 (0.91–1.37)	
Charlson Index, median (range)	2 (0–11)	1 (0–10)	3 (0–11)†	1.12 (1.08–1.16)†	1.06 (1.01–1.12)†
Age, y					
<70	927 (69)	699 (75)	228 (25)		
≥70	418 (31)	245 (59)	173 (41)†	1.83 (1.50–2.23)†	1.57 (1.23–2.01)†
Valve					
Native valve	1020 (76)	750 (74)	270 (26)	1	1
Prosthetic valve	325 (24)	194 (60)	111 (40)†		
Early IE	128 (39)	63 (49)	65 (51)†	2.17 (1.65–2.85)†	1.58 (1.16–2.15)†
Late IE	197 (61)	131 (66)	66 (33)	1.36 (1.04–1.78)*	1.49 (1.07–2.08)†
Prosthesis					
Mechanical	230 (17)	150 (65)	80 (35)	1	
Biological	95 (7)	64 (68)	31 (32)	1.20 (0.83–1.74)	
Affected valve					
Aortic	628 (47)	456 (73)	172 (27)	1	
Mitral	559 (41)	388 (69)	171 (31)	1.10 (0.89–1.36)	
Aortic and mitral	158 (12)	100 (63)	58 (37)*	1.31 (0.97–1.77)	
Causal agents					
VGS	280 (21)	241 (86)	39 (14)†	0.38 (0.28–0.54)†	
Staphylococcus aureus	263 (20)	137 (52)	126 (48)†	2.28 (1.85–2.82)†	2.25 (1.72–2.94)†
CNS	179 (13)	101 (56)	78 (44)†	1.70 (1.32–2.17)†	2.05 (1.50–2.60)†
Enterococcus spp	168 (12)	119 (71)	49 (29)		
Anticoagulant therapy					
Yes	241 (18)	156 (65)	85 (35)†	1.34 (1.07–1.69)†	1.21 (0,88-1,66)
No	1104 (82)	788 (71)	316 (29)	1	1
Vegetation size, mm					
<10	669 (50)	508 (76)	161 (24)†	0.70 (0.57–0.87)†	
≥10	447 (33)	301 (67)	146 (33)†	1.29 (1.04–1.60)*	1.25 (0.99–1.57)
≥20	133 (10)	85 (64)	48/133 (36)*	1.35 (0.99–1.83)	
≥30	24 (2)	15 (63)	9 (37)	1.44 (0.74–2.87)	
Surgical intervention					
Yes	523 (39)	359 (69)	164 (31)	1.06 (0.87–1.29)	
No	822 (61)	585 (71)	237 (29)	1	
Complications					
Septic shock‡	154 (12)	41 (27)	113 (74)†	4.65 (3.72–5.80)†	2.24 (1.69–2.95)†
Acute renal failure§¤	424 (32)	222 (52)	202 (48)†	2.56 (2.10–3.13)†	1.65 (1.30–2.10)†
Heart failure‖	675 (51)	394 (58)	281 (42)†	2.63 (2.12–3.27)†	2.35 (1.80–3.07)†
Neurological complications	340 (25)	188 (55)	152 (45)†	2.05 (1.67–2.51)†	1.58 (1.23–2.02)†
Type of complication¶					
Encephalitis/meningitis	86 (6)	44 (50)	43 (50)*	2.10 (1.53–2.88)†	0.94 (0.61–1.45)
Total ischemic complications	192 (14)	114 (59)	78 (41)†	1.59 (1.24–2.03)†	1.67 (1.27–2.19)†

(*Continued*)

Table 5. Continued

	Total Cohort (n=1345)	Survivors (n=944)	Nonsurvivors (n=401)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Small ischemic complication	138 (10)	82 (59)	56 (41)†	1.42 (0.93–2.19)	
Moderate-severe ischemic complication	54 (4)	32 (59)	22 (41)	1.59 (1.19–2.10)†	1.63 (1.19–2.22)†
Cerebral hemorrhage	60 (4)	28 (47)	32 (53)†	2.04 (1.42–2.92)†	1.73 (1.10–2.71)*

Data in the first 3 columns are expressed as n (%). CI indicates confidence interval; CNS, coagulase-negative staphylococci; IE, infective endocarditis; NC, neurological complications; and VSG, *viridans* group streptococci.

*$P<0.05$.

†$P<0.001$.

‡Analyzed in 1256 patients.

§Analyzed in 1336 patients.

‖Analyzed in 1328 patients.

¶A separate regression analysis was performed for each neurological complication.

results of several studies in which the various types of complications were not differentiated.[4,8] Furthermore, standardized severity grading (clinical or radiological) of cerebrovascular complications is provided in very few reports.[19] In the present study, only moderate-severe ischemic events, particularly cerebral hemorrhages, were significantly associated with a poorer outcome, as has been pointed by others.[35] Hemorrhagic complications were clearly related to *S aureus* and anticoagulant therapy, which was mainly used in patients with mechanical valves. Furthermore, patients in whom anticoagulant therapy was maintained experienced a larger number of hemorrhagic events, even after 1 week of antimicrobial therapy. On the basis of these results, we agree with the recommendations of Tornos et al,[36] who advise temporary discontinuation of anticoagulant therapy in cases of *S aureus* IE until the septic phase of the disease is overcome and the risk of embolization has decreased with antimicrobial therapy. Future studies are needed to further clarify this important point.

In the present study, cardiac surgery was strongly conditioned by the development of neurological complications, with a considerably lower number of interventions when they were present, even in patients with a clear indication for valve repair. The impact of valve surgery on the outcome in IE patients with cerebrovascular complications is a subject of debate, and there is a great deal of concern about the risk of postoperative neurological impairment when surgery is performed early after an ischemic or hemorrhagic episode. The literature contains contradictory results in this line: Some authors have found the risk of exacerbation to be low when surgery was performed within 72 hours,[37] whereas others have reported that the risk is highest in early surgery and gradually decreases as the delay between the neurological event and the operation increases.[9] Because of the lack of controlled studies, recommendations are based on the results of published reports, and the generally accepted advice is to delay surgery for ≥2 weeks in the case of severe ischemic strokes and 4 weeks for hemorrhagic events.[38] The results of the present study are in line with these recommendations, although the risk of postoperative complications was low after a small ischemic event, and therefore, minor events should not be an impediment to surgical valve repair when it is necessary.

The present study has several limitations. First, brain CT scans were not routinely performed in all patients,

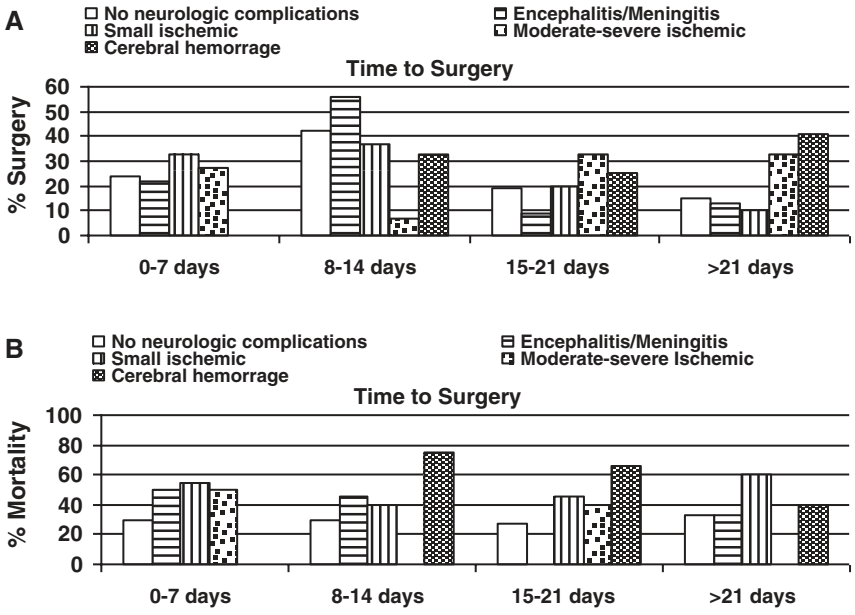

Figure 2. A, Percentage of patients undergoing cardiac surgery and timing of the procedure by type of neurological complication. **B**, Percentage of patients with each neurological complication who had a fatal outcome after cardiac surgery according to the time to surgery (only patients who had operations are included).

Table 6. Characteristics and Outcome of Patients With Valve Surgery and Neurological Complications

	Time From Event to Surgery				
	0–7 d	8–14 d	15–21 d	> 21 d	Total
n (%)	120 (24)	202 (40)	97 (20)	78 (16)	497*
EuroSCORE median (P25, P75)	10 (7, 13)	10 (7, 12)	9 (7, 11)	7 (5, 11)	9 (7, 12)
No neurological complications	93	164	76	60	393
Encephalitis/meningitis	5	13	2	3	23
Small ischemic complication	18	20	11	5	54
Moderate-severe ischemic complication	4	1	5	5	15
Cerebral hemorrhage	0	4	3	5	12
Bleeding/death of bleeding/total deaths					
No neurological complications	0/0/28	6/5/49	1/1/21	1/1/14	8/7/112
Encephalitis/meningitis	0/0/3	4/3/6	0/0/0	0/0/1	4/3/10
Small ischemic complication	2/2/10	2/1/8	3/3/5	0/0/3	7/6/26
Moderate-severe ischemic complication	1/1/2	0/0/0	1/1/2	0/0/0	2/2/4
Cerebral hemorrhage	0/0/0	2/2/3	1/1/2	1/1/2	4/4/7

EuroSCORE indicates European System for Cardiac Operative Risk Evaluation; P25, 25th percentile; and P75, 75th percentile.
*In 26 patients, the date of surgery was not recorded.

and the true incidence of ischemic complications is likely underestimated in the present cohort. Studies using magnetic resonance imaging[39–41] have shown that acute brain embolizations are significantly more prevalent than has been reported previously in studies based on clinical findings and CT scanning (30% of undetected events). With this taken into account, it is possible that some less symptomatic elderly patients in the present study were wrongly classified as having no neurological complications and that several patients with negative CT scans and symptoms labeled as encephalitis may have had multiple small embolisms that would have been detected with other imaging techniques. However, other reports[19,42] have shown that small ischemic complications have no effect on the final outcome of IE (in accordance with the present findings), and therefore, the essential conclusions would not be changed. Second, because of the lengthy recruitment of this cohort (>20 years), transesophageal echocardiography was only available in the second study period, and therefore, echocardiographic reading was not centralized or blinded to clinical status. Hence, evaluation of the echocardiographic data (vegetation size) may be biased. It would not be inconceivable for an echocardiographer with knowledge of the patient's clinical course (eg, a neurological event), to unconsciously exercise bias when interpreting the severity of the echocardiographic features. Furthermore, many echocardiographic studies were performed after neurological complications had developed, and it is likely that vegetation size was larger before the embolism; however, this further supports the fact that large vegetations are a particularly important risk factor for these events. Third, this was an observational study, and some results, such as the effect of cardiac surgery on neurological complications, should be interpreted with caution. The multicenter character of the cohort implies that there may have been somewhat different approaches between the hospitals regarding aspects such as surgical treatment or the timing of surgery after the event. Nonetheless, there were no significant differences in the operation rates or mortality between the participating hospitals with cardiac surgery departments (data not shown), and the increase in operations in the second period likely reflects the current trend toward more proactive and earlier surgery in IE.[43,44]

Conclusions

The results of the present study may help to identify IE patients who are at an increased risk of neurological complications. The outcome in this population appears to depend on the type of event, with moderate-severe ischemic strokes and brain hemorrhage being associated with a significant excess in mortality. It is advisable to revise anticoagulant therapy in episodes associated with a high risk of neurological events, such as cases caused by *S aureus*, mitral valve involvement, and large vegetations. Despite appropriate antimicrobial treatment, which clearly reduces the rate of events after 1 week, large vegetation size should lead to consideration of an early surgical intervention. Even though valve repair may exacerbate cerebral damage after cerebrovascular events, the risk of postoperative bleeding appears to be low in cases with small ischemic strokes when surgery is performed immediately and in moderate-severe episodes when the intervention takes place after 2 weeks. In patients with cerebral hemorrhage, it may be advisable to postpone valve replacement for ≥4 weeks.

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Disclosures

None.

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CLINICAL PERSPECTIVE

This observational study describes the incidence of neurological complications in a large, well-defined multicenter cohort of left-sided infective endocarditis. The risk factors for developing these events were analyzed carefully, and the influence of antimicrobial treatment and anticoagulant therapy in this scenario was considered. In addition, the results of early surgical intervention in this context were evaluated to assess the risk of new neurological damage that was time dependent. In the present study, vegetation size ≥3 cm, *Staphylococcus aureus* as the causative microorganism, and involvement of the mitral valve were risk factors related to the development of neurological complications; conversely, antimicrobial treatment reduced their incidence. Moderate to severe ischemic strokes and brain hemorrhages were associated with a significantly worse prognosis, and maintenance of anticoagulant therapy was associated with a higher incidence of hemorrhagic events. Finally, a higher mortality was observed when valvular surgery was performed within 4 weeks of a brain hemorrhage. The conclusion is that early and appropriate antimicrobial treatment is critical to avoid neurological complications in infective endocarditis and that a temporary withdrawal of anticoagulant therapy should be considered. Valvular surgery should be deferred when hemorrhage is present.

Correction

In the article by Garcia-Cabrera et al, "Neurologic Complications of Infective Endocarditis: Risk Factors, Outcome, and Impact of Cardiac Surgery: A Multicenter Observational Study," which appeared in the June 11, 2013 issue of the journal (*Circulation.* 2013;127:2272–2284), Dr Radka Ivanova-Georgieva's affiliation was listed incorrectly. Dr Ivanova-Georgieva is affiliated with the Internal Medicine Unit at Hospital Universitario Virgen de la Victoria in Malaga, Spain and not the Infectious Disease Service. In addition, there was an error in the alignment of data in Table 1 for rows "Casual agent" through "Unknown cause."

The current online version of the article has been corrected. The authors regret the error.

(*Circulation*. 2013;128:e60.)

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Supplemental data

Table 1. Main characteristics of the hospitals contributing to the databases

	HUVR	HUVM	HUVV	HUCH	HUVN	HJRJ	HCdS	HUVH
Beds	1205	1034	581	1156	917	741	384	1192
Catchment Population	1,434,013	547,462	457,086	1,453,409	442,523	496,508	372,964	1,411,227
Emergencies/year	317,955	224,971	158,783	343,811	246,116	113,503	123,893	230,598
Admissions/year	52,035	37,100	19,818	38,907	43,757	22,523	18,760	46,575
IE cases	376	149	178	49	190	37	39	327
Cardiac surgery	yes	yes	yes	yes	yes	no	no	yes

HUVR: Hospital Universitario Virgen del Rocío, Seville
HUVM: Hospital Universitario Virgen Macarena, Seville
HUV: Hospital Universitario Virgen de la Victoria, Malaga
HUCH. Hospital Universitario Carlos Haya, Malaga
HUVN: Hospital Universitario Virgen de las Nieves, Granada
HJRJ: Hospital Juan Ramón Jiménez, Huelva
HCdS: Hospital Costa del Sol, Marbella
HUVH: Hospital Universitario Vall d´Hebron, Barcelona

Table 2. Main characteristics of patients in the two registries

Demographic Data	**Andalusian hospitals (N=1018) N (%) [95% CI]**	**Vall d'Hebron Hospital (N=327) N (%) [95% CI]**
Male sex	694 (68) [65-71]	217 (66) [61-71]
Age, median (IQR), y	59 (25)	66 (23.5)
Elderly (≥70 years)	290 (28) [26-31]	128 (39) [34-45]
Charlson Index, median (range)	1 (0-10)	2 (0-11)
Type of infective endocarditis		
Native valve IE	762 (75) [72-77]	258 (79) [74-83]
Early prosthetic valve IE	99 (10) [8-12]	29 (9) [6-12]
Late prosthetic valve IE	157 (15) [13-17]	40 (12) [9-16]
Affected valve		
Aortic	472 (46) [43-49]	156 (48) [42-53]
Mitral	431 (42) [39-45]	128 (39) [34-44]
Aortic and mitral	115 (11) [9-13]	43 (13) [10-17]
Etiological Agents		
VGS	208 (20) [18-23]	73 (22) [18-27]
Staphylococcus aureus	198 (19) [17-22]	65 (20) [16-25]
CNS	148 (14) [12-17]	31 (9) [7-13]
Enterococcus spp.	120 (12) [10-14]	48 (15) [11-19]
Unknown etiology	108 (11) [9-13]	22 (7) [4-10]
Cardiac surgery	394 (39) [36-42]	129 (39) [34-45]
Early mortality	313 (31) [28-34]	88 (27) [22-32]

VGS, viridans group streptococci; CNS, coagulase-negative staphylococci

Table 3. Indications for surgery and reasons why surgery was not performed, although indicated

Indications	**N=523**	**95% CI**
Left ventricular failure	355 (67.9%)	63.7 – 71.7
Intracardiac complications*	140 (26.8%)	23.1 – 30.7
Sepsis	22 (4.2%)	2.8 – 6.3
Repeated embolisms	6 (1.1%)	0.5 – 2.5
Reasons for no surgery	**N=187**	**95% CI**
Neurological complications	24 (12.8%)	8.8 – 18.0
Refused by the patient	22 (11.8%)	7.9 – 17.2
Poor clinical status	91 (48.7%)	41.6 – 55.8
Underlying disease	26 (13.9%)	9.7 – 19.6
Death before scheduled intervention	24 (12.8%)	8.7 – 18.4

*Severe valvular regurgitation, abscess, or fistula

Anticoagulant therapy

Patients receiving anticoagulation were classified into 4 groups

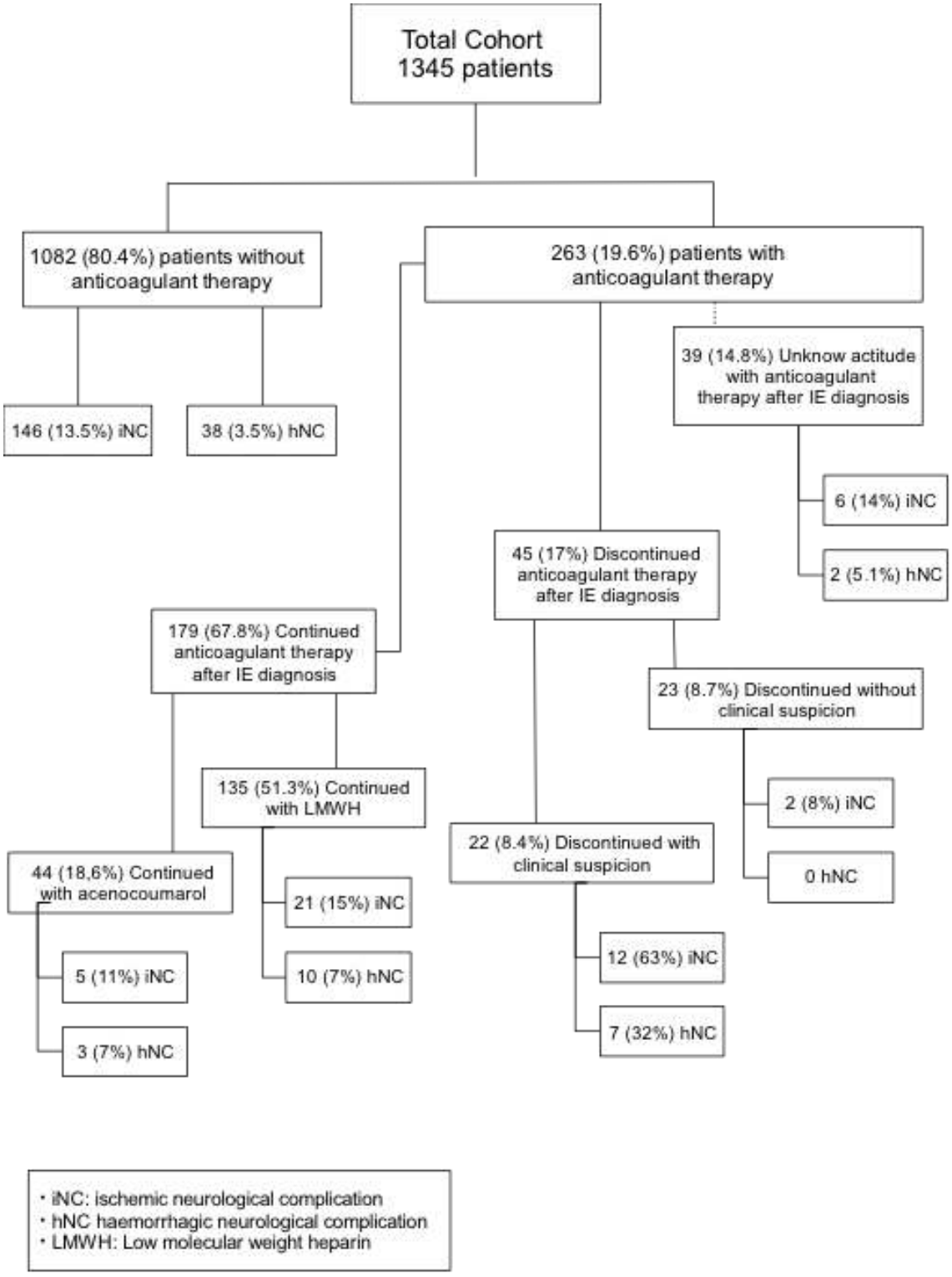
1. Patients in whom anticoagulant therapy with dicoumarin was continued after the IE diagnosis and during the entire episode if no neurological event occurred, or until the neurological event presented. These patients were considered as "receiving anticoagulant therapy".

2. Patients in whom dicoumarin was switched to heparin after the IE diagnosis, following the same scheme as above. These patients were also considered as "receiving anticoagulant therapy"

3. Patients in whom any form of anticoagulation was temporarily discontinued (one to two weeks) after the IE diagnosis and with a clinically suspected vascular neurologic event. This therapy was re-started if there were no neurological events after initiation of antimicrobial therapy. These patients were classified as "no anticoagulant therapy" and the effect of dicoumarin was reversed in the preceding 24 hours with vitamin K administration.

4. Patients in whom anticoagulants were discontinued at the time of the IE diagnosis, and with high clinical suspicion of a neurological event. The suspected event was then confirmed or ruled out based on the patients' clinical course and/or CT findings. This group was excluded from the analysis.

The following flow chart shows the final distribution of patients and the outcome according to the therapeutic decision:



Second box down on the right, after 14.8% : Anticoagulant therapy use after IE diagnosis was unknown

Table 4. Characteristics of patients receiving or not* anticoagulant therapy after the diagnosis of infectious endocarditis

	Receiving anticoagulant therapy **N = 179 (%)**	**No anticoagulant therapy** **N = 23 (%)**	*p*
Male sex	115 (64.2)	17 (73.9)	0.36
Median age (p25, p75)	62 (52, 71)	69 (63, 75)	0.02
Elderly (>70 years)	59 (33)	11 (47.8)	0.16
Median Charlson Index (p25, p75)	1 (0, 4)	2 (1, 4)	0.12
Type of infective endocarditis			
Native valve IE	37 (20.7)	8 (34.4)	0.13
Early prosthetic valve IE	47 (26.3)	8 (34.4)	0.39
Late prosthetic valve IE	85 (50.3)	7 (30.4)	0.12
Affected valve			
Aortic	64 (35.8)	12 (52.2)	0.13
Mitral	98 (54.7)	9 (39.1)	0.16
Aortic and mitral	17 (9.5)	2 (8.6)	0.99
Etiological Agents			
No etiology	25 (14)	3 (13)	0.99
Streptococcus viridans	19 (10.6)	3 (13)	0.72
Staphylococcus aureus	23 (12.8)	6 (26)	0.11
Coagulase-negative staphylococci	42 (23.5)	5 (21.7)	0.85
Enterococcus spp.	30 (16.8)	3 (13)	0.99
Others	40 (22.3)	3 (13)	0.42
Cardiac surgery	68 (38)	13 (56.5)	0.88
Mortality	60 (33.5)	12 (52.2)	0.07

*Patients receiving anticoagulants correspond to anticoagulant Groups 1 and 2 defined above, and those not receiving anticoagulants correspond to Group 3.
The only significant difference is that physicians tended to temporary discontinue anticoagulation in elderly patients.

The following two tables depict the risk of vascular neurologic events (ischemic or hemorrhagic) according to whether patients were receiving anticoagulation or not. Data from the total cohort are shown in Table 5 and data only from patients with prosthetic valve IE are presented in Table 6.

Table 5. Use of anticoagulant therapy and risk of a neurologic complication (NC). Data from the total cohort

	N	Ischemic NC	OR (95% CI)	Hemorrhagic NC	OR (95% CI)
Not anticoagulated	1082	146 (13.5%)	1	38 (3.5%)	1
Anticoagulated	263	46 (17.5%)	1.36 (0.94-1.95)	22 (8.4%)	2.5 (1.45-4.32)
Continued with acenocoumarol	44	5 (11.4%)	0.82 (0.32–1.12)	3 (6.8%)	2.0 (0.59-6.78)
Continued with heparin	135	21 (15.5%)	1.17 (0.71– .92)	10 (7.4%)	2.2 (1.06-4.08)
Discontinued without suspicion	23	2 (8.7%)	0.61 (0.14–2.63)	0	-
Discontinued with suspicion	22	12 (57%)	8.55 (3.54–20.6)	7 (31.9%)	12.8 (4.94-3.2)

Table 6. Use of anticoagulant therapy and risk of a neurologic complication (NC). Data from patients with prosthetic valve infective endocarditis

	N	Ischemic NC	OR (95% CI)	Hemorrhagic NC	OR (95% CI)
Not anticoagulated	124	15 (12%)	1	3 (2.4%)	1
Anticoagulated	201	32 (16%)	1.37 (0.71-2.66)	14 (7%)	3.9 (0.85-10.7)
Continued with acenocoumarol	36	5 (11%)	0.66 (0.18-1.24)	3 (7%)	3.66 (0.71-19)
Continued with heparin	104	15 (14%)	1.21 (0.56-2.61)	7 (6.7%)	2.88 (0.73-11.4)
Discontinued without suspicion	15	1 (6.6%)	0.51 (0.64-4.23)	0	-
Discontinued with suspicion	15	9 (60%)	21.8 (5.3-89.6)	4 (26%)	14.6 (1.98-61)