

# Prognostic Value of Serial C-Reactive Protein Measurements in Left-Sided Native Valve Endocarditis

Dominique W. M. Verhagen, MD; Jeroen Hermanides, MD; Joke C. Korevaar, PhD; Patrick M. M. Bossuyt, MD, PhD; Renee B. A. van den Brink, MD, PhD; Peter Speelman, MD, PhD; Jan T. M. van der Meer, MD, PhD

**Background:** The clinical course of left-sided native valve infective endocarditis varies from uncomplicated disease to fulminant infection. Although several factors are known to affect clinical outcome, it is difficult to predict morbidity and mortality in individual patients. The objective of this study was to determine the value of serial C-reactive protein (CRP) measurements as a predictor of clinical outcome.

**Methods:** One hundred twenty-three consecutive patients who fulfilled the Duke criteria for definite left-sided native valve infective endocarditis were prospectively enrolled. Poor outcome was defined as serious infectious complications or death. Patients were followed up for 12 weeks after the end of antimicrobial therapy. Multivariate analysis was used to examine the relative importance of the CRP level as a predictor of poor outcome after adjusting for age, abscess, multivalvular involvement, and *Staphylococcus aureus* infection.

**Results:** After 1 week of therapy, the adjusted odds ratio for poor outcome was 10.3 (95% confidence interval, 2.2-49.4) for patients with CRP levels in the highest tertile ( $>122$  mg/L [to convert to nanomoles per liter, multiply by 9.524]) vs the lowest tertile (1-69 mg/L). A low percentage decline during the first week of treatment was statistically significantly associated with a higher risk of poor outcome (logistic regression coefficient, 1.1;  $P=.009$ ). At no point in time did CRP level predict the need for cardiac surgery.

**Conclusion:** High CRP level after 1 week of treatment and a slow percentage decline in CRP level during the first week of treatment are indicators of poor clinical outcome.

*Arch Intern Med.* 2008;168(3):302-307

**Author Affiliations:** Division of Infectious Diseases, Tropical Medicine, and AIDS, Department of Internal Medicine (Drs Verhagen, Hermanides, Speelman, and van der Meer), and Departments of Clinical Epidemiology (Drs Korevaar and Bossuyt) and Cardiology (Dr van den Brink), Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. Dr Verhagen is now with the Department of Internal Medicine, Medisch Centrum Jan van Goyen, Amsterdam.

**T**HE TERM *INFECTIVE ENDOCARDITIS* (IE) encompasses a collection of distinct clinical entities. The most severe is prosthetic valve endocarditis, which requires diagnostic and therapeutic management that differs from that of native valve endocarditis.<sup>1</sup> Native valve endocarditis in turn can be subdivided into right-sided and left-sided endocarditis. Right-sided native valve endocarditis is a disease that is often without life-threatening complications, and antimicrobial therapy for 2 weeks has been proven as successful treatment.<sup>2</sup> Left-sided native valve endocarditis, on the other hand, generally requires a longer course of antimicrobial therapy.<sup>3</sup> The clinical course of patients with left-sided native valve endocarditis varies from uncomplicated disease with minor valve abnormalities to fulminant infection with massive valve destruction, life-threatening embolic complications, and death. Known determinants of clinical outcome are age, vegetation size, and the infecting

microorganism.<sup>3-7</sup> These factors provide a rough epidemiological estimate of morbidity and mortality. However, more specific predictors of clinical outcome in individual patients are needed because early identification of individuals at risk for complications can be crucial.

During the treatment of IE, one would expect higher values or a less rapid decline of inflammatory variables in complicated cases. One of the most frequently used clinical inflammatory variables that can be obtained routinely in every laboratory is C-reactive protein (CRP) level.<sup>8</sup> The only determinant of the serum level is the rate of CRP production in the liver, which closely reflects the activity of infection. Two studies<sup>9,10</sup> investigated the prognostic value of serial CRP measurements in patients with IE. Unfortunately, both studies combined patients with prosthetic valve endocarditis and with native valve endocarditis into a single study population. Olaison et al<sup>9</sup> concluded that elevated CRP levels are statistically significantly prolonged in episodes with com-

plicated courses compared with episodes with uncomplicated courses. However, a clear definition of a complicated course is not given by the authors, which makes it difficult to apply the results clinically. The second study, by Heiro et al,<sup>10</sup> was a retrospective study during a 20-year period, and CRP measurements were obtained without a clear protocol. It is likely that CRP measurements were obtained more often in episodes with a complicated clinical course, which renders the finding of elevated CRP levels in this patient group more likely. The objective of the present prospective study was to determine the value of serial CRP measurements as a predictor of clinical outcome in patients with left-sided native valve IE.

---

## METHODS

---

### PATIENTS

The study was designed as a prospective cohort study in 23 hospitals in the Netherlands, 8 of which are cardiothoracic surgery centers. The selection of hospitals was based on an earlier nationwide epidemiological study<sup>7</sup> in which 70% of the patients with IE were admitted to those centers. The study was approved by the medical ethics committees of all participating hospitals.

Between November 1, 2000, and October 31, 2003, all adult patients ( $\geq 18$  years) who were suspected of having left-sided native valve IE were referred to the study center. Endocarditis was defined according to the Duke Endocarditis Service criteria,<sup>11</sup> and only definite cases of endocarditis were included in the analysis. Patients who had already started antimicrobial treatment in the absence of CRP measurements were excluded from the study. The standard duration of antimicrobial treatment was defined according to the American Heart Association guidelines.<sup>12</sup>

### CLINICAL DATA

Eligible patients were informed about the study and were asked for written consent. All consenting patients were visited during their stay at the hospital. Clinical data were extracted from the medical records or by direct questioning or examination of the patient. Data included injection drug use, demographic characteristics, signs of metastatic infection, physical examination results, vascular and immunologic phenomena, previously documented cardiac conditions, and the presence of new or known cardiac murmurs. Also collected were surgical, serologic, pathologic, echocardiographic, microbiologic culture, and radiologic and laboratory study data.

### OUTCOME

The end point of the study was poor outcome, which was defined as serious infectious complications or death from the time of diagnosis through 3 months after the end of antimicrobial therapy. Arthritis, meningitis, osteomyelitis, visceral abscess, peripheral emboli, mycotic aneurysm, septic pulmonary infarction, and intracranial hemorrhage or infarction were considered serious infectious complications.

### CRP MEASUREMENTS

C-reactive protein measurements were obtained locally in the laboratories of the participating hospitals. The CRP level was obtained at the start of antimicrobial treatment (baseline) and

was measured each Monday, Wednesday, and Friday thereafter until the end of therapy. The reference value of CRP level was less than 5 mg/L (to convert to nanomoles per liter, multiply by 9.524). For patients who were admitted with a serious adverse event, only the CRP level at baseline was included in the analysis. When patients reached the end point of poor outcome or underwent cardiac surgery, whichever came first, their time to an event was considered to be censored, and CRP levels determined after this were excluded from the analysis.

### FOLLOW-UP

All patients were followed up until 12 weeks after the last date of antimicrobial treatment. Follow-up data were collected by contacting the patient or his or her general practitioner by telephone 3 months after hospital discharge. If a patient had been readmitted during this period, additional data were collected from the corresponding hospital.

### STATISTICAL ANALYSIS

To express the ability of CRP level to predict poor outcome, we constructed receiver operating characteristic (ROC) curves at baseline and at different times during antimicrobial treatment. In a ROC curve, sensitivity (y-axis) is plotted vs 1 minus specificity (x-axis) for each possible cutoff value of CRP level. The area under the curve represents the discriminative power of the test. Values are between 0.0 and 1.0 (higher values indicate better accuracy), with 1.0 for a perfectly accurate test result and 0.5 for a test result that is not better than flipping a coin.

To determine the predictive value of CRP levels at different times during antimicrobial treatment, we divided the range of baseline CRP levels into tertiles and included them in a logistic regression model with poor outcome as the dependent variable. In the model, we included age, abscess, multivalvular involvement, *Staphylococcus aureus* as causative microorganism, and CRP tertile. We also determined the prognostic value of the percentage decline from baseline in CRP levels after 1 and 2 weeks of treatment. The percentage decline in CRP level was calculated by dividing the CRP levels after 1 and 2 weeks by the CRP level at baseline. The result was log transformed and incorporated into the logistic regression model as a continuous variable with poor outcome as the dependent variable and was adjusted for age, abscess, multivalvular involvement, and *S aureus* as causative microorganism. Data analysis was performed using commercially available software (SPSS version 12.0; SPSS Inc, Chicago, Illinois).

---

## RESULTS

---

Of 251 patients who were referred to the study center, 42 had prosthetic intracardial material, 4 had right-sided endocarditis, and 2 were younger than 18 years. Endocarditis was rejected in 28 patients. Of 175 remaining eligible patients, 52 (29.7%) were excluded: 27 patients in whom antimicrobial treatment had been started before study enrollment in the absence of CRP measurements, 3 patients who died before inclusion, and 22 patients who declined to provide informed consent. **Table 1** gives demographic and clinical characteristics, infecting microorganisms, and site of infection in the remaining 123 patients. All patients fulfilled the Duke Endocarditis Service criteria for definite endocarditis. In 36 patients (29.3%), material obtained by cardiac surgery

**Table 1. Demographic, Clinical, Microbiologic, and Echocardiographic Characteristics of 123 Patients With Left-Sided Native Valve Infective Endocarditis<sup>a</sup>**

Characteristic	Value
Age, median (range), y	58 (18-88)
Male-female ratio	86:37
Definite endocarditis according to	
Clinical Duke Endocarditis Service criteria	123 (100.0)
Pathologic Duke Endocarditis Service criteria	36 (29.3)
Infecting microorganism	
Viridans streptococci	43 (35.0)
<i>Staphylococcus aureus</i>	24 (19.5)
<i>Streptococcus bovis</i>	19 (15.4)
Enterococci	11 (8.9)
HACEK microorganisms	8 (6.5)
Coagulase-negative staphylococci	5 (4.1)
Culture negative	3 (2.4)
Other	10 (8.1)
Echocardiography, site of infection	
Aortic valve	55 (44.7)
Mitral valve	50 (40.7)
Aortic and mitral valve	13 (10.6)
Other <sup>b</sup>	5 (4.1)

Abbreviation: HACEK, *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella kingae*.

<sup>a</sup>Data are given as number (percentage) unless otherwise indicated.

<sup>b</sup>In 5 patients, no definite vegetation or abscess was detected.

or at autopsy demonstrated histologic signs of active infection. Community-acquired IE was present in 107 patients (87.0%); in the other patients, IE was nosocomial (n=9) or health care related (n=7). Five patients had experienced a prior episode of endocarditis 8 months, 4.5 years, 5 years, 10 years, and 38 years before the current episode. Of 123 patients, 49 (39.8%) had concomitant serious disease at the time of admission, including kidney failure (n=17 [8 required chronic dialysis]), diabetes mellitus with secondary complications (n=15), autoimmune diseases requiring immunosuppressive medication (n=14), cancer (n=10), chronic obstructive pulmonary disease with chronic bronchitis (n=5), and human immunodeficiency virus (n=1). Some patients had more than 1 concomitant disease. Echocardiography was performed in all patients. Both transthoracic and transesophageal echocardiography were performed in 90 patients, transesophageal echocardiography only was performed in 17 patients, and transthoracic echocardiography only was performed in 16 patients. Echocardiography demonstrated 1 vegetation or more (n=109), intracardiac abscess (n=3), or a combination of both (n=6); in 5 patients, no vegetations or abscesses were detected.

**Table 2** gives the clinical outcome of patients. Fourteen patients (11.4%) died before the end of antimicrobial treatment, and the cause of death was attributed to IE. Six patients (4.9%) died within 3 months after treatment ended, and death was attributed to endocarditis in 4 of these patients. Serious infectious complications were diagnosed in 35 patients (28.5%). The most frequent serious complication was cerebral vascular accident. Ischemic cerebral infarction was present in 15 patients and hemorrhagic infarction in 4 patients. Cerebral vascular

**Table 2. Clinical Outcome of 123 Patients With Left-Sided Native Valve Infective Endocarditis**

Clinical Outcome	No. (%)
Death	20 (16.3)
Infectious complication	35 (28.5) <sup>a</sup>
Cerebral embolization or hemorrhage	19 (15.4)
Vascular peripheral embolization	6 (4.9)
Visceral abscess	5 (4.1)
Osteomyelitis or arthritis	5 (4.1)
Other	3 (2.4)
Poor outcome	46 (37.4) <sup>b</sup>
Cardiac surgery	58 (47.2)

<sup>a</sup>Several patients had more than 1 complication.

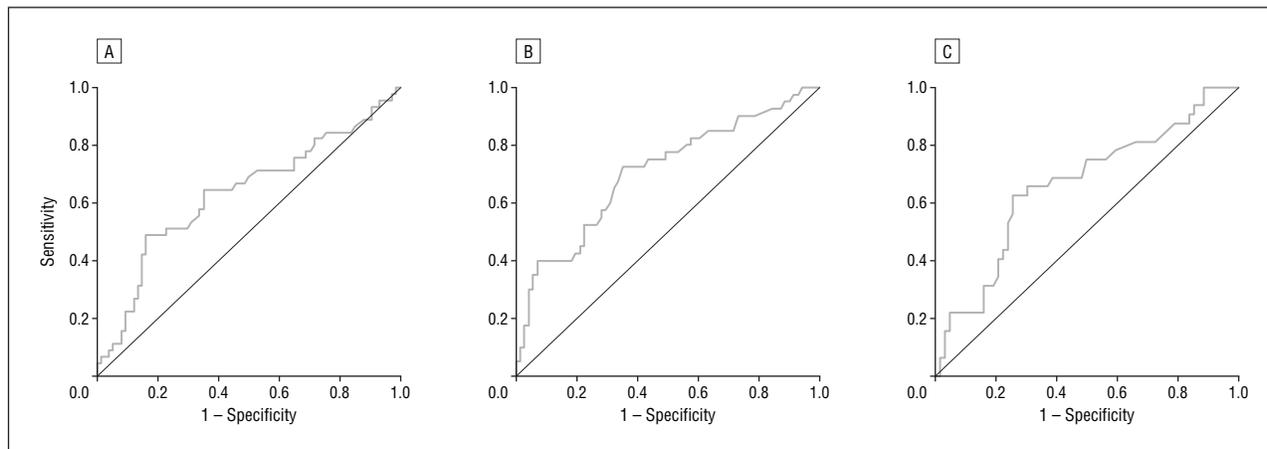
<sup>b</sup>This number is smaller than the sum of the numbers of patients with infectious complications and those who died because several patients with infectious complications died.

accident was present at the time of diagnosis of endocarditis in 6 of these patients. The median time from diagnosis of endocarditis until cerebral vascular accident was 13 days (range, 1-32 days) in the remaining 13 patients. In the patients with serious complications other than cerebral vascular accident, the complication was present before or at the time of diagnosis of IE in 7 patients. In the remaining 12 patients, the complication manifested after a median of 8 days (range, 2-24 days) from diagnosis of endocarditis. In total, there were 46 patients (37.4%) with poor outcome. This number is less than the sum of the patients who died and those with serious infectious complications because several patients with an infectious complication died.

At baseline, CRP levels were elevated (range, 20-687 mg/L) in all 123 patients. The mean CRP level at baseline was 89 mg/L (range, 20-324 mg/L) in patients infected with viridans streptococci, 89 mg/L (range, 22-186 mg/L) in patients infected with *Streptococcus bovis*, 67 mg/L (range, 26-191 mg/L) in patients infected with enterococci, and 179 mg/L (range, 39-483 mg/L) in patients infected with *S aureus*.

The median CRP level declined during antimicrobial treatment, although there was large interindividual variability. The median CRP level was 83 mg/L (range, 20-687 mg/L) at baseline, 38.5 mg/L (range, 1-296 mg/L) after 1 week, 27 mg/L (range, 1-231 mg/L) after 2 weeks, 21 mg/L (range, 1-253 mg/L) after 3 weeks, 16 mg/L (range, 1-228 mg/L) after 4 weeks, 13 mg/L (range, 1-223 mg/L) after 5 weeks, and 9 mg/L (range, 1-171 mg/L) after 6 weeks. The area under the ROC curve for CRP level to predict poor outcome in patients with left-sided native valve IE was 0.63 (95% confidence interval [CI], 0.52-0.74) at baseline, 0.70 (95% CI, 0.60-0.81) at 1 week, and 0.66 (95% CI, 0.54-0.78) at 2 weeks after the start of antimicrobial therapy (**Figure**).

Patients were divided into tertiles based on CRP level at baseline. Adjusted odds ratios (ORs) for poor outcome are given in **Table 3**. At baseline, the adjusted OR for poor outcome (serious infectious complications or death) was 2.3 (95% CI, 0.9-6.3) among patients with CRP levels in the highest tertile (>122 mg/L) compared with patients with CRP levels in the lowest tertile (20-69



**Figure.** Receiver operating characteristic (ROC) curves of C-reactive protein (CRP) levels at baseline (A) and at 1 week (B) and 2 weeks (B) after start of treatment vs poor outcome.

**Table 3. Adjusted Odds Ratios (OR) of Poor Outcome by C-Reactive Protein (CRP) Levels at Baseline, 1 Week, and 2 Weeks<sup>a</sup>**

Tertile <sup>b</sup>	Baseline (n = 119)			1 wk (n = 98)			2 wk (n = 80)				
	CRP Level, mg/L	OR (95% CI)	P Value	Tertile	CRP Level, mg/L	OR (95% CI)	P Value	Tertile	CRP Level, mg/L	OR (95% CI)	P Value
1	20-69	1 [Reference]	...	1	1-69	1 [Reference]	...	1	1-69	1 [Reference]	...
2	70-122	0.7 (0.2-1.9)	.43	2	70-122	2 (0.7-10.3)	.13	2	70-122	2.4 (0.5-12.4)	.68
3	>122	2.3 (0.9-6.3)	.1	3	>122	10.3 (2.2-49.4)	.003	3	>122	3.8 (0.4-37.4)	.92

Abbreviation: CI, confidence interval.

SI conversion factor: To convert CRP level to nanomoles per liter, multiply by 9.524.

<sup>a</sup>Adjusted for age, abscess, multivalvular involvement, and *Staphylococcus aureus* as causative microorganism; calculated in a logistic regression model.

<sup>b</sup>Patients were divided into tertiles based on CRP level at baseline.

mg/L). After 1 week of treatment, the adjusted OR for poor outcome was 10.3 (95% CI, 2.2-49.4) among patients with CRP levels in the highest tertile (>122 mg/L) compared with patients with CRP levels in the lowest tertile (1-69 mg/L).

The percentage decline in CRP levels after 1 and 2 weeks was transformed into a log scale, was analyzed in a logistic regression model as a continuous variable with poor outcome as the dependent variable, and was adjusted for age, abscess, multivalvular involvement, and *S aureus* as causative microorganism. The logistic regression coefficient after 1 week was 1.1 ( $P=.009$ ) and after 2 weeks was 0.7 ( $P=.09$ ), indicating a statistically significant increased risk of poor outcome with a decreasing percentage decline. For example, a patient with a percentage decline of 75% after 1 week had a probability of 19% of having a poor outcome, whereas the probability was 52% of having a poor outcome when there was no decline in CRP level after 1 week.

Fifty-eight patients (47.2%) underwent cardiac surgery, 35 before the end of the standard treatment course and 23 patients thereafter. The area under the ROC curve for CRP level to predict the need for cardiac surgery in patients with left-sided native valve IE was 0.46 (95% CI, 0.36-0.56) at baseline, 0.46 (95% CI, 0.34-0.57) after 1 week of antimicrobial treatment, and 0.52 (95% CI, 0.39-0.65) after 2 weeks of treatment.

## COMMENT

The present study showed the value of serial CRP measurements in predicting poor outcome (serious infectious complications or death) in 123 patients with left-sided native valve IE. The CRP level after 1 week of treatment and the percentage decline in CRP level during the first week of treatment were strong predictors of poor outcome. Demographic and clinical characteristics and the infecting microorganisms in the patients of this study were comparable to those in patients with left-sided native valve IE in other studies.<sup>13-15</sup>

Most studies<sup>16-21</sup> that addressed the role of CRP level in patients with IE studied its value in affirming or rejecting the diagnosis of endocarditis. In these studies, CRP level was shown to be elevated in 98% to 100% of patients with IE. In 1997, Lamas and Eykyn<sup>22</sup> suggested the addition of a high CRP level (>100 mg/L) to the Duke Endocarditis Service criteria for diagnosis of IE. Few studies investigated the value of CRP level at hospital admission<sup>6</sup> or through serial CRP measurements during antimicrobial treatment<sup>9,10,23-25</sup> as a predictor of poor outcome in IE. In a study by Durante Mangoni et al,<sup>6</sup> CRP level at the time of hospital admission was an independent variable associated with an increased incidence of embolic events. In our study, we found comparable results; the

OR for poor outcome at baseline was more than 2-fold higher in the patients with CRP levels in the highest tertile (>122 mg/L) compared with patients with CRP levels in the lowest tertile (20-69 mg/L).

Studies addressing the value of serial CRP measurements as a predictor of clinical outcome in IE have yielded conflicting results. In a prospective study,<sup>23</sup> CRP level was measured serially in 21 patients with IE who were initially treated using antimicrobial treatment alone. In contrast to the present study, the investigators included patients with native and prosthetic valve IE. In 13 patients, CRP levels returned to normal at 6 to 30 days (mean, 13 days) after treatment initiation. One of these 13 patients who experienced early prosthetic valve endocarditis died of mechanical problems with the valve soon after the start of treatment. Antimicrobial treatment was successful in the 12 remaining patients. In 8 patients in whom CRP levels did not return to normal, 5 required valve replacement, 2 experienced relapse of infection, and 1 died during treatment. The study did not investigate the prognostic value of CRP measurements at different times during antimicrobial treatment. The authors concluded that a progressive return of CRP level to normal possibly correlated with satisfactory recovery, despite the fact that the numbers were too small to produce statistically significant results. In another prospective study,<sup>9</sup> the authors stated that a statistically significant decline in serum CRP levels was found after 2, 3, and 4 weeks of antimicrobial treatment in uncomplicated episodes compared with complicated episodes. These results were only presented graphically, and exact numbers or *P* values were not given. We did not include cardiac surgery in the definition of poor outcome because in most patients with IE the indication for surgery is not persistent infection but heart failure due to valve regurgitation.<sup>25</sup> Kocazeybek et al<sup>24</sup> serially measured CRP levels in 50 patients with IE and did not find a statistically significant difference in CRP levels between the group that necessitated cardiac surgery and the group that did not. In the present study, neither absolute values nor percentage decline in CRP level predicted the need for cardiac surgery. In an additional analysis in which cardiac surgery was included in the definition of poor outcome, the predictive value of absolute CRP level or percentage decline in CRP level was generally lower than the ORs using the original definition of poor outcome (data not shown).

Heiro et al<sup>10</sup> published a retrospective study investigating the value of serial CRP measurements in assessing the outcome of IE. The main study findings were that none of the patients with normal CRP levels by week 10 died of IE, none of 22 patients who had normal CRP levels by week 4 needed cardiac surgery, and only 2 of 33 patients who had normal CRP levels by week 6 needed cardiac surgery. Fifty-six of 81 patients (69.1%) who had elevated CRP levels at week 6 recovered without complications. However, CRP levels at week 6 do not seem to be relevant for the management of patients with IE.

The aim of serial CRP measurements in patients with IE is to identify, at an early stage, patients with the highest risk of poor outcome. Identification of these patients should lead to earlier recognition of complications, which can then be managed promptly and appropriately. Also,

the identification of patients in whom a favorable course of disease is to be expected might facilitate therapeutic management of these patients. For example, treatment could be sought in an outpatient or home setting, by oral instead of intravenous antibiotics, or with shorter duration of treatment. On the other hand, identifying patients with poor prognosis could lead to intensified antimicrobial treatment schedules or earlier timing of cardiac surgery.

The results of the present study indicate that serial CRP measurements during the first week of antimicrobial treatment can be used as a prognostic factor for poor outcome. C-reactive protein measurements should probably be limited to days 1 and 7 of the first week of treatment. However, it was impossible to determine a cut-off value with high sensitivity and specificity to identify high-risk patients. Consequently, CRP level cannot be used as a sole prognostic factor, but it should be applied in combination with other clinical variables that have yet to be identified.

**Accepted for Publication:** September 10, 2007.

**Correspondence:** Jan T. M. van der Meer, MD, PhD, Division of Infectious Diseases, Tropical Medicine, and AIDS, Department of Internal Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, F4-217, 1105 AZ Amsterdam, the Netherlands (j.t.vandermeer@amc.uva.nl).

**Author Contributions:** Dr Verhagen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Verhagen, Bossuyt, and van der Meer. *Acquisition of data:* Verhagen. *Analysis and interpretation of data:* Verhagen, Hermanides, Korevaar, Bossuyt, van den Brink, Speelman, and van der Meer. *Drafting of the manuscript:* Verhagen. *Critical revision of the manuscript for important intellectual content:* Hermanides, Korevaar, Bossuyt, Speelman, and van der Meer. *Statistical analysis:* Hermanides, Korevaar, and Bossuyt. *Obtained funding:* Verhagen, Speelman, and van der Meer. *Administrative, technical, and material support:* Verhagen, van den Brink, and van der Meer. *Study supervision:* van der Meer.

**Financial Disclosure:** None reported.

**Funding/Support:** This study was supported by ZonMW Dutch governmental Organization for Health Research and Development.

**Additional Contributions:** Cardiologists, internists, and microbiologists of the following centers in the Netherlands referred patients and participated in the study: Academic Medical Center (Amsterdam), Bosch Medicentrum (Den Bosch), Catharina Ziekenhuis (Eindhoven), Diaconessenhuis (Utrecht), Erasmus Medisch Centrum (Rotterdam), Groene Hart Ziekenhuis (Gouda), Ziekenhuis Hilversum (Hilversum), Isala Klinieken (Zwolle), Kennemer Gasthuis (Haarlem), Lucas-Andreas Ziekenhuis (Amsterdam), Leids Universitair Medisch Centrum (Leiden), Leyenburg Ziekenhuis (Den Haag), Maxima Medisch Centrum (Eindhoven), Meander Medisch Centrum (Amersfoort), Medisch Centrum Alkmaar (Alkmaar), Onze Lieve Vrouwe Gasthuis (Amsterdam), Rijnstate Ziekenhuis (Arnhem), Slotervaart

Ziekenhuis (Amsterdam), Spaarne Ziekenhuis (Haarlem), Stichting St Antonius Ziekenhuis (Nieuwegein), St Joseph Ziekenhuis (Veldhoven), and Utrechts Medisch Centrum (Utrecht).

## REFERENCES

1. Romano G, Carozza A, Della Corte A, et al. Native versus primary prosthetic valve endocarditis: comparison of clinical features and long-term outcome in 353 patients. *J Heart Valve Dis.* 2004;13(2):200-208.
2. Hecht SR, Berger M. Right-sided endocarditis in intravenous drug users: prognostic features in 102 episodes. *Ann Intern Med.* 1992;117(7):560-566.
3. Hasbun R, Vikram HR, Barakat LA, Buenconsejo J, Quagliarello VJ. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. *JAMA.* 2003;289(15):1933-1940.
4. Di Salvo G, Thuny F, Rosenberg V, et al. Endocarditis in the elderly: clinical, echocardiographic, and prognostic features. *Eur Heart J.* 2003;24(17):1576-1583.
5. Cabell CH, Pond KK, Peterson GE, et al. The risk of stroke and death in patients with aortic and mitral valve endocarditis. *Am Heart J.* 2001;142(1):75-80.
6. Durante Mangoni E, Adinolfi LE, Tripodi MF, et al. Risk factors for "major" embolic events in hospitalized patients with infective endocarditis. *Am Heart J.* 2003;146(2):311-316.
7. van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in the Netherlands, I: patient characteristics. *Arch Intern Med.* 1992;152(9):1863-1868.
8. Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human CRP in health and disease. *J Clin Invest.* 1993;91(4):1351-1357.
9. Olaison L, Hogevik H, Alestig K. Fever, CRP and other acute-phase reactants during treatment of infective endocarditis. *Arch Intern Med.* 1997;157(8):885-892.
10. Heiro M, Helenius H, Sundell J, et al. Utility of serum CRP in assessing the outcome of infective endocarditis. *Eur Heart J.* 2005;26(18):1873-1881.
11. Durack DT, Lukes AS, Bright DK; Duke Endocarditis Service. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Am J Med.* 1994;96(3):200-209.
12. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for health-care professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation.* 2005;111(23):e394-e434.
13. Hoen B, Alla F, Selton-Suty C, et al; Association pour l'Etude et la Prévention de l'Endocardite Infectieuse (AEPEI) Study Group. Changing profile of infective endocarditis: results of a 1-year survey in France. *JAMA.* 2002;288(1):75-81.
14. Nunley DL, Perlman PE. Endocarditis: changing trends in epidemiology, clinical and microbiologic spectrum. *Postgrad Med.* 1993;93(5):235-238, 241-244, 247.
15. Hogevik H, Olaison L, Andersson R, Lindberg J, Alestig K. Epidemiologic aspects of infective endocarditis in an urban population: a 5-year prospective study. *Medicine (Baltimore).* 1995;74(6):324-339.
16. Hellgren U, Julander I. Are white blood cell count, platelet count, erythrocyte sedimentation rate and CRP useful in the diagnosis of septicemia and endocarditis? *Scand J Infect Dis.* 1986;18(5):487-488.
17. Hogevik H, Olaison L, Andersson R, Alestig K. C-reactive protein is more sensitive than erythrocyte sedimentation rate for diagnosis of infective endocarditis. *Infection.* 1997;25(2):82-85.
18. Lindbäck S, Hellgren U, Julander I, Hansson LO. The value of C-reactive protein as a marker of bacterial infection in patients with septicemia/endocarditis and influenza. *Scand J Infect Dis.* 1989;21(5):543-549.
19. Mueller C, Huber P, Laifer G, Mueller B, Perruchoud AP. Procalcitonin and the early diagnosis of infective endocarditis. *Circulation.* 2004;109(14):1707-1710.
20. Koegelenberg CF, Doubell AF, Orth H, Reuter H. Infective endocarditis: improving the diagnostic yield. *Cardiovasc J S Afr.* 2004;15(1):14-20.
21. Alter P, Hoeschen J, Ritter M, Maisch B. Usefulness of cytokines interleukin-6 and interleukin-2R concentrations in diagnosing active infective endocarditis involving native valves. *Am J Cardiol.* 2002;89(12):1400-1404.
22. Lamas CC, Eykyn SJ. Suggested modifications to the Duke criteria for the clinical diagnosis of native valve and prosthetic valve endocarditis: analysis of 118 pathologically proven cases. *Clin Infect Dis.* 1997;25(3):713-719.
23. McCartney AC, Orange GV, Pringle SD, Wills G, Reece IJ. Serum C reactive protein in infective endocarditis. *J Clin Pathol.* 1988;41(1):44-48.
24. Kocazeybek B, Küçükoğlu S, Oner YA. Procalcitonin and C-reactive protein in infective endocarditis: correlation with etiology and prognosis. *Chemotherapy.* 2003;49(1-2):76-84.
25. Blaustein AS, Lee JR. Indications for and timing of surgical intervention in infective endocarditis. *Cardiol Clin.* 1996;14(3):393-404.