Open Forum Infectious Diseases

MAJOR ARTICLE

End-of-Therapy Echocardiography May Not Be Needed in All in Patients With Endocarditis

Abinash Virk,[1] Kirsten M. Schutte,[2] James M. Steckelberg,[1] Walter R. Wilson,[1] Lawrence J. Sinak,[3] and Larry M. Baddour[1,3]

[1]Division of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA, [2]Division of Infectious Diseases, Asante Health System, Medford, Oregon, USA, and [3]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA

Background. The American Heart Association (AHA) guidelines for infective endocarditis (IE) management recommend end-of-therapy (EOT) echocardiography (ETE) to "establish a new baseline" and based on "expert opinion."

Methods. Medical records of IE patients treated between January 2005 and December 2011 were reviewed. Utilization of ETE and cumulative incidence of re-treatment with antimicrobials or cardiovascular surgery (re-Rx/CVS) within 1 year after EOT were evaluated.

Results. A total of 243 patients completed clinical follow-up at EOT and 170 at 1 year after EOT. One hundred seventy-seven of 243 (72.8%) underwent ETE, the majority (51.4%) transthoracic echocardiography. One hundred thirty-three of 177 (75.1%) were without new/worsened signs or symptoms (new/w-SSx). One hundred forty-one of 177 (79.7%) overall and 117/133 (87.9%) patients without new/w-SSx had no new ETE findings as compared with initial echocardiography. Among 36/177 (20.3%) with new ETE findings, 20/36 (55.6%) had new/w-SSx; ETE findings were more likely in patients with new/w-SSx (39.2% vs 8.3%; $P < 0.001$) at EOT. Patients were at increased risk of re-Rx/CVS with either new ETE findings (hazard ratio [HR], 25.86; 95% confidence interval [CI], 7.64–87.56; $P < .001$) or new/w-SSx (HR, 5.35; 95% CI, 2.87–9.95; $P < .001$). The highest risk of re-Rx/CVS was in patients with both new/w-SSx and new ETE findings (HR, 45.94; 95% CI, 19.07–110.71). Conversely, only 7/187 (3.4%) patients without new/w-SSx who had an ETE required re-Rx/CVS.

Conclusions. The majority of patients without new/w-SSx at EOT will not have new ETE findings or need re-Rx/CVS within 1 year after EOT. EOT new/w-SSx is associated with new ETE findings and predicts the need for re-Rx/CVS. Further study is needed to determine whether patients without new/w-SSx need ETE.

Keywords. echocardiography; end of therapy; infective endocarditis; outcomes.

The American Heart Association (AHA) guidelines for infective endocarditis (IE) management endorsed by the Infectious Disease Society of America (IDSA) [1] and the guidelines of the Task Force on Infective Endocarditis of the European Society of Cardiology (ESC) [2] include a recommendation that echocardiography be routinely performed at the end of antimicrobial IE therapy (EOT) to establish baseline valvular morphology. The ESC guidelines also recommend that a transthoracic echocardiogram (TTE) be done at 1, 3, 6, and 12 months during the first year after EOT [2]; in contrast, the AHA guidelines do not include a recommendation for serial echocardiography. These recommendations were based on expert opinion, not clinical data. Because of limited data, a further examination of these recommendations is warranted. We sought to evaluate end-of-treatment echocardiography (ETE) use and its contribution to optimal patient management.

ETE seems reasonable, as IE patients are at risk of valve complications or new ("repeat") episodes of IE. Some IE sequelae include cardiovascular structural damage that may deteriorate with time and require serial follow-up to determine potential need for subsequent cardiovascular surgery (CVS) intervention despite microbiologic cure with antimicrobial therapy. ETE's immediate benefit, however, is to identify patients with evidence of new valvular complications who may require additional management such as repeat antimicrobial treatment and/or surgical intervention (re-Rx/CVS).

In general, echocardiography is deemed appropriate to assess changes in an individual's clinical status or management [3]. Application of this principle to the optimal use of ETE, however, remains largely undefined. Therefore, our primary goal was to evaluate ETE utilization and its impact on patient outcomes, in particular, re-Rx/CVS over the subsequent year. A secondary aim was to identify risk factors associated with the development of post-IE complications to facilitate risk stratification of patients.

Received 26 November 2019; editorial decision 17 February 2020; accepted 26 February 2020.
Correspondence: Abinash Virk, MD, Division of Infectious Diseases, Mayo Clinic, 200 First St. SW, Rochester, MN 55905 (virka@mayo.edu).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofaa069

METHODS

Study Design and Population

A retrospective chart review was performed for all patients with an IE diagnosis at the Mayo Clinic in Rochester, Minnesota, between January 1, 2005, and December 31, 2011. Patients were identified via an internal database and included in the study if they were ≥18 years of age at the time of diagnosis and met modified Duke Criteria for definite or possible IE [4]. Cases were excluded if they did not meet the aforementioned criteria, lacked research involvement consent, or had incomplete medical records. Only the initial episode was included for patients experiencing >1 episode of IE. Subsequent IE events within 1 year were considered complications related to the initial IE episode (Figure 1).

Data Collection, Definition of Variables, and Outcomes

Data for 419 patients meeting inclusion criteria were obtained via retrospective chart review and managed using REDCap electronic collection data capture tools [5]. Data were recorded for 3 study periods: Phase 1: initial IE diagnosis and treatment; Phase 2: EOT up to 8 weeks after completion of the initially planned antimicrobial course; and Phase 3: 8 weeks to 1 year after EOT. ETE was defined as an echocardiography performed during Phase 2. Baseline data collected are outlined in Appendix A.

Antimicrobial choice and duration were abstracted and were consistent with AHA guidelines [1]. Clinical factors that prompted surgery were documented, and if a decision to proceed with CVS via either sternotomy or a percutaneous approach was made before EOT, then surgery was considered planned from Phase 1 whether surgical intervention occurred immediately, during, or soon after EOT.

Information collected during subsequent study periods included the presence of new or worsening signs or symptoms (new/w-SSx) of IE (Appendix A), whether ETE was performed,

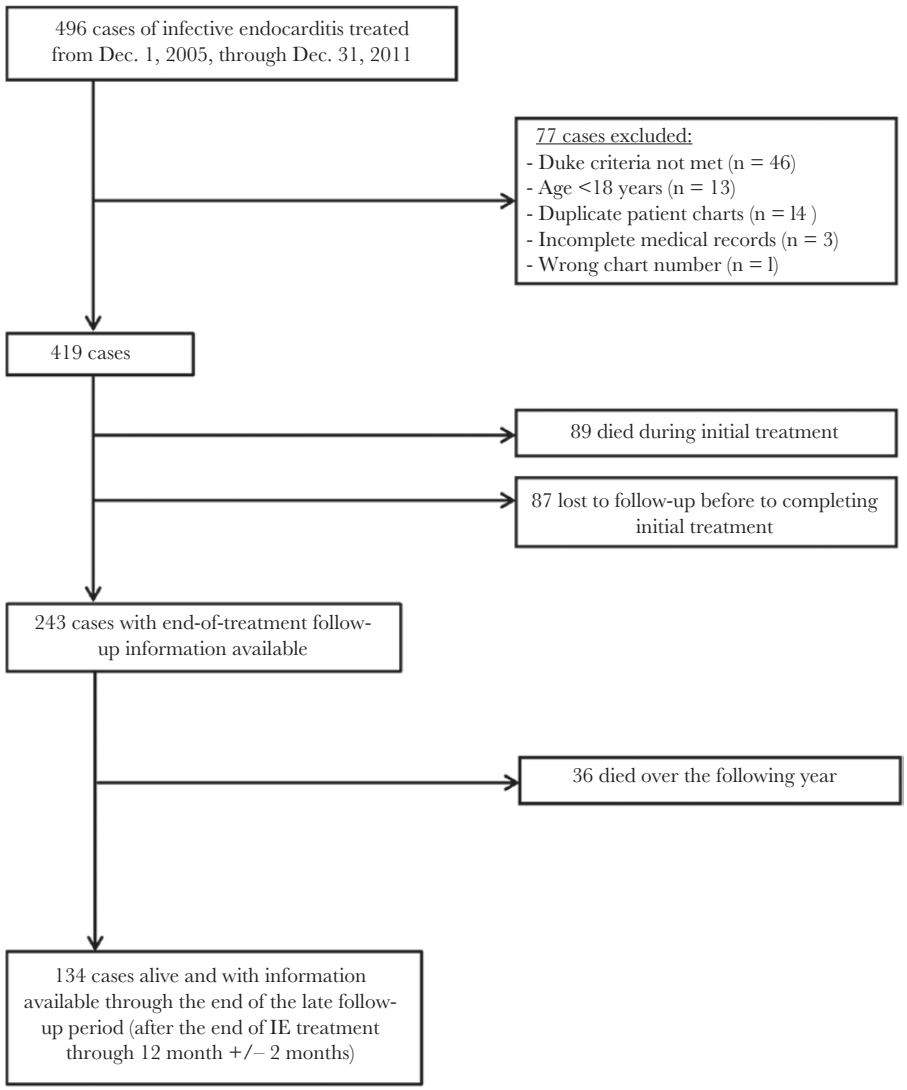

Figure 1. Study participant selection. Abbreviation: IE, infective endocarditis.

type of echocardiography obtained, the presence of new or worsened echocardiographic findings, serologic and blood culture results, and decisions to either re-treat with antimicrobial agents (defined as a new full course of therapy based on a known or suspected organism), proceed with CVS (if this decision was made after EOT), maximize pharmacotherapy for CHF, or monitor closely and repeat echocardiography at a future date. Throughout all study periods, data were collected on mortality and patients lost to follow-up.

The primary aims were use of ETE and need for re-Rx/CVS for relapsing or repeat IE within 1 year after EOT. Secondary aim was to correlate ETE findings with presence of new/w-SSx.

Statistical Analysis

Patients who completed initial treatment were included in the analysis, whereas those who died or were lost to follow-up before completing initial antimicrobial therapy were excluded. Patient baseline characteristics and ETE were profiled using descriptive statistics, and associations between baseline variables including ETE were evaluated using standard statistical tests (eg, analysis of variance, chi-square test). With time 0 considered the first day post-treatment, the Kaplan-Meier product limit method was used to estimate the rate of subsequent treatment failure, defined as a combined end point of antibiotic re-Rx and/or CVS (except where these outcomes are explicitly stated to have been considered separate end points) over follow-up of ~1 year. Patients free of treatment failure were censored at the time of the nearest 1-year follow-up visit, up to 1 year after completion of the initial course of therapy for IE, or before then if only partial follow-up was available (ie, those who died or were lost to follow-up before 1 year). To assess patterns of treatment failure, baseline characteristics were analyzed separately to determine if there was an association with re-Rx/CVS via univariate Cox proportional hazards (PH) regression modeling, from which hazard ratios (HRs) and 95% confidence interval (CIs) were reported to measure the strength of the association. Data analyses were performed using the statistical software packages JMP (version 10.0.0) and SAS (version 9.3; SAS Institute, Cary, NC, USA). Results with a P value <.05 were considered significant.

Human Subjects Oversight

This study was approved by the Mayo Clinic Institutional Review Board. All study participants agreed to use of their health record data for research.

RESULTS

Overall, 496 patients with IE were treated at the Mayo Clinic, and 419 were eligible for study inclusion, with 385 meeting definite criteria for IE. Baseline data from Phase 1 for the subjects are included in Table 1. Eighty-nine patients died, and 87 were lost to follow-up during Phase 1 (Figure 1). Thirty-six patients died, and 73 patients were lost to follow-up in Phase 2 and Phase 3 collectively. Therefore, statistical analysis regarding outcomes was performed for 243 patients who had EOT follow-up. Individuals were censored at the point when they were either lost to follow-up or died over the months following EOT.

End-of-Treatment Echocardiography Utilization

One hundred seventy-seven (72.8%) of 243 total patients underwent an ETE, with transthoracic echocardiogram (TTE) in 91 (51.4%) patients, transesophageal echocardiogram (TEE) in 72 (40.7%) patients, and both in 13 (7.3%) patients. One patient had follow-up imaging at an outside facility, and although details of the image findings were available, the type of echocardiogram performed was not documented. No ETE was performed in 66/243 (27.1%).

A majority (141/177, 79.7%) of patients had no new findings on ETE; of these, 81/141 (57.5%) had TTE, 53 (37.5%) had TEE, and 5 had both. New or worsened ETE findings were seen in 36/177 (20.3%); 9 (25%) had undergone TTE, 23 (63.8%) had TEE, and 4 (11.1%) had both studies. The most common finding was new regurgitation; enlarging vegetation and perivalvular abscess were also frequently seen. Of patients with new ETE findings, 20/36 (55.5%) had new/worsened signs or symptoms (new/w-SSx). ETE findings were more likely in patients with new/w-SSx (39.2% vs 8.3%; $P < 0.001$) at EOT.

Overall, 133/177 (75.1%) patients with ETE were without new/w-SSx. Of the 133 without new/w-SSx patients, a majority, 117 (87.9%), did not have new or worsened ETE findings. None of these 117 patients underwent re-treatment or CVS (Figure 2). New or worsened ETE findings were observed in 16/133 (12.0%), 10 on TEE and 6 on TTE. The presence or absence of a prosthetic valve or the need for surgery at the time of IE diagnosis was not correlated with type of ETE. The study was not sufficiently powered to detect an association between causative organism and type of ETE obtained.

Patient Symptoms, ETE, and Outcomes

At EOT, 192/243 (79.0%) patients were without new/w-SSx, whereas 51 (21%) had new/w-SSx, dyspnea being the most common symptom (8.6%). Of the 51 patients with new/w-SSx, 44 (86.3%) underwent ETE, of whom 20 (45.5%) had new or worsened echocardiographic findings. A majority (13/20, 65.0%) underwent a TEE, 3 had a TTE, and 4 had both TTE and TEE. Of 66 patients who did not undergo an ETE, 54 (81.8%) were without new/w-SSx.

Overall, 41 (16.9%) of 243 patients had re-Rx and/or CVS. Of 41 patients, 37 had CVS and 21 had re-Rx (20 [48.8%] had CVS alone, 17 [41.5%] had both CVS and re-Rx, and 4 [9.8%] had re-Rx alone). The median time to CVS (interquartile range [IQR]) was 97 (35–215) days, and 16 (43.2%) cases occurred within the first 2 months of follow-up.

Of the 20 patients who had CVS alone without antimicrobial treatment, 5 cases that occurred during Phases 2 and

Table 1. Baseline Characteristics and the Need for Re-treatment or Cardiac Valve Surgery Within 1 Year of Completion of Therapy for Infective Endocarditis

Variable	Total (n = 243), No. (%) or Mean ± SD	Univariate Results, HR (95% CI) [*P* Value]
Demographics		
Age, y	60.6 ± 16.7	0.94 (0.79–1.12) [.478]
Male	162 (67)	2.22 (1.02–4.81) [.043]
Baseline characteristics		
Congenital heart disease, yes	16 (7)	1.01 (0.31–3.27) [.991]
Intravenous drug use, yes	8 (3)	0.76 (0.10–5.52) [.785]
Immunocompromised,[a] yes	35 (14)	0.81 (0.32–2.07) [.665]
Diabetes, yes	57 (23)	0.80 (0.37–1.74) [.581]
Malignancy, yes	32 (13)	0.13 (0.02–0.98) [.048]
Episode of IE		0.53 (0.15–1.92) [.335]
1	222 (91)	
2	17 (7)	
3	3 (1)	
4	1 (0)	
Causative microorganism		Overall, *P* = .514 (5 d.f.)
Staphylococcus aureus	56 (23)	1.92 (0.75–4.87)
Coagulase-negative staphylococci	37 (15)	1.79 (0.63–5.10)
Viridans group streptococci	48 (20)	1.0 (referent)
Enterococcus spp.	36 (15)	0.75 (0.22–2.56)
Culture-negative	17 (7)	1.24 (0.32–4.79)
Other microorganism[b]	49 (20)	1.15 (0.42–3.18)
Mitral valve		Overall, *P* = .330 (2 d.f.)
No involvement	128 (53)	1.0 (referent)
Native	93 (38)	1.39 (0.71–2.69)
Prosthetic	22 (9)	1.95 (0.77–4.95)
Aortic valve		Overall, *P* = .301 (2 d.f.)
No involvement	121 (50)	1.0 (referent)
Native	74 (30)	0.63 (0.29–1.35)
Prosthetic	48 (20)	1.28 (0.59–2.76)
Tricuspid valve		Overall, *P* = .472 (2 d.f.)
No involvement	210 (86)	1.0 (referent)
Native	30 (12)	0.53 (0.16–1.72)
Prosthetic	3 (1)	1.78 (0.24–13.01)
Pulmonic valve		—[c]
Vegetation, yes	212 (87)	1.27 (0.45–3.58) [.645]
Perforation/regurgitation, yes	153 (63)	0.87 (0.47–1.64) [.675]
Abscess, yes	40 (16)	1.75 (0.81–3.81) [.156]
Surgery at time of diagnosis, yes	121 (50)	0.43 (0.22–0.83) [.011]
Signs/symptoms at diagnosis		
Constitutional,[d] yes	205 (84)	1.20 (0.47–3.05) [.707]
Dyspnea, yes	83 (34)	0.83 (0.43–1.63) [.598]
CNS symptoms,[e] yes	68 (28)	1.68 (0.89–3.18) [.108]
Other signs/symptoms, yes	115 (47)	0.97 (0.53–1.80) [.932]
Murmur, yes	97 (40)	1.98 (1.07–3.68) [.030]
CHF, yes	49 (20)	0.46 (0.17–1.30) [.144]
Embolic event,[f] yes	109 (45)	1.29 (0.70–2.37) [.420]
Weight loss, yes	45 (19)	1.44 (0.72–2.87) [.301]

Abbreviations: CHF, congestive heart failure; CI, confidence interval; CNS, central nervous system; IE, infective endocarditis; HR, hazard ratio.

[a]Includes treatment with immunosuppressive medications, neutropenia with absolute neutrophil count <500, HIV with CD4 count <200, or end-stage renal disease requiring dialysis.

[b]Other microorganisms include HACEK and fungi, among others.

[c]Not reported; numbers too small to be reliable.

[d]Constitutional symptoms include fever, chills, or sweats.

[e]CNS symptoms include new focal neurologic deficit or altered mental status.

[f]Evidence of embolic sequelae of endocarditis on exam, or evidence of emboli to the lungs, kidney, spleen, or brain on imaging studies.

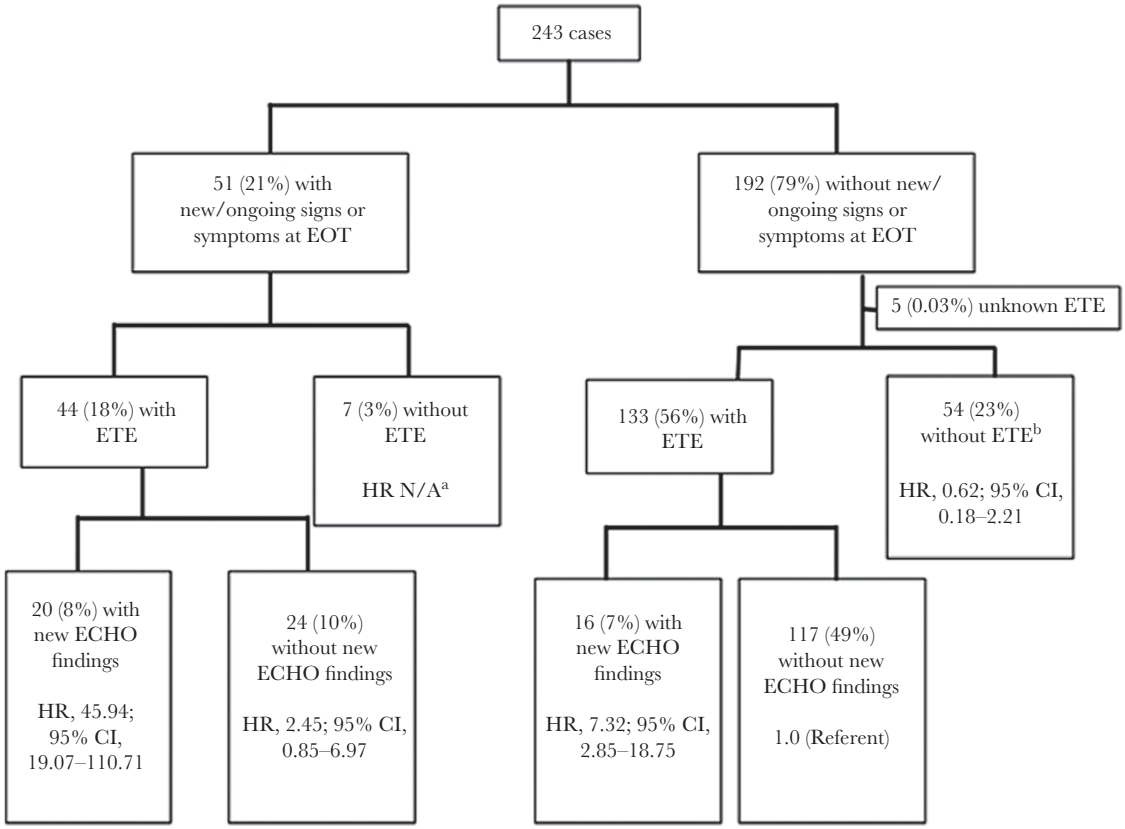

Figure 2. Risk of re-treatment with antimicrobials and/or cardiac valve surgery within 1 year in patients with or without new signs or symptoms of infective endocarditis at end-of-treatment followup by status and findings on the end-of-treatment echocardiogram (ETE). [a]Numbers too small to be relable. [b]ECHO status at end-of-treatment follow-up was unknown for 5 additional patients, as their initial posttreatment care was provided elsewhere. All of these patients were later seen again at our institution, however, and medical records summarizing their post-treatment care and outcomes indicated that none required retreatment with antibiotics or CVS over the following year. Abbreviations: Abx, antibiotics; CI, confidence interval; CVS, cardiac valve surgery; ECHO, echocardiogram; EOT, end of treatment; ETE, end-of-treatment echocardiography; HR, hazard ratio.

4 (80%) were without new/w-SSx. Fifteen patients underwent CVS alone during Phase 3; 73.3% (11/15) were without new/w-SSx.

Of the 21 individuals who underwent re-Rx, 15 (71.4%) were re-treated in Phase 2 (median time from EOT to re-treatment, 29 days); 9 (60%) had new/w-SSx, and 10 (66.6%) had CVS. Microbiologic confirmation occurred in 7/15; 6/7 (85.7%) had the same organism as the initial IE pathogen, whereas 1 had a new pathogen. In comparison, 6/21 (28.6%) patients underwent re-Rx in Phase 3 (median time from EOT to re-treatment, 138 days); all had new/w-SSx. Of these 6, 4 had a new pathogen IE, 1 had the same pathogen as the initial organism, and 1 was culture-negative due to ongoing antibiotics. Of these 6 patients, 5 (83.3%) required CVS. Two individuals required re-treatment twice, once each in Phase 2 and Phase 3, and were included in the analysis of both groups.

Patients with new/w-SSx at EOT had a higher likelihood of undergoing echocardiography (HR, 4.25; 95% CI, 1.31–13.75; $P = .016$) and re-Rx/CVS over the subsequent year (HR, 5.35; 95% CI, 2.87–9.95; $P < .001$). New or worsened ETE findings (especially enlarging vegetations) in individuals without new/w-SSx were also associated with re-Rx/CVS (HR, 25.86; 95% CI, 7.64–87.56; $P < .001$). However, the highest risk was observed in individuals with both EOT new/w-SSx and new or worsened ETE findings (HR, 45.94; 95% CI, 19.07–110.71; overall $P < .001$) (Table 2, Figure 2). Of the 192 patients without new/w-SSx, no re-Rx/CVS was necessary in 171 (89.1%). In the 133 who underwent an ETE, 16 had a new finding on the ETE. Of these, only 7 required additional intervention. Five patients underwent surgery at a median (IQR) of 30 (9–52) days after EOT, with the predominant ETE findings being worsened regurgitation or enlarged vegetations. Only 2 patients underwent repeat antibiotic treatment without surgery; both had positive staphylococcal blood cultures within 8 weeks with persistent vegetations that were treated as possible endocarditis. Hence, the ETE was beneficial in 3.7% (7/187) of patients without new/w-SSx, corresponding to a number-needed-to-echo of 27 for the benefit of 1 patient. That ratio was lower (37.4:1) after removing the 2 patients with positive

Table 2. End-of-Treatment Variables and the Need for Re-treatment or Cardiac Valve Surgery Within 1 Year of Completion of Therapy for Infective Endocarditis

Variable	No. Missing, Total (%)	Total (n = 243), No. (%)	Univariable Results, HR (95% CI) [*P* Value]
End-of-treatment ECHO status & type			
Any ECHO performed, yes	5 (2)	177 (74)	4.25 (1.31–13.75) [.016]
Post-treatment ECHO type	1 (<1)		Overall, *P* < .001 (3 d.f.)
None		61 (26)	0.36 (0.10–1.27)
TTE		91 (38)	1.0 (referent)
TEE		72 (30)	2.04 (1.02–4.08)
Both		13 (5)	4.28 (1.53–11.96)
End-of-treatment ECHO findings			
New/enlarging vegetation, yes		13 (5)	35.87 (16.93–76.00) [<.001]
New/worsened perforation or regurgitation, yes		25 (10)	8.59 (4.36–16.92) [<.001]
New abscess, yes		10 (4)	7.70 (2.97–19.98) [<.001]
Signs/symptoms at end of treatment			
Any new/persistent sign or symptom, yes		51 (21)	5.35 (2.87–9.95) [<.001]
Constitutional,[a] yes		18 (7)	5.17 (2.38–11.24) [<.001]
Dyspnea, yes		21 (9)	2.09 (0.74–5.92) [.167]
CNS,[b] yes		9 (4)	6.50 (2.54–16.65) [<.001]
Other signs/symptoms, yes		12 (5)	6.15 (2.72–13.90) [<.001]
Murmur, yes		9 (4)	4.34 (1.54–12.20) [.005]
CHF, yes		11 (5)	4.90 (1.70–14.18) [.003]
Embolic event,[c] yes		9 (4)	9.00 (3.73–21.73) [<.001]
Weight loss, yes		2 (1)	11.00 (1.43–84.91) [.016]
End-of-treatment signs/symptoms by ECHO status and findings	5 (2)		Overall, *P* < .001 (5 d.f.)
No symptoms, ECHO not performed		54 (23)	0.62 (0.18–2.21)
No symptoms, negative ECHO		117 (49)	1.0 (referent)
No symptoms, positive ECHO		16 (7)	7.32 (2.85–18.75)
Symptoms, ECHO not performed		7 (3)	—[d]
Symptoms, negative ECHO		24 (10)	2.45 (0.86–6.97)
Symptoms, positive ECHO		20 (8)	45.94 (19.07–110.71)

Abbreviations: CHF, congestive heart failure; CNS, central nervous system; d.f., degrees of freedom; ECHO, echocardiogram; TEE, trans-esophageal echocardiogram; TTE, trans-thoracic echocardiogram.

[a]Constitutional symptoms include fever, chills, or sweats.

[b]CNS symptoms include new focal neurologic deficit or altered mental status.

[c]Evidence of embolic sequelae of endocarditis on exam or evidence of emboli to the lungs, kidney, spleen, or brain on imaging studies.

[d]Not reported; numbers too small to be reliable.

blood cultures and possible IE. Of the 54 patients who did not have an ETE, 3 underwent elective surgery based on persistent findings on echocardiography done previously or in Phase 3; none received antibiotics.

Male sex (HR, 2.22; 95% CI, 1.02–4.81; *P* = .04) and presence of a new or more severe murmur at the time of initial diagnosis (HR, 1.98; 95% CI, 1.07–3.68; *P* = .03) were identified by univariate analysis as baseline characteristics associated with re-Rx and/or CVS within the year after EOT. In contrast, several factors were associated with a decreased likelihood of requiring re-Rx/CVS, including active malignancy (HR, 0.13; 95% CI, 0.02–0.98; *P* = .05) and the decision to pursue surgical intervention at the time of initial treatment of IE, whether performed initially or immediately after EOT (HR, 0.43; 95% CI, 0.22–0.83; *P* = .01) (Table 1). No association with valve location(s) or valve type (native vs prosthetic) or causative microorganism was observed.

DISCUSSION

The 2015 AHA guidelines for the management of IE included a weak (Class IIa) recommendation that was largely consensus-based (Level of Evidence C) for ETE with TTE [1]. Therefore, the current investigation was conducted to evaluate the utilization of ETE and to determine ETE's role in the current or future need for re-treatment/CVS in conjunction with symptoms [6]. Although 2011 was the most recent year of patient inclusion, echocardiographic techniques have not appreciably changed in recent years and permit a contemporary evaluation. Seventy-three percent of patients underwent ETE. A majority (79.7%) of patients who underwent ETE did not have any new or worsened valve or cardiac morphology or function, and for many (37.5%) ETE was a TEE, suggesting that TEE may have been overutilized. Among the patients who were without new/w-SSx and had no new ETE findings, none were at risk of re-treatment or CVS during the immediate post-EOT or 1-year time frame.

A majority, 55.6% (20/36), of patients with new ETE findings detected also had new/w-SSx that may have warranted echocardiographic evaluation and resulted in an intervention of re-Rx/CVS in 70.0% (14/20). Among patients without new/w-SSx, new or worsened ETE findings were uncommon (8.3%), but 7/16 (43.8%) did require re-Rx/CVS, suggesting that these patients may have had poor function from the initial diagnosis. Although there was a stronger association between TEE findings and re-Rx/CVS within the ensuing year, our study lacked sufficient power to confirm the superiority of a type of echocardiographic modality.

Two baseline factors, male sex and presence of a new or more severe murmur at the time of IE diagnosis, were modestly associated with an increased risk for re-Rx/CVS over the year after EOT. It is unclear why active malignancy was associated with a decreased risk of these outcomes. The finding that a decision to pursue surgical intervention as part of the initial treatment plan was associated with a decreased risk of re-Rx/CVS over the subsequent year is supported by other investigations [7–10].

The 2 factors most predictive of re-Rx/CVS during the year after EOT were new/w-SSx and new or worsened echocardiographic findings at EOT. The risk of these outcomes was compounded in individuals with both new/w-SSx and new echocardiographic findings at follow-up. Individuals with new/w-SSx or who underwent ETE regardless of the presence of new/w-SSx at EOT had a similar hazard ratio for re-Rx/CVS over the following year. The fact that ETE was associated with an increased risk of re-Rx/CVS, regardless of the type of imaging or the presence of new echocardiographic findings, may be, in part, explained by a propensity of a treating clinician to obtain imaging in patients believed to be at increased risk for IE complications, either due to the patient's underlying valvular status, comorbidities, or other factors not evaluated in this investigation. Alternatively, it is possible that identification of new or worsened echocardiographic findings predisposed clinicians toward earlier surgical intervention in individuals without new/w-SSx who might not have undergone surgery before experiencing clinical progression of valvular heart disease had these findings remained undetected.

As patients at highest risk of re-Rx/CVS had both new/w-SSx and new echocardiographic findings, the presence of EOT new/w-SSx may be an underutilized stratification in determining which individuals should preferentially undergo ETE. Although some individuals may require re-Rx/CVS without EOT new/w-SSx, a majority of patients experiencing early treatment failure would have been identified due to ongoing symptoms and as individuals who would also benefit from cardiac imaging. Our findings that new/w-SSx at EOT correlates with new/worsened findings on ETE as well as the need for re-Rx/CVS, that simply obtaining ETE was associated with re-Rx/CVS over the subsequent year, and that between 73% and 80% of individuals undergoing CVS for valvular sequelae without microbiologic failure had no new/w-SSx raise the question of whether ETE (and by extension valvular surgery) could have been safely postponed in these patients. Although prospective studies are required to more definitively address this question, our findings suggest that it may be reasonable to avoid ETE in individuals who are without new/w-SSx or have stable symptoms of valvular dysfunction and can be followed closely after EOT.

The limitations of the study include the retrospective design and lack of clarity of why some ETEs were done. The inability to determine a reason for a specific type of ETE is another limitation, as presence of symptoms may have resulted in a TEE for diagnostic purposes. Factors responsible for not obtaining ETEs in 27% of patients were not identified and may limit the generalizability of our findings. Involvement of a specific valve or valve type and whether surgery was performed during Phase 1 similarly failed to account for the type of ETE. Our study was not sufficiently powered to detect an association with the causative microorganism. Additionally, we had a lower proportion of *Staphylococcus aureus* IE and IE in people with intravenous drug use. Finally, we did not collect information on the presence of cardiovascular implantable electronic devices, either present at the time of diagnosis or placed during the initial treatment period, both of which may have played a role in management decisions about ETE.

Despite the potential for new/w-SSx at EOT to assist in decision-making regarding ETE, it should not be the sole determinant of whether to obtain an echocardiogram. Clinical judgment remains a crucial factor in the decision to pursue ETE in patients without new/w-SSx. Further research is needed to determine how ETE may be best utilized in this patient population, perhaps by limiting imaging to patients with the highest risk of progressive valvular disease, those at increased risk of perivalvular infectious complications (eg, with aortic root thickening on initial imaging studies), or those with complex anatomy in whom baseline imaging may be invaluable for future medical decision-making. Moreover, a TTE may provide adequate information in most patients after IE treatment and deserves additional investigation.

In conclusion, ETE in patients with infective endocarditis may not be necessary in all IE patients but may be more relevant in patients with post-treatment signs or symptoms and to establish a baseline for patients without new/w-SSx with complex anatomy, or in patients who are at high risk of sequelae of IE.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Financial support. This publication was made possible by the Mayo Clinic CCaTS through grant number UL1 TR000135 from the National

Center for Advancing Sciences (NCATS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The study database was created through REDCap (grant UL1 TR000135).

Potential conflicts of interest. A.V. reports being an Inventor with Travel and Wellness, LLC, and has received funds (<$26 000) from the University of Minnesota for research in the past year. L.M.B. reports royalty payments (authorship) from UpToDate, Inc. (<$10 000), and consultant payments from Boston Scientific (<$20 000). Remaining authors: no disclosures. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclose.

Author contributions. All authors have significantly contributed to the work and have seen and approved the manuscript. All authors had access to the data and played a role in writing the manuscript.

Prior presentation. The manuscript was presented in abstract form at IDWeek 2013.

References

1. Baddour LM, Wilson WR, Bayer AS, et al; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation **2015**; 132:1435–86.
2. Habib G, Lancellotti P, Antunes MJ, et al; ESC Scientific Document Group. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J **2015**; 36:3075–128.
3. American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. J Am Coll Cardiol **2011**; 57(9):1126–66.
4. Habib G, Hoen B, Tornos P, et al; ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for infection and cancer. Eur Heart J **2009**; 30:2369–413.
5. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **2009**; 42:377–81.
6. Steckelberg JM, Wilson WR. Risk factors for infective endocarditis. Infect Dis Clin North Am **1993**; 7:9–19.
7. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med **2012**; 366:2466–73.
8. Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: challenges and perspectives. Lancet **2012**; 379:965–75.
9. Chirouze C, Alla F, Fowler VG Jr, et al; ICE Prospective Investigators. Impact of early valve surgery on outcome of *Staphylococcus aureus* prosthetic valve infective endocarditis: analysis in the International Collaboration of Endocarditis-Prospective Cohort Study. Clin Infect Dis **2015**; 60:741–9.
10. Baddour LM, Wilson WR, Bayer AS, et al; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; Council on Cardiovascular Disease in the Young; Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia; American Heart Association; Infectious Diseases Society of America. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare 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:e394–434.