

ORIGINAL RESEARCH

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# Influence of Vegetation Size on the Clinical Presentation and Outcome of Lead-Associated Endocarditis

## Results From the MEDIC Registry

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**OBJECTIVES** The purpose of this study was to determine whether the clinical presentation of lead-associated endocarditis (LAE) is related to the size of lead vegetations and how size is related to bacteriology and clinical outcomes.

**BACKGROUND** Cardiac implantable electronic device (CIED) infection may present as either local pocket infection or bloodstream infection with or without LAE. LAE is associated with significant morbidity and mortality.

**METHODS** The clinical presentation and course of LAE were evaluated by the MEDIC (Multicenter Electrophysiologic Device Cohort) registry, an international registry enrolling patients with CIED infection. Consecutive LAE patients enrolled in the MEDIC registry between January 1, 2009 and December 31, 2012 were analyzed. The clinical features and outcomes of 2 groups of patients were compared based on the size of the lead vegetation detected by echocardiography (> or <1 cm in diameter).

**RESULTS** There were 129 patients with LAE enrolled into the MEDIC registry. Of these, 61 patients had a vegetation <1 cm in diameter (Group I) whereas 68 patients had a vegetation ≥1 cm in diameter (Group II). Patients in Group I more often presented with signs of local pocket infection, whereas Group II patients presented with clinical evidence of systemic infection. *Staphylococcus aureus* was the organism most often responsible for LAE, whereas infection with coagulase-negative staphylococci was associated with larger vegetations. Outcomes were improved among those who underwent complete device removal. However, major complications were associated with an open surgical approach for device removal.

**CONCLUSIONS** The clinical presentation of LAE is influenced by the size of the lead vegetation. Prompt recognition and management of LAE depends on obtaining blood cultures and echocardiography, including transesophageal echocardiography, in CIED patients who present with either signs of local pocket or systemic infection. (J Am Coll Cardiol Img 2014;7:541–9) © 2014 by the American College of Cardiology Foundation

The rate of cardiac implantable electronic device (CIED) infection has increased out of proportion to the increase in CIED implantations (1–5). This is likely due to an aging population of CIED recipients with associated medical comorbidities such as diabetes, heart failure, and renal sufficiency (5). CIED infection is associated with substantial morbidity and mortality, as well as the financial costs associated with treatment (6–9). Prompt recognition and management may improve outcomes and lower costs. CIED infection may present as local pocket infection or bloodstream

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infection with or without lead associated endocarditis (LAE) or valve endocarditis (6). Treatment of CIED infection with LAE includes prompt removal of all CIED hardware and a prolonged course of intravenous antibiotics (6,7). There is some concern about performing percutaneous extraction in patients with large lead vegetations due to the risk of pulmonary emboli. Moreover, some clinicians may delay lead removal in such patients by prescribing a course of intravenous antibiotics in the hope that the lead vegetation would decrease in size. The present study analyzed whether the clinical presentation, bacteriology, and outcomes of LAE were influenced by the size of the lead vegetation.

#### ABBREVIATIONS AND ACRONYMS

**CIED** = cardiac implantable electronic device

**CoNS** = coagulase-negative staphylococci

**LAE** = lead-associated endocarditis

**TEE** = transesophageal echocardiography

#### METHODS

MEDIC (Multicenter Electrophysiologic Device Infection Cohort) is an international registry consisting of 10 academic medical centers (see the [Online Appendix](#) for a list of enrolling centers) that prospectively enrolled patients with CIED infection. The institutional review board at each site

approved the study protocol. A cohort of patients with a diagnosis of LAE and evidence of a lead vegetation detected by echocardiography who were enrolled in MEDIC between January 1, 2009 and December 31, 2012 were included in this analysis. Patients were followed for 6 months following enrollment into MEDIC. Patient demographics, clinical, and laboratory data at the time of LAE diagnosis, as well as treatment outcomes were entered into the MEDIC database.

**Definitions.** A diagnosis of LAE was based on the modified Duke criteria (7,10). LAE was present if there was persistent bloodstream infection, documented by positive blood cultures and the presence of a lead vegetation documented by echocardiography. Patients with an unexplained intracardiac lead vegetation who presented with local pocket or systemic symptoms but had already been treated with antibiotics prior to obtaining blood cultures were also included. Patients with unexplained fever and persistent unexplained bloodstream infection in the absence of a documented intracardiac lead vegetation on echocardiography were not included in this analysis.

A vegetation was defined as an oscillating intracardiac mass on a pacemaker or ICD lead or cardiac valve, which was present in >1 echocardiographic plane. For the purposes of the present analysis, vegetations that were <1 cm in diameter in a single plane were characterized as small (Group I) and vegetations ≥1 cm were classified as large (Group II). Patients with a cardiac valve vegetation in addition to a lead vegetation were also included in this analysis.

The time from the most recent CIED procedure was measured in months. The initial implant was defined as the first CIED procedure. All subsequent procedures including pulse generator replacement, lead revision, or system upgrade were, therefore, classified as revisions.

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To assess medical comorbid conditions, we used the Charlson comorbidity index, which consists of 19 different disease comorbidity categories, weighted from 1 to 6 based on adjusted relative risk of 1-year mortality and summed to provide a total score. The Charlson comorbidity index has previously been validated as a good predictor of crude mortality (11). **Diagnosis and treatment.** Multiple blood cultures were obtained in each patient. All patients underwent transthoracic echocardiography. Most patients also underwent transesophageal echocardiography (TEE). The diameter of the largest intracardiac vegetation was recorded by either transthoracic or transesophageal echocardiography. All patients underwent an attempt at either percutaneous or open surgical removal of all hardware. Lead and pulse generator pocket cultures were obtained. Following the procedure, the patients received a prolonged course of intravenous antibiotics based on published guidelines (7). Reimplantation was performed at the discretion of the treating physician. Patients were followed for 6 months from the date of enrollment. A relapse was defined as a recurrence of infection with the same organism based on antimicrobial sensitivity.

**Statistical analysis.** Summary statistics were generated for patient demographic information and baseline clinical presentation to characterize the study population. This included mean  $\pm$  SD for continuous variables with nonskewed distribution, median (interquartile range) for continuous variables with skewed distribution, and frequency distribution for categorical variables. A chi-square test or Fisher exact test was used to compare categorical variables between early and late LAE patients. Continuous variables with nonskewed distribution were compared using a 2-sample Student *t* test, otherwise a Wilcoxon sum rank test was used. All tests were 2-sided, and a *p* value  $<0.05$  was considered statistically significant. Survival curves were constructed with the Kaplan-Meier method. Differences between the groups were evaluated using a log-rank test. To explore the relationship between vegetation size and 6-month mortality, the local polynomial regression smoothing method was used to estimate the mortality for each vegetation size and its 95% confidence interval (12).

## RESULTS

**Patient demographics.** A total of 129 patients with LAE were prospectively identified and enrolled into the MEDIC registry. Group I included 61 patients, whereas Group II included 68 patients with a

**Table 1. Patient Demographics**

	Group I (n = 61)	Group II (n = 68)	p Value
Age, yrs	71.3 (61.0, 79.0)	62.7 (52.3, 73.7)	0.017
Male	73.7	66.1	NS
Race, white	68.8	80.8	NS
PPM/ICD	31 (51)/30 (49)	36 (53)/32 (47)	NS
Most recent procedure			NS
Initial implant	23 (37)	34 (50)	
Revision	38 (63)	34 (50)	
Total procedures			NS
1	29 (47.5)	35 (51.4)	
2	23 (37.7)	18 (26.4)	
$\geq 3$	9 (14.7)	15 (22.0)	
Months from most recent procedure	10.7 (1.2, 28.1)	20.2 (4.6, 37.7)	NS
Total leads	2.2 $\pm$ 0.8	2.3 $\pm$ 0.8	NS
EF, %	37.1 $\pm$ 16.1	35.7 $\pm$ 15.4	NS
Vegetation size, mm	5.1 $\pm$ 1.9	19.3 $\pm$ 9.0	

Values are median (interquartile range), %, n (%), or mean  $\pm$  SD.  
 EF = ejection fraction; ICD = implantable cardioverter-defibrillator; PPM = permanent pacemaker; NS = not significant.

vegetation  $\geq 1$  cm. The patient demographics are summarized in Table 1. Patients in Group I were older than Group II patients (*p* = 0.017). However, the groups were similar with respect to sex, race, type of CIED device, and time from recent surgery. The most recent CIED procedure in Group I patients was an initial implant in 23 of 61 (37%) as compared to 34 of 38 (50%) patients in Group II. The total number of procedures was similar in both

**Table 2. Patient Comorbidities**

	Group I (n = 61)	Group II (n = 68)	p Value
CAD	37 (60.6)	24 (35.2)	0.002
CABG surgery	16 (26.2)	9 (13.2)	NS
Congestive heart failure	42 (68.8)	38 (55.8)	NS
Congenital heart disease	5 (8.2)	7 (10.2)	NS
Hemodialysis	10 (16.3)	12 (17.6)	NS
Prosthetic valve	6 (9.8)	9 (13.2)	NS
Anticoagulation	14 (22.9)	22 (32.3)	NS
Immunosuppressive use	3 (4.9)	8 (11.7)	NS
Steroid use	2 (3.2)	8 (11.7)	NS
Implanted central catheter	12 (19.7)	15 (22.0)	NS
Vascular graft	11 (18.0)	7 (10.2)	NS
Charlson comorbidity index $>4$	30 (49.1)	24 (35.3)	NS

Values are n (%).  
 CABG = coronary artery bypass graft; CAD = coronary artery disease; NS = not significant.

groups. The median time from the most recent device-related procedure was approximately twice as long in Group II versus Group I (20.2 vs. 10.7 months), but this did not reach statistical significance.

The 2 groups were similar with respect to major comorbid conditions with the exception of the presence of coronary artery disease (Table 2). A majority of Group I patients had coronary artery disease (60.6%) versus less than one-half among those in Group II (35.2%,  $p = 0.002$ ). Major medical comorbidities were observed in both groups. There was a high incidence of congestive heart failure in both groups (68.8% vs. 55.8%,  $p = \text{NS}$ ). A Charlson comorbidity index of  $>4$  was observed in 49.1% of Group I patients and 35.3% of Group II patients. The need for hemodialysis or the presence of an implanted central venous catheter was observed in approximately one-third of the cohort with LAE. In Group I, 10 of 61 (16.4%) were on hemodialysis, whereas 12 of 61 (19.7%) had an implanted central venous catheter. In Group II, 12 of 68 (17.6%) were on hemodialysis, whereas 15 of 68 (22%) had an implanted central venous catheter.

The presenting symptoms of LAE differed based on the size of the lead vegetation (Table 3). Patients with smaller vegetations (Group I) more often presented with local signs of infection such as pocket erythema, pain, swelling, warmth, or drainage.

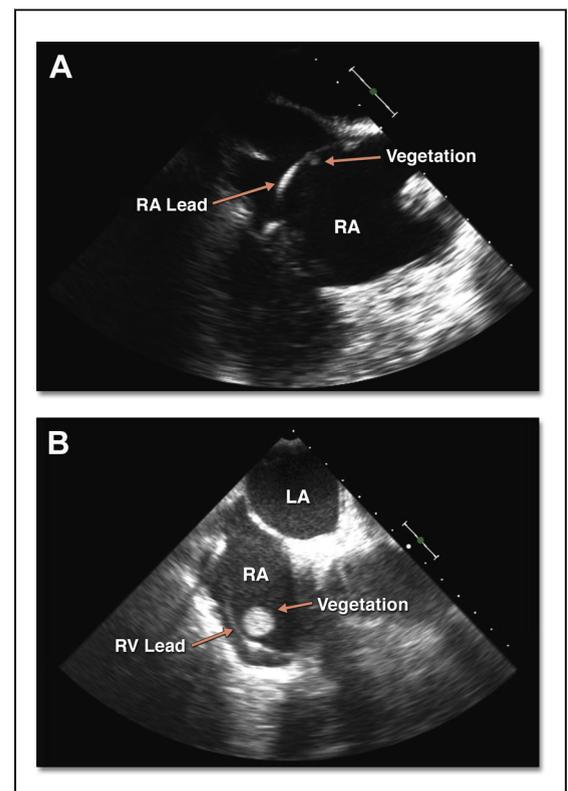
**Table 3. Presenting Symptoms**

	Group I (n = 61)	Group II (n = 68)	p Value
Signs of local infection			
Erythema	26 (42.6)	11 (16.1)	<0.001
Pain	25 (40.9)	10 (14.7)	<0.001
Swelling	16 (26.2)	5 (7.3)	<0.001
Warmth	19 (31.1)	5 (7.3)	<0.001
Pus	12 (19.6)	9 (13.2)	NS
Drainage	15 (24.5)	8 (11.7)	0.026
Signs of systemic infection			
Fever $>38^{\circ}\text{C}$	38 (62.3)	53 (77.9)	0.028
Chills/sweats	31 (50.8)	51 (75.0)	0.002
Sepsis	14 (22.9)	35 (51.4)	<0.001
Leukocytosis	22 (36.0)	38 (55.8)	0.016
Peripheral signs			
Emboli	9 (14.7)	10 (14.7)	NS
Evidence of valve involvement			
New tricuspid valve regurgitation	2 (3.2)	15 (22.0)	0.001
Valve vegetation	12 (19.6)	15 (22.0)	NS

Values are n (%).  
NS = not significant.

These signs were observed in a minority of patients with larger vegetations (Group II). In contrast, Group II patients with LAE and larger vegetations more frequently presented with signs of systemic infection such as fever, chills, signs of sepsis, and leukocytosis. Peripheral emboli were seen with similar frequency in both groups (14.7% vs. 14.7%,  $p = \text{NS}$ ). Concomitant valve vegetations were equally observed in both groups (19.6% vs. 22.0%,  $p = \text{NS}$ ) as well. In Group I patients, a vegetation was seen on the aortic valve in 1 (1.6%), the mitral valve in 3 (4.9%), and tricuspid valve in 8 (13.1%). In contrast, in Group II patients, a vegetation was seen on the aortic valve in 3 (4.4%), the mitral valve in 3 (4.4%), and the tricuspid valve in 9 (13.2%). Of note, new tricuspid valve regurgitation was more commonly observed in patients with larger vegetations (22.0% vs. 3.2%,  $p = 0.001$ ).

TEE was the imaging modality used to assess a vegetation in most patients (Fig. 1). A vegetation



**Figure 1. Vegetations Detected by Echocardiography in Patients With LAE**

(A) A small 0.7-cm vegetation (arrow) was detected on the right atrial (RA) lead in a Group I patient with *S. aureus* lead-associated endocarditis. (B) A large 2.4-cm vegetation (arrow) was detected on the proximal portion of the right ventricular (RV) lead as it passed through the RA in a Group II patient with gram-negative lead-associated endocarditis. LA = left atrium; LAE = lead-associated endocarditis.

was assessed by transthoracic echocardiography in only 6 of 61 (9.8%) Group I patients and 5 of 68 (7.3%) Group II patients ( $p = \text{NS}$ ). It is assumed that all patients had a transthoracic echocardiogram prior to a TEE. Therefore, although the median lead vegetation diameter was 17.5 mm in Group II patients, TEE was the imaging modality for defining the size of a vegetation in most cases.

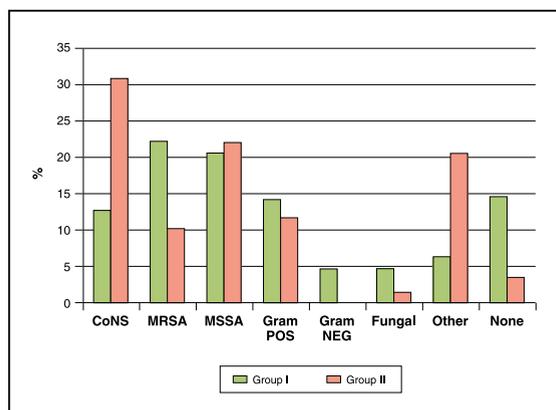
**Bacteriology.** Blood cultures were positive in 39 of 61 (65%) Group I patients and 55 of 68 (80%) Group II patients ( $p = 0.042$ ). The number of patients who received antibiotics prior to obtaining blood cultures at a MEDIC site is not known. Staphylococci, the most frequent pathogens associated with LAE, were cultured in 35 of 61 (55%) Group I patients and 43 of 68 (63%) patients in Group II ( $p = 0.002$ ) (Fig. 2). The distribution of *S. aureus* and coagulase-negative staphylococcal infection varied between the groups. The coagulase-negative staphylococci (CoNS) cultured refer to a broad group of species that generally inhabit the skin. These include organisms such as *S. epidermidis*, *S. hominis*, and *S. lugdunensis*. *S. aureus* was responsible for LAE in 27 of 61 (44.2%) Group I cases, whereas CoNS were responsible for only 6 of 61 (9.8%) Group I cases. In contrast, in Group II patients with larger vegetations, CoNS were responsible for 21 of 68 (30.8%) cases of LAE, whereas *S. aureus* infection was present in 22 of 68 (32.2%) patients. Methicillin resistance was commonly observed with *S. aureus* LAE. Methicillin

resistance was present in 14 of 27 (52%) Group I patients and 7 of 22 (32%) Group II patients. Other gram-positive organisms were cultured in 9 (14.7%) Group I patients and 8 (11.7%) Group II patients. The gram-positive organisms included viridans group streptococci (Group I = 0, Group II = 1 [1.4%]), *Enterococcus* (Group I = 5 [8.6%], Group II = 6 [8.8%]), *Propionibacterium* (Group I = 2 [3.2%], Group II = 0), and Group B beta hemolytic strep (Group I = 2 [3.2%], Group II = 1 [1.4%]). Gram-negative bacilli were only cultured in Group I patients ( $n = 3$  [4.9%]). These included *Klebsiella* ( $n = 2$  [3.2%]) and *Serratia* ( $n = 1$  [1.5%]). No organism was cultured in 9 of 61 Group I patients (14.7%) and only 2 of 68 Group II patients (3%). Many patients were likely on intravenous antibiotics at the time of evaluation at a MEDIC site, which probably accounts for the observed rate of negative cultures.

**Outcome.** The entire CIED system was removed in all Group I patients and in 65 of 68 (96%) Group II patients. The system was removed at the time of initial presentation in 37 of 61 (60.6%) Group I patients and 55 of 68 (80.8%) Group II patients. A laser sheath was used in 62.2% of Group I patients and 49.0% of the Group II patients. An operative thoracotomy/sternotomy was performed in 4 (6.5%) Group I patients and 13 (19.0%) Group II patients. The 17 patients who underwent open thoracotomy/sternotomy had larger vegetations than did the 112 patients who had their CIED system removed using a percutaneous approach ( $19.8 \pm 13.7$  mm vs.  $11.2 \pm 8.5$  mm,  $p < 0.001$ ).

The indications for an open thoracotomy/sternotomy in the 4 Group I patients were: crossover from percutaneous extraction in 1 (vascular trauma); need for epicardial leads in 1; and the need for concomitant valve surgery in 2. Therefore, only 3 Group I patients went directly for surgical extraction. In the 13 Group II patients who underwent an open thoracotomy/sternotomy, the indications included: crossover from percutaneous extraction in 3 (vascular trauma in 1 and failed extraction in 2); need for epicardial leads in 1; concomitant valve surgery in 2; and reported size of the vegetation (median = 2.6 cm, range 2.5 to 4.1 cm) in 6; and unknown in 1. Therefore, 10 Group II patients went directly to the operating room for open sternotomy/thoracotomy.

Major procedure-related complications, as a result of CIED removal, occurred in 1 (1.6%) Group I patient versus 7 (12.1%,  $p = 0.09$ ) Group II patients. The complication in the Group I patient was a respiratory arrest or anesthesia-related



**Figure 2. Microbiology of LAE**

Staphylococci were the most frequent pathogens associated with lead-associated endocarditis (LAE). *S. aureus* was the predominant pathogen in Group I patients with LAE, whereas in Group II patients with larger vegetations, coagulase-negative staphylococci (CoNS) and *S. aureus* were equally observed. CoNS infection was seen in a minority of Group I patients. Gram POS = gram-positive; Gram NEG = gram-negative; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.

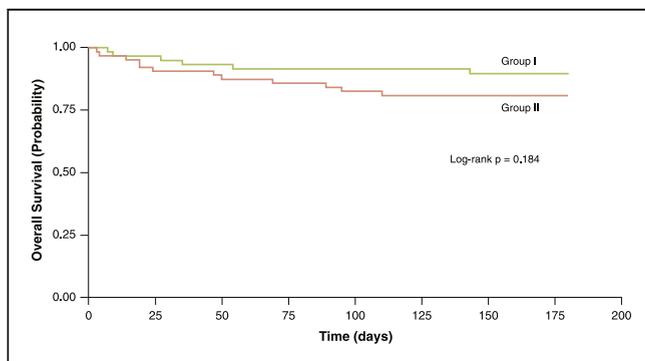
complication that lead to prolonged hospitalization. There were no other vascular complications in this group of patients. In addition, there were no complications in the 3 Group I patients who proceeded directly to open thoracotomy/sternotomy. In contrast, major complications were observed in 2 of 10 Group II patients who went directly to an open thoracotomy/sternotomy and 5 of 58 Group II patients who had attempted percutaneous removal of their CIED system. The major complications associated with direct open sternotomy/thoracotomy included respiratory failure in 1 and remote infection in 1 patient. The 5 major complications associated with percutaneous removal included a vascular tear in 2 (1 requiring operative repair), stroke in 1, and pulmonary embolism in 2 patients. There were no operative deaths.

Patients were treated with a prolonged course of intravenous antibiotics. The duration of antibiotics was longer in Group II patients than in Group I patients ( $p < 0.01$ ). A new device was implanted in 50% of patients and did not differ across the groups ( $p = 0.925$ ).

In-hospital mortality was 9.8% (6 of 61) in Group I and 11.7% (8 of 68) in Group II ( $p = \text{NS}$ ). Complete 6-month follow-up data was available for 124 of 129 patients with LAE. Two patients had relapse or suspected recurrent device infection, 1 in each group. Six-month mortality was 10.1% in Group I and 18.4% in Group II ( $p = \text{NS}$ ) (Fig. 3). Six-month mortality was also evaluated as a function of vegetation size. Mortality significantly increased as a function of vegetation size (Fig. 4).

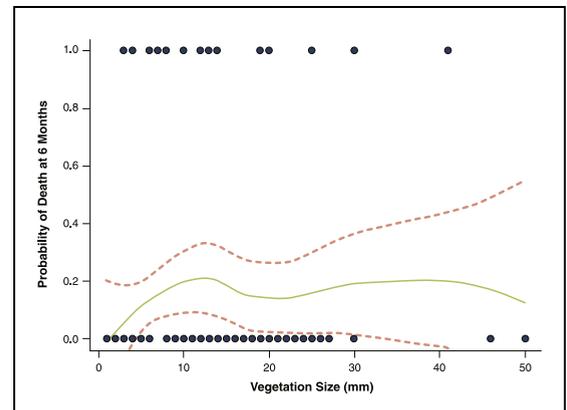
## DISCUSSION

An analysis of this large cohort of patients with LAE provides the following insights: 1) the clinical



**Figure 3. 6-Month Survival in Patients With LAE**

There was a trend toward worsened survival in Group II patients with larger vegetations. LAE = lead-associated endocarditis.



**Figure 4. Relationship Between Vegetation Size and 6-Month Mortality**

The dots represent the observed 6-month patient survival (alive or dead), whereas the solid line is the estimated mortality based on the local polynomial regression smoothing method. The dotted lines give the 95% confidence interval.

presentation of LAE differs based on vegetation size; 2) patients with LAE who present with local pocket infection usually have smaller vegetations, whereas those presenting with systemic manifestations of infection tend to have larger vegetations; 3) whereas *S. aureus* is the predominant pathogen associated with LAE, patients with LAE due to coagulase-negative staphylococci tend to have larger vegetations; and 4) major complications are more common in patients with larger vegetations, principally due to the increased use of open surgical intervention in this group.

**Clinical presentation of LAE.** CIED infection may present as local pocket infection or systemic bloodstream infection associated with LAE (7,13–15). LAE represents 19% to 23% of total CIED infection and may present many months after the most recent CIED procedure (16–18). Patients with LAE may present with signs of local pocket inflammation and bacteremia or as a systemic illness with fever, chills, sweats, and signs of sepsis. Our previous analysis of 145 patients with LAE showed that the time from the most recent CIED procedure influenced the clinical presentation (16). Patients who developed LAE soon after a CIED procedure were more likely to present with local infection. In contrast, those with LAE that occurred more than 6 months following a CIED procedure were more likely to present with signs of systemic infection. This is likely due to the fact that early LAE is usually due to progression of pulse generator infection that involves the leads, whereas late LAE is frequently due to hematogenous seeding from remote sources of infection such as dialysis

catheters, central venous catheters, arteriovenous fistulae, or peripheral abscesses.

In this study, we analyzed the importance of vegetation size on the clinical presentation and outcome of LAE in a large, prospective cohort of patients. Patients were categorized in 2 groups that were based on the size of the largest lead vegetation seen on echocardiography. Demographics and medical comorbidities of patients with vegetations  $\geq 1$  cm or  $< 1$  cm were similar except that those with smaller vegetations (Group I) were older and had a higher incidence of coronary artery disease. Group I patients were more likely to present with signs of local infection, whereas Group II patients more frequently presented with systemic symptoms or sepsis. Emboli or concomitant valve involvement were equally prevalent in both groups, though, not surprisingly, Group II patients had more evidence of new tricuspid valve regurgitation.

The diagnosis of LAE relies on the detection of a lead vegetation on echocardiography as well as the documentation of bloodstream infection (6,7,19). Importantly, patients with LAE may present with signs of pocket infection without systemic manifestation of infection. Therefore, it is critical that blood cultures be obtained in all patients with suspected CIED infection at initial presentation, before starting empiric antibiotics, regardless of the clinical presentation. TEE is most often required to detect lead vegetations (7). Consequently, the importance of performing a TEE in any CIED patient with unexplained fever or bacteremia, especially when due to a staphylococcal species, cannot be overemphasized.

LAE may be present without a vegetation detected by standard imaging. In our previous study of 145 CIED patients with LAE based on modified Duke criteria, 24% had no evidence of a lead vegetation by either transthoracic echocardiography or TEE (16). The present study only analyzed patients who had a vegetation detected on echocardiography. Recently, Narducci *et al.* (20) found that intracardiac echocardiography was more sensitive than TEE in identifying LAE. This suggests that intracardiac echocardiography may be an additional modality to detect lead vegetations in patients with a negative TEE but a high index of suspicion for underlying endocarditis.

**Detection of lead masses or vegetations.** Lead masses or vegetations may be found in patients who do not have infection. Novak *et al.* (21) performed a special autopsy in 78 patients (pacemaker = 67, implantable cardioverter-defibrillator = 11) with various modes of death to evaluate the intracardiac

leads in CIED patients. Thrombi along the lead were present in 26 (33%) patients. Previous investigators have found incidental lead masses in 5% to 10% of patients without a suspicion for LAE who undergo TEE (22,23). In addition, mobile thrombi have been detected on CIED leads in 30% of patients undergoing intracardiac echocardiography as part of a cardiac ablation procedure (24). The morphology of these incidental masses has not been systematically compared with those in infected patients. Therefore, the characteristics of a pathologic mass or vegetation remain to be defined. For these reasons, masses or vegetations on intracardiac leads must be interpreted within the clinical context as we suggest in our definition of lead-associated endocarditis.

**Bacteriology of LAE.** Staphylococcal species are the predominant organisms responsible for CIED infection and LAE (6,13,25). Previous studies have shown that *S. aureus* is responsible for approximately two-thirds of cases. However, more indolent organisms such as the coagulase-negative staphylococci are important pathogens, particularly in late-onset LAE (16,26). Our previous investigation of LAE showed that CoNS was responsible for LAE in 7 of 43 (16.3%) cases presenting  $< 6$  months from the most recent CIED procedure but 25 of 102 (24.5%) cases of late-onset LAE (16). Le *et al.* (26) highlighted the distinct clinical features of *S. aureus* and CoNS CIED infection. They observed that pocket infection due to *S. aureus* tended to occur early after a CIED procedure, whereas systemic infection tended to present later. In contrast, with CoNS infection, the timing of the CIED procedure did not impact whether patients developed local infection versus systemic infection. Patients with endovascular CoNS were more likely to have had previous CIED infection, more CIED procedures, and more abandoned leads. The association between *S. aureus* bacteremia and LAE is well known (27,28). However, Madhavan *et al.* (29) found that the underlying CIED infection was also present in 36% of patients with CoNS bacteremia and 20% in those with non-gram-positive coccid bacteremia. These data and findings from our current analysis reinforce the importance of obtaining blood cultures and TEE in patients with a pre-existing CIED who present with systemic illness including fever, chills, or signs of sepsis.

**Impact of vegetations on the clinical presentation and course of LAE.** We found that patients presenting local pocket infection had smaller vegetations, whereas larger vegetations were more commonly associated with signs of systemic illness. Larger vegetations may be the result of indolent

infection or a delay in the diagnosis of LAE, allowing existing vegetations to enlarge. An analysis of the MEDIC data does not allow us to make this distinction because we are unable to measure the time from onset of illness to diagnosis. However, in our series, larger vegetations were more commonly associated with CoNS infection. It has previously been noted that CoNS infection does not present with systemic illness as often as it does with *S. aureus* infection (26). This suggests that CoNS infection is more indolent with slower disease progression, thus presenting with larger vegetation size. These data also suggest that management of potential pocket infection is crucial because a delay in definitive treatment may lead to a more serious situation with larger vegetations and increased morbidity and mortality.

American Heart Association and Heart Rhythm Society guidelines recommend complete device removal with a prolonged course of antibiotics in any patient with CIED infection (7). Lead removal can be accomplished in most cases using percutaneous techniques (30,31). Clinically significant pulmonary emboli secondary to percutaneous extraction are rare. This is even true for patients with large vegetations seen on echocardiography (30). An open surgical approach is usually reserved for those patients with concomitant valvular endocarditis or those with extremely large vegetations, generally >3 cm (7,31). In our study cohort, the CIED system was successfully removed in all but 3 of 129 patients, all of whom had large vegetations. A direct open surgical approach was used in a minority of our patients: 3 in Group I and 10 in Group II. Four additional patients (1 in Group I and 3 in Group II) went for an open surgical approach either as the result of a failed percutaneous extraction or a vascular tear related to the procedure. Complications of lead removal were more common in those with larger vegetations, driven by complications in those requiring an open surgical approach. Therefore, earlier diagnosis of LAE when vegetations are relatively smaller could help avoid the need for open surgery and reduce the complications associated with this approach.

**Study limitations.** The decision to use 1 cm as the vegetation size separating the 2 groups was arbitrary but represented the approximate median vegetation

size of the cohort. The present study was designed to answer the question of whether the clinical presentation and course of LAE was influenced by vegetation size. Unfortunately, it will not resolve the debate regarding which patients should undergo surgical extraction. It was not designed to answer the question of the safety of percutaneous extraction of large vegetations because only 12 of 129 patients had a vegetation >2.5 cm. In addition, this study was not able to systematically review all of the cardiac imaging performed on these patients. Therefore, we are unable to directly compare the sensitivity of transthoracic versus transesophageal echocardiography in detecting and measuring an intracardiac vegetation. However, in our cohort, a vegetation was measured by transthoracic echocardiography in only 9.8% of Group I and 7.3% of Group II patients. Although the measurement of the largest diameter of a vegetation was consistent, we are not able to characterize vegetation morphology, location, or characteristics, such as calcification or mobility. Data was obtained from MEDIC sites using multiple echocardiographers. Therefore, we are unable to make any conclusions regarding vegetation morphology and clinical outcomes. Finally, the patient population studied in MEDIC reflects those referred to academic medical centers for treatment and may not be representative of all patients with LAE.

## CONCLUSIONS

Data from our large prospective cohort of patients with LAE and intracardiac vegetations suggest that the clinical presentation and clinical course of patients with CIED infection are influenced by vegetation size. Prompt diagnosis of LAE may impact clinical outcome as complications, including the need for an open surgical approach, are more common in those with large vegetations.

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- Key Words:** endocarditis ■ implantable cardioverter-defibrillator ■ permanent pacemaker.
- **APPENDIX**
- For a list of enrolling centers, please see the online version of this paper.