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ORIGINAL ARTICLE

Early transthoracic echocardiography has useful prognostic value in left-sided native valve endocarditis despite limited diagnostic performance

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Abstract

To investigate the prognostic implications of findings on early transthoracic echocardiography (TTE) in patients with definite left-sided native valve infective endocarditis (LNVIE). We reviewed a 10-year retrospective cohort of consecutive patients with definite LNVIE treated at a tertiary cardiothoracic centre. TTE studies performed within the first seven days of the index blood culture (for culture-positive cases) or hospital admission (for culture-negative cases) were reviewed for the presence of valvular vegetations, perivalvular abscesses, aortic or mitral regurgitation of moderate or greater severity or a bicuspid aortic valve. Six-week outcomes included all-cause mortality, cardiac surgery for endocarditis or new embolic cerebral infarction. Early TTE was performed in 118 of 151 episodes of definite LNVIE at a median of two days after the index blood culture or hospital admission. Findings on these studies included valvular vegetations or abscesses in 74 patients, moderate or severe aortic or mitral regurgitation in 67 patients and a bicuspid aortic valve in 19 patients. The presence of any of these findings conferred a relative risk of any adverse six-week outcome of 4.80 (95% confidence interval 1.6–17, $p = 0.001$). The presence of a bicuspid aortic valve appeared particularly predictive of the need for cardiac surgery, including for clinically occult paravalvular abscesses. Early TTE can be used to stratify patients with LNVIE by the risk of major endocarditis-related adverse outcomes occurring within the first six weeks of treatment.

Keywords Endocarditis · Bacteremia · Echocardiography · Prognosis · Diagnosis

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Introduction

Transthoracic echocardiography (TTE) has inferior diagnostic performance compared with transesophageal echocardiography (TEE) for the detection of endocardial vegetations and perivalvular abscesses in patients with infective endocarditis affecting left-sided native valves [1]. As a result, most guidelines recommend TEE in cases of suspected endocarditis, particularly when an initial TTE is negative [2, 3].

In contrast to its limited diagnostic capability, TTE may be adequate for the demonstration of echocardiographic features of prognostic importance [4–6], suggesting that a false-negative TTE may confer a more benign prognosis among patients ultimately diagnosed with native valve endocarditis [7, 8].

In this study, we aimed to characterize the prognostic implications of TTE performed early in the clinical course of patients with left-sided native valve infective endocarditis.

Methods

This retrospective cohort study was conducted at a metropolitan tertiary referral centre in Melbourne, Australia, with on-site cardiology, cardiac surgery and infectious disease services. Patients with definite infective endocarditis according to the modified Duke criteria [9] admitted to our institution between 2006 and 2016 were identified from a pre-existing institutional endocarditis database. From these, we selected those with left-sided valvular involvement (as demonstrated by echocardiography, surgery, autopsy or systemic emboli) who did not have a permanent intra-cardiac prosthetic device (prosthetic valves, permanent pacemakers and implantable cardioverter-defibrillators), forming a cohort of consecutive patients with left-sided native valve endocarditis (LNVIE). Patients were excluded from analysis if six-week follow-up data were not available.

For each included patient, we extracted demographic data, clinical details of the episode of endocarditis, diagnostic criteria and sites of metastatic complications from the pre-existing database supplemented by hospital records. Echocardiography records were reviewed to identify transthoracic studies performed within seven days of either the time of collection of the first positive blood culture (where positive, including cultures collected prior to admission to our institution) or the date patients were first admitted to hospital in culture-negative cases (early TTE), including studies performed at referring hospitals prior to transfer to our institution. Reports of these studies were reviewed for the presence of three echocardiographic findings known to be of prognostic value ("adverse findings") [6, 7, 10, 11]: (i) valvular vegetations (of any size) or perivalvular abscesses; (ii) aortic or mitral valvular regurgitation of moderate or greater echocardiographic severity as assessed by the reporting cardiologist; or (iii) the presence of a bicuspid aortic valve. Throughout the study period, TTE images were collected according to a systematic examination protocol by experienced sonographers and reported by echocardiography subspecialist cardiologists.

We examined all available hospital records to identify the occurrence of three major infective endocarditis adverse outcomes by six weeks after the initial positive blood culture or hospital admission for culture-negative cases: (i) new symptomatic cerebral embolism (defined as new focal neurological deficits with either concordant neuroimaging findings of cerebral ischemia or a clinical diagnosis of stroke occurring after the initial positive blood culture or hospital admission for culture-negative cases); (ii) cardiac surgery for complications of endocarditis; and (iii) all-cause mortality. The primary outcome for the analysis was the occurrence of any of these three adverse outcomes within the six-week follow-up period (the "composite outcome").

Categorical variables were compared with the Fisher exact test and non-parametric continuous variables were compared with the Kruskal-Wallis log rank test. Wilson score 95% confidence intervals were calculated for simple proportions and score-based 95% confidence intervals were calculated for relative risk estimates using the "PropCIs" package for the *R* statistical environment [12].

This project was approved by the human research ethics committee at our institution.

Results

We identified 151 episodes of definite LNVIE managed at our institution during the study period. Six-week follow-up data were available in 147 episodes. Of these, 118 (80%) underwent TTE within seven days of either the first positive blood culture or hospital admission (in culture-negative cases) and formed the cohort for our analysis. There were no significant differences in clinical or microbiological variables between the patients undergoing and not undergoing early TTE (Table 1).

TTE was performed a median of two days (interquartile range one to four days) after the first positive blood culture (culture-positive episodes) or hospital admission (culture-negative episodes). Valvular vegetations adherent to left-sided cardiac structures were identified on early TTE studies in 74 cases (sensitivity 63%, 53–70%), with perivalvular abscesses also noted on four. All but eight of the 44 episodes without vegetations seen on the initial early TTE had diagnostic findings on subsequent echocardiography studies, with the remainder diagnosed on autopsy findings or a combination of the Duke major microbiological criterion and multiple accompanying minor criteria. Other findings on early TTE included

Table 1 Baseline characteristics of 151 consecutive patients with left-sided native valve endocarditis stratified by inclusion in the study cohort

	Included ($n = 118$)	Excluded ($n = 33$)	p
Age in years (median, IQR)	51 (39–69)	58 (50–68)	0.25
Male (n, %)	83 (71%)	26 (79%)	0.39
History of intravenous drug use	32 (27%)	5 (15%)	0.18
Previous endocarditis	5 (4%)	1 (3%)	1.00
Nosocomial acquisition of endocarditis	7 (6%)	3 (9%)	0.46
Modified Duke criteria (n, %)			
Pathological diagnosis	38 (32%)	13 (39%)	0.53
Two major criteria	99 (84%)	30 (91%)	0.41
One major and three minor criteria	19 (16%)	3 (9%)	
Five minor criteria	0	0	
Major echocardiographic criterion	109 (92%)	30 (91%)	0.73
Major microbiological criterion	97 (82%)	27 (81%)	1.00
Causative organism (n, %)			
Staphylococcus aureus	58 (49%)	15 (45%)	0.71
Methicillin-susceptible	53	12	
Non-beta hemolytic streptococci[a]	26 (22%)	7 (21%)	
E. faecalis	9 (8%)	4 (12%)	
Other[b]	22 (19%)	5 (15%)	
No organism identified	3 (3%)	2 (6%)	
Valvular involvement (n, %)			
Aortic valve	58 (49%)	15 (45%)	0.84
Mitral valve	72 (61%)	22 (67%)	0.69
Additional right-sided involvement	6 (5%)	2 (6%)	0.67
Systemic embolism (n, %)			
Embolic stroke	26 (22%)	6 (18%)	0.81
Other systemic embolism	39 (33%)	5 (15%)	0.05
Metastatic abscess (n, %)	18 (15%)	4 (12%)	0.79
Bone and joint	10	2	
Central nervous system	4	1	
Pyomyositis	4	0	
Intra-abdominal	2	1	

[a] Excluding *S. pneumoniae*

[b] Beta-hemolytic streptococci 5, *Abiotrophia* spp. 5, *S. pneumoniae* 4, coagulase-negative staphylococci 2, *Coxiella burnetii* 2, unique organisms 9

aortic or mitral valvular regurgitation of at least moderate severity in 67 episodes, and a bicuspid aortic valve in 19 episodes. In 17 episodes, the early TTE did not identify any of these three findings; 16 of these episodes had findings of endocarditis identified on subsequent TEE.

A total of 59 patients (50%) suffered one or more adverse endocarditis outcomes within six weeks. Although 22 patients (19%) had suffered an embolic stroke prior to presentation, only four patients (3%, 95% confidence interval 1–8%) suffered a new symptomatic cerebral embolism occurring after the first positive blood culture or hospital admission. Cardiac surgery was performed during the first six weeks in 40 patients (34%), at a median of 13 days (interquartile range seven to 25 days) after documented bacteremia or admission. The indication for cardiac surgery was based on findings that were clinically evident in 32 episodes (progressive heart failure, 25; heart failure with perivalvular abscess, 6; uncontrolled infection, 1) and on echocardiographic features alone in 8 episodes (perivalvular abscess without heart failure, 6; vegetation morphology suggestive of high embolic risk, 2). The all-cause mortality at six weeks was 19% (22 of 118 cases).

Findings on early TTE studies were predictive of adverse endocarditis outcomes occurring within six weeks. The composite outcome occurred after the identification of each of the three adverse findings at roughly the same incidence (Table 2), and the number of adverse findings was strongly predictive of the risk of a six-week adverse outcome (Table 3). In contrast, patients without any of the three findings had a low incidence of adverse outcomes (two of 17 episodes—one patient underwent non-emergent surgery for clinically evident heart

Table 2 Proportion of patients with definite left-sided native valve endocarditis suffering adverse endocarditis outcomes within six weeks by findings on early transthoracic echocardiography

Findings on early TTE	n	New cerebral embolism *n* (%)	Cardiac surgery *n* (%)	Death *n* (%)	Composite outcome *n* (%)
All	118	4 (3%)	40 (34%)	22 (19%)	59 (50%)
Valvular vegetation or perivalvular abscess	74	2 (3%)	29 (39%)	18 (24%)	43 (58%)
At least moderate aortic or mitral regurgitation	67	4 (6%)	30 (45%)	14 (21%)	41 (61%)
Bicuspid aortic valve	19	1 (5%)	11 (58%)	2 (11%)	12 (63%)
None of these findings	17	0	1 (6%)	1 (6%)	2 (12%)

TTE, transthoracic echocardiography

failure on day 24, and the other died of multi-organ failure on day 26). The absence of vegetations or abscess alone (a "negative" early TTE) was protective (relative risk 0.63 for the composite outcome, 95% confidence interval 0.40–0.97), but 16 of 44 (36%) of these patients suffered an adverse endocarditis outcome within six weeks, including 11 (25%) who required surgical intervention.

Patients with bicuspid valves underwent cardiac surgery for complications of endocarditis more commonly than those with a trileaflet aortic valve (relative risk 2.0, 95% confidence interval 1.1–3.1). There was also a strong association between this congenital abnormality and the development of a perivalvular abscess: nine of 19 (47%) patients with a bicuspid aortic valve had a perivalvular abscess found on echocardiography or at surgery, compared with only eight of 99 (8%) patients with a trileaflet aortic valve (relative risk 5.9, 95% confidence interval 2.6–13, $p < 0.001$). This association was not explained by diagnostic bias due to differences in the proportion of patients undergoing a TEE, surgery or autopsy (17 of 19 with a bicuspid valve compared with 79 of 99 with a trileaflet aortic valve, $p = 0.52$).

Discussion

In this series of patients with definite LNVIE, the results of TTE performed at a median of two days after the first positive blood culture successfully predicted the risk of adverse endocarditis outcomes occurring during the subsequent six weeks. As adverse findings on these initial studies accumulated, the risk of death, cardiac surgery or a new embolic stroke rose from 12% (with no adverse findings) to more than 50% (with two or more). These results may be useful to clinicians managing patients with known or suspected LNVIE, particularly for decisions regarding the clinical utility of TEE after a reassuring early TTE.

Our findings are in line with the limited available data examining the prognostic value of TTE findings in patients with endocarditis. De Castro et al. [13] reported that systemic embolism (occurring at any time, including prior to diagnosis) was more common among patients with LNVIE who had vegetations visible on fundamental frequency TTE compared with those without (relative risk 2.8, 95% confidence interval 1.0–10). Likewise, Fowler et al. [7] reported that among 59 patients with *S. aureus* endocarditis (including prosthetic valve and right-sided endocarditis), those with vegetations noted on TTE had a higher mortality and incidence of major systemic embolism than those without (RR 4.1, 95% confidence interval 2.5–20). Sekar et al. [8] reported that of 28 patients with *S. aureus* bacteremia and findings of endocarditis on TEE, those with diagnostic findings also found on TTE were more likely to require cardiac surgery for complications of endocarditis than those with negative transthoracic studies (RR 3.7, 95% confidence interval 1.2–10). A recent large registry-based study [14] also suggested that patients with definite endocarditis by the modified Duke criteria but with negative echocardiography had a lower incidence of embolism or cardiac surgery than those with positive studies,

Table 3 Adverse findings on early transthoracic echocardiography and the incidence of the composite outcome at six weeks

Findings on early TTE	n	Composite outcome *n* (%)	Relative risk	95% confidence interval	*p*
0 adverse findings	17	2 (12%)	Referent		
1 adverse findings	49	23 (47%)	3.99	1.29–14.6	0.01
2 adverse findings	45	29 (64%)	5.48	1.82–19.9	< 0.001
3 adverse findings	7	5 (71%)	6.07	1.71–22.9	0.009
≥ 1 adverse finding	101	57 (56%)	4.80	1.61–17.3	0.001

TTE, transthoracic echocardiography

although direct comparison to our data is limited by the inclusion of patients with prosthetic valve infection and various echocardiography strategies, including transesophageal echocardiography.

While a significant proportion of patients in our series suffered an embolic stroke (22%), new symptomatic cerebral embolic events after documentation of bacteremia or hospital admission were uncommon, affecting only four patients. This incidence is consistent with previous series making the distinction between new and total embolic events in unselected patients with LNVIE [10, 11, 15, 16]. Although there is some disagreement among studies addressing echocardiographic predictors of embolism in endocarditis, studies reporting the outcome of cerebral embolism occurring after the initiation of antimicrobial therapy do seem to consistently suggest that these events occur almost exclusively in patients with large vegetations that are more likely to be identified on TTE [4, 10, 11, 15].

Our data also reiterate the importance of identifying bicuspid aortic valves in patients with native valve endocarditis. In our series, 22 patients (15%) were found to have a bicuspid aortic valve, which is a significant over-representation compared with the estimated 1% population prevalence [17]. These patients developed perivalvular abscesses and progressed to cardiac surgery much more commonly than those with a trileaflet aortic valve, a result that is consistent with previous series examining the prognosis of patients with endocarditis and bicuspid aortic valves [6, 18, 19]. The identification of this relatively common congenital abnormality should be recognized as an important facet of the echocardiographic assessment of patients with endocarditis.

Truly occult indications for surgery that are only identifiable on echocardiography appear to be rare in LNVIE. In our series, these indications led to surgery in eight patients (7%): perivalvular abscess without clinical heart failure in six, and high-risk vegetation morphology in two. Consistent with the results noted above, these occult indications were more common in patients with a bicuspid aortic valve noted on early TTE, with four of 19 patients with bicuspid valves (21%) found to have a clinically occult indication for surgery (all perivalvular abscess) compared with only four of 99 (4%) patients with trileaflet aortic valves.

A common clinical scenario where our findings may be of use to clinicians is the one in which bacteremia is demonstrated in the context of a known extra-cardiac focus of infection requiring prolonged antimicrobial therapy. In many of these situations, which include patients with cerebral abscess, spinal epidural abscesses or axial osteomyelitis and discitis due to staphylococci or streptococci, the antimicrobial regimens used are often identical to those that might be used if LNVIE was documented on echocardiography [20–22]. This is particularly relevant with the recent publication of the POET trial [22], which may further align the regimens used for extra-thoracic infection with those used for apparently uncomplicated endocarditis, particularly for staphylococcal disease.

This situation appears to be a frequent reason for TEE deferral in patients at risk of endocarditis [23]. As clinically occult intra-cardiac complications are rare in the subset of these patients who have endocarditis (and non-existent in the majority who do not), a single assessment with TTE early after the demonstration of bacteremia may be sufficient in these patients if reassuring findings are documented. A similar situation arises for clinicians who would extend parenteral treatment for *S. aureus* bacteremia to four to six weeks in patients with adverse clinical features (such as community acquisition or persistent bacteremia) even if a TEE were negative for endocarditis [21, 24]. In this latter case, the value of TEE is limited to identifying clinically occult structural complications that may require cardiac surgery. Our results suggest that a TEE may also reasonably be deferred for patients with no adverse findings on early TTE.

Our study has a number of limitations that stem from its single-centre retrospective design. Most notably, the limited number of included patients results in significant imprecision in our estimates of risk. While patients were prospectively identified for inclusion in the source endocarditis database, many data points were collected retrospectively. Nevertheless, the echocardiographic criteria and endocarditis adverse outcomes we have selected to study were objective and based on contemporaneously recorded clinical information. Early TTE was not a prescribed component of the management of patients with endocarditis at our institution during the study period, resulting in the potential for selection bias in the analysable subset. As noted above, however, early TTE was performed in the majority of episodes of LNVIE during the study period (80%), and the patients who did not undergo this investigation were comparable with those who did (Table 1). Additionally, survivor bias did not appear to be a problem in our series: only nine of the 151 patients in the entire LNVIE series died within the first week after demonstration of bacteremia or hospital admission and all underwent early TTE prior to death. Finally, although short-term follow-up data were almost universally available (97% at 42 days), later outcomes were not included in our analysis. Six-month follow-up was available in 91 (75%) of the patients who underwent early TTE in our series. Only two of these patients suffered adverse endocarditis outcomes between 42 days and six months; both underwent cardiac surgery for the late development of clinically evident heart failure.

Conclusions

In conclusion, findings of early TTE studies can be used to stratify patients with LNVIE by the risk of major endocarditis-related adverse outcomes occurring within the first six weeks of treatment. The identification of valvular vegetations, perivalvular abscess, moderate or severe aortic regurgitation

or a bicuspid aortic valve on these studies all contribute to a markedly increased risk of adverse outcomes compared with those with reassuring TTE results.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Human Research Ethics Committees of St Vincent's Hospital Melbourne and Monash University.

Informed consent Not required.

References

1. Bai AD, Steinberg M, Showler A, Burry L, Bhatia RS, Tomlinson GA, Bell CM, Morris AM (2017) Diagnostic accuracy of transthoracic echocardiography for infective endocarditis findings using transesophageal echocardiography as the reference standard: a meta-analysis. J Am Soc Echocardiogr 30(7):639–646
2. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O'Gara P, Taubert KA (2015) Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 132(15):1435–1486
3. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL, Erol Ç, Nihoyannopoulos P, Aboyans V, Agewall S, Athanassopoulos G, Aytekin S, Benzer W, Bueno H, Broekhuizen L, Carerj S, Cosyns B, De Backer J, De Bonis M, Dimopoulos K, Donal E, Drexel H, Flachskampf FA, Hall R, Halvorsen S, Hoen B, Kirchhof P, Lainscak M, Leite-Moreira AF, Lip GY, Mestres CA, Piepoli MF, Punjabi PP, Rapezzi C, Rosenhek R, Siebens K, Tamargo J, Walker DM, Reviewers D (2015) 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 36(44):3075–3128
4. Reynolds HR, Jagen MA, Tunick PA, Kronzon I (2003) Sensitivity of transthoracic versus transesophageal echocardiography for the detection of native valve vegetations in the modern era. J Am Soc Echocardiogr 16(1):67–70
5. Anguera I, Miro JM, Evangelista A, Cabell CH, San Roman JA, Vilacosta I, Almirante B, Ripoll T, Fariñas MC, Anguita M, Navas E, Gonzalez-Juanatey C, Garcia-Bolao I, Muñoz P, de Alarcon A, Sarria C, Rufi G, Miralles F, Pare C, Fowler VG, Mestres CA, de Lazzari E, Guma JR, Moreno A, Corey GR, Group A-CFiEW (2006) Periannular complications in infective endocarditis involving native aortic valves. Am J Cardiol 98(9):1254–1260
6. Tribouilloy C, Rusinaru D, Sorel C, Thuny F, Casalta JP, Riberi A, Jeu A, Gouriet F, Collart F, Caus T, Raoult D, Habib G (2010) Clinical characteristics and outcome of infective endocarditis in adults with bicuspid aortic valves: a multicentre observational study. Heart 96(21):1723–1729
7. Fowler VG Jr, Sanders LL, Kong LK, McClelland RS, Gottlieb GS, Li J, Ryan T, Sexton DJ, Roussakis G, Harrell LJ, Corey GR (1999) Infective endocarditis due to Staphylococcus aureus: 59 prospectively identified cases with follow-up. Clin Infect Dis 28(1):106–114
8. Sekar P, Johnson JR, Thurn JR, Drekonja DM, Morrison VA, Chandrashekhar Y, Adabag S, Kuskowski MA, Filice GA (2017) Comparative sensitivity of transthoracic and transesophageal echocardiography in diagnosis of infective endocarditis among veterans with Staphylococcus aureus bacteremia. Open Forum Infect Dis 4(2):ofx035
9. Durack DT, Lukes AS, Bright DK (1994) New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 96(3):200–209
10. Thuny F, Di Salvo G, Belliard O, Avierinos JF, Pergola V, Rosenberg V, Casalta JP, Gouvernet J, Derumeaux G, Iarussi D, Ambrosi P, Calabro R, Riberi A, Collart F, Metras D, Lepidi H, Raoult D, Harle JR, Weiller PJ, Cohen A, Habib G (2005) Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation 112(1):69–75
11. Hill EE, Herijgers P, Claus P, Vanderschueren S, Peetermans WE, Herregods MC (2008) Clinical and echocardiographic risk factors for embolism and mortality in infective endocarditis. Eur J Clin Microbiol Infect Dis 27(12):1159–1164
12. R Core Team (2017) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna https://www.R-project.org/
13. De Castro S, Magni G, Beni S, Cartoni D, Fiorelli M, Venditti M, Schwartz SL, Fedele F, Pandian NG (1997) Role of transthoracic and transesophageal echocardiography in predicting embolic events in patients with active infective endocarditis involving native cardiac valves. Am J Cardiol 80(8):1030–1034
14. Vicent L, Saldivar HG, Bouza E, Munoz P, Cuerpo G, de Alarcon A, Vidal B, Cobo M, Goenaga MA, Carrasco-Chinchilla F, Montejo M, Galvez-Acebal J, Hidalgo-Tenorio C, Vinuesa-Garcia D, Martinez-Selles M, investigators G (2018) Prognostic implications of a negative echocardiography in patients with infective endocarditis. Eur J Intern Med
15. Di Salvo G, Habib G, Pergola V, Avierinos JF, Philip E, Casalta JP, Vailloud JM, Derumeaux G, Gouvernet J, Ambrosi P, Lambert M, Ferracci A, Raoult D, Luccioni R (2001) Echocardiography predicts embolic events in infective endocarditis. J Am Coll Cardiol 37(4):1069–1076
16. Dickerman SA, Abrutyn E, Barsic B, Bouza E, Cecchi E, Moreno A, Doco-Lecompte T, Eisen DP, Fortes CQ, Fowler VG Jr, Lerakis S, Miro JM, Pappas P, Peterson GE, Rubinstein E, Sexton DJ, Suter F, Tornos P, Verhagen DW, Cabell CH, Investigators ICE (2007) The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE prospective cohort study (ICE-PCS). Am Heart J 154(6):1086–1094
17. Nistri S, Basso C, Marzari C, Mormino P, Thiene G (2005) Frequency of bicuspid aortic valve in young male conscripts by echocardiogram. Am J Cardiol 96(5):718–721
18. Chen J, Lu S, Hu K, Yang Z, Pan S, Hong T, Wang C (2017) Clinical characteristics and surgical treatment of infective endocarditis with bicuspid aortic valve. Int Heart J 58(2):220–224

19. Kiyota Y, Della Corte A, Montiero Vieira V, Habchi K, Huang CC, Della Ratta EE, Sundt TM, Shekar P, Muehlschlegel JD, Body SC (2017) Risk and outcomes of aortic valve endocarditis among patients with bicuspid and tricuspid aortic valves. Open Heart 4(1): e000545
20. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, M JR, Talan DA, Chambers HF (2011) Clinical practice guidelines by the Infectious diseases society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis 52(3):285–292
21. Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, Hendershot EF, Holtom PD, Huddleston PM 3rd, Petermann GW, Osmon DR, Infectious Diseases Society of A (2015) 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 61(6):e26–e46
22. Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, Bruun NE, Hofsten DE, Fursted K, Christensen JJ, Schultz M, Klein CF, Fosboll EL, Rosenvinge F, Schonheyder HC, Kober L, Torp-Pedersen C, Helweg-Larsen J, Tonder N, Moser C, Bundgaard H (2018) Partial Oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med
23. Young H, Knepper BC, Price CS, Heard S, Jenkins TC (2016) Clinical reasoning of infectious diseases physicians behind the use or nonuse of transesophageal echocardiography in Staphylococcus aureus bacteremia. Open Forum Infect Dis 3(4): ofw204
24. Strnad L, Beekmann SE, Polgreen PM, Chambers H, Liu C (2017) Clinical practice variation in the management of *Staphylococcus aureus* bacteremia: results from an Emerging Infections Network Survey. Open Forum Infect Dis. Oxford University Press US, pp S553–S553