



A clinical practice guideline appraisal for appropriate use of echocardiography in adult infective endocarditis—when and by which mode to perform an Echo?

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Abstract

Background

Echocardiography (Echo) is the primary imaging modality of infective endocarditis (IE). However, the recommendations on timing and mode selection for transesophageal echocardiography (TEE) and transthoracic echocardiography (TTE) are not fully in agreement among different guidelines, which can be confusing for clinical decision makers. In this case, we aim to appraise the quality of recommendations by appraising the quality of guidelines.

Methods

A search of guidelines containing recommendations for the appropriate use of Echo in IE adult patients published in English between 2007 and 2020 has been conducted. APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION II (AGREE II) instrument is applied independently by two reviewers to assess the integrated quality of identified guidelines. The recommendations of concern are extracted from related chapters.

Results

A total of 9 guidelines meet the criteria with AGREE II score ranging from 36% to 79%, and the domain of “stakeholder involvement” receives the lowest score. The most contentious issue is, whether a follow-up TEE is mandatory in uncomplicated native valve IE with initial positive TTE. And conflicting recommendations on it are presented with low evidence level for hardly any related evidence based on.

Conclusions

In general, the recommendations proposed in the 9 identified guidelines on the appropriate use of Echo are satisfying. And the guideline quality score could be taken into account by the clinicians when evaluating the recommendations for making clinical decision. More researches are needed in the future, which should be with high evidence level on the most controversial issues of whether a subsequent TEE is mandatory in uncomplicated native valve IE with an initial positive TTE.

Background

Echocardiography (Echo) is the primary imaging modality for infective endocarditis. A positive Echo defined as vegetation or abscess, or new dehiscence of prosthetic valve is included as a major modified Duke criterion along with positive microorganisms[1]. Besides, echocardiographic examination is also available to show the hemodynamics and mechanism severity[2]. The appropriate use of Echo should be cost-effectiveness, time-efficiency and concern about the potential associated complications[3, 4]. In the meantime, it should be available for timely and accurate guidance for the diagnosis and management of IE. As per a single-center study, a considerable number of transesophageal echocardiography (TEE) studies were rated as rarely appropriate tests for infective endocarditis (IE)[5]. Over the past 15 years,

there are 9 guidelines that cover IE diagnosis and contain evidence-based recommendations on the appropriate use of Echo (only in English language, and the latest version of updating guidelines). However, these guidelines differ in the recommendations on TEE and transthoracic echocardiography (TTE) application in certain clinical scenarios, which can be confusing for clinical decision makers. AGREE is an instrument for comprehensive guideline evaluation from 6 different domains, including scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. And AGREE II, as the updated version developed in 2013, carries some modifications on certain items compared with the original version[6]. A systematic review of the appropriate use of Echo based on critical assessment and the quality comparison of different guidelines was presented to allow clinicians to make better decisions in certain confusing clinical scenarios.

Methods

Searching process

A literature search of current clinical practice guidelines which contain recommendations on IE imaging examination was conducted on Pubmed, Embase, Web of science and websites of guideline development societies (websites of organizations and societies is shown in Table S1). “adult” “infective endocarditis” “echocardiography” “transesophageal echocardiography” and “transthoracic echocardiography” were searched either singly or in combination (the detailed search strategy of databases is shown in table S2). The search covered the guidelines published in English from 5 June, 2007 to 5 July, 2019.

Including criteria

An included guideline needs to meet the following criteria:

1. The definition of a guideline given by The Institution of Medicine[7] should be followed, which was described as “systematically developed statements to assist practitioner and patient decisions on appropriate healthcare for specific clinical circumstance”.
2. Contain recommendations on the appropriate use of Echo in diagnosis, treatment, or follow-up process of IE.
3. Target at adult patients.
4. Be the latest version with updated guidelines.
5. Be free for the full text.
6. Written in English, including translated version of other languages.

Titles and abstracts were reviewed by 2 reviewers independently. After that, the disagreements were discussed before reaching a consensus with the presentation of the third party. At last, the final selection of guidelines was performed by the 2 reviewers together.

Guideline appraisal and recommendation extraction

A comprehensive evaluation was performed to the 9 selected guidelines from 6 domains as per AGREE II instrument, which includes: i) scope and purpose, ii) stakeholder involvement, iii) rigor of development, iv) clarity of presentation, v) applicability, and vi) editorial independence. Two reviewers evaluated 23 items from 6 domains independently in the form of scoring with numbers ranging from 1 to 7, where 1 represents the strong disagreement to which no relevant information was given or the concept was barely reported, and 7 represents the strong agreement of which the reporting quality was exceptional or fully met the criteria set by AGREE II. The final score of each domain was obtained by the calculation formula given by AGREE II: the scaled domain score = (Obtained score – Minimum possible score) / (Maximum possible score – Minimum possible score). In the case that the difference between the scores given by both reviewers for a certain item is greater than 20% of the lower score, a third reviewer would be introduced for the review and evaluation of the guidelines[8]. The guidelines with the average score higher than 60% was marked with “Strongly recommended”, while those with scores ranging from 30% to 60% will be marked with “Recommended with some modification”, the others with scores lower than 30% will be marked with “Not recommended”[9].

Except for the two guidelines of Chinese Society of Cardiology, version 2015 and Swedish Society of Infectious Diseases, version 2007 (CSC 2015, SSID 2007) without the report of Conflicts of Interest (COI) [10, 11], we calculated the proportion of panel members with an industrial relationship (RWI) of authors reported in other guidelines, and analyzed the correlation between RWI ratio and AGREE II score using SPSS 25.0. The case with $\alpha < 0.05$ indicates the statistical significance[8].

All recommendations on the appropriate use of Echo, including the timing and mode (TTE and TEE) were extracted from the relevant chapters. In an effort to avoid phrasing confusion, the class of recommendation and the level of evidence quoted from SSID 2007 were converted into a unified form that is consistent with those used in other guidelines[11]. The grade of recommendation and the level of evidence denoted hereafter were uniformly expressed as I/II/III and A/B/C respectively.

Results

Guidelines meet the criteria

A total of 1015 records were searched out during the literature search, from which 1006 records were removed after the review on title, abstract, and the full-text (Figure 1). As the outcome, 9 guidelines reported by 8 host organizations (some of them are joint-work) finally meet the requirements of including criteria: National Heart Association of Malaysia, version 2017 (NHAM 2017); American Heart Association, version 2015 (AHA 2015); European Society of Cardiology, version 2015 (ESC 2015); British Society for Antimicrobial Chemotherapy, British Heart Rhythm Society, version 2014, (BSAC/BHRS 2014); Japanese Circulation Society, version 2017, (JCS 2017); British Society for Antimicrobial Chemotherapy, version 2011 (BSAC 2011); Spanish Society of Infectious Diseases and Clinical Microbiology, version 2015 (SEIMC 2015); CSC 2015; SSID 2007[10-18]. References of the guidelines is shown in Table S3. Guideline

identifier, host organization, region, average AGREE II score, COI, number of Echo recommendations and RWI are summarized in Table 1.

Guidelines appraisal by AGREE II

The scores of each guideline are presented in the radar charts (Figure 2) and Table S4. The AGREE II scores of all guidelines are ranging from 36% to 79% with the median of 55%, among them, 4 guidelines (NHAM 2017, AHA 2015, ESC 2015, BSAC/BHRS 2014)[12-15] are rated as “Strongly recommended” with the score higher than 60%, while the others (JCS 2017, BSAC 2011, SEIMC 2015, CSC 2015, SSID 2007) [10, 11, 16-18] are marked with “Recommended with some modifications” with the score from 36% to 55%. No guideline is rated as “Not recommended” with the score lower than 30%. There is no item with the difference between the scores given by the two reviewers greater than 20%.

The focus of Domain1 (scope and purpose) includes the items about the overall goal, the specific health issues contained in the guideline, and its target population. While in contrast with other domains, guidelines’ performance in this domain is uneventful, that is, most of them generally summarized the concerning issues without any further elaboration. NHAM 2017, BSAC/BHRS 2014, BSAC 2011[12, 15, 17] specifically expounded on the items following the AGREE II rules, thus receiving a relatively high score.

The concern of Domain2 (stakeholder involvement) includes that whether the guideline was developed by appropriate stakeholders and whether the views of its intended users was considered. This domain received the lowest average score when two-thirds of the guidelines are not higher than 33%. Only NHAM 2017, BSAC/BHRS 2014, and JCS 2017[12, 15, 16] specified that to which department the clinical guideline should apply for the specialists. In addition, the view of the patients as the target population was only reported by BSAC/BHRS 2014[15] in the external review, which was not mentioned by the rest of the guidelines of at all.

Domain 3 (rigour of development) is comprised of the processes of evidence synthesizing, the formulation of the recommendations and the procedure for updating. CSC 2015 and SSID 2007[10, 11] reported no information in regard to the selection of evidence, while BSAC/BHRS 2014, JCS 2017 and BSAC 2011[15-17] had only a little description on this subject. Besides, no updated statements or detailed information on external expert review are presented by the guidelines other than AHA 2015, ESC 2015[13, 14] and NHAM 2017[12]. The narrative of methods for formulating the recommendations is relatively clear, therefore, higher scores were given to the items concerned.

Domain 4 (clarity of presentation) involves the clarity of the description and the format of the guideline, of which the average score is the highest of all domains, and the discreteness of scores is the smallest.

Domain 5 (applicability) deal with the practical implementation, efforts for improving uptake, and resource implications. No additional disseminating materials were provided by the guidelines except for NHAM 2017 ESC 2015 and AHA 2015[12-14]. There are few guidelines made mention of the cost

implication. Yet the monitoring and auditing criteria was set precisely by all guidelines with the average score higher than 80%.

Domain 6 (editorial independence) pertains to the transparency declarations, including the funding body and competing interests of guideline development group members. Neither clarification on the funding body nor its influence on the content was mentioned by JCS 2017, CSC 2015 and SSID 2007[10, 11, 16]. Besides, no records on the disclosure of potential COI were mentioned by SSID 2007[11] and CSC 2015[10]. As a result, there is no correlation between RWI and AGGEE II score (Pearson's correlation $r = -0.081$ $P = 0.863$) for the rest of the guidelines.

It was found out that more than half of the guidelines (5 out of 9) had received scores less than 60%. According to the independent-sample t-test, t'-test (editorial independence) and Wilcoxon Rank-Sum test (clarify of presentation), the guidelines marked with "recommended with modification" are statistically different from those with "strongly recommended" in the domains of "rigour of development" ($P=0.015$), "applicability" ($P=0.005$) and "editorial independence" ($P=0.024$) (Figure 3). With regards to the specific items, 8 out of 9 guidelines had received the score of zero on the item of "target population", which indicates that the existing guidelines generally failed to consider the view of a patient during the formulation of recommendations.

Recommendations on appropriate use of Echo

Recommendations for different clinical scenarios were organized and listed in Table S5 (recommendations with controversies) and Table S6 (recommendations without controversies). As shown in the tables, both consensus and controversy are listed, and the consensus outweighs the controversy.

As per the 5 out of 9 guidelines, when a first-line TTE is proved to be non-diagnostic due to its poor echocardiographic window, a further TEE will be recommended considering its higher sensitivity than TTE (class of recommendation: I, level of evidence: B-C)[1].

For patients with suspected IE under a prosthetic heart valve/intracardiac device, TEE is recommended by 5 out of 9 guidelines (class of recommendation: I, level of evidence: B-C). Furthermore, suggestion for patients with implantable cardiac electronic device (ICED) was given by the guideline of BSAC/BHRS 2014, recommending that Echo should be conducted for patients with implantable cardiac electronic device lead infection (LCED-LI), implantable cardiac electronic device associated native or prosthetic valve endocarditis (LCED-IE) and suspected generator pocket infection concurrent ICED-LI or ICED-IE (level of evidence: B-C)[15].

Echo is recommended for patients with S.aureus bacteremia (SAB) by 7 out of 9 guidelines.(class of recommendation: IIa, level of evidence: B-C).

Follow-up Echo (no mode was not specified) was advised by 5 out of 9 guidelines after the onset of a suspected IE (class of recommendation: I, level of evidence: B-C). Among them, ESC 2015 and CSC 2015

further make it clear that the clinical manifestations of a complication include new murmur, embolism, persisting fever, heart failure, abscess, and atrioventricular block[10, 14], while SSID 2007 only counts a new or progressive heart failure as the indication for a repeated Echo[11].

For patients under medical therapy, 3 out of 9 guidelines recommended follow-up Echo (class of recommendation: I-IIa, level of evidence: B-C). Besides, the recommended follow-up Echo is only for complicated IE in SSID 2007 (strength of evidence: II C) and IE with suspected development of complications in AHA 2015 (strength of evidence: I B). Moreover, SSID 2007 addressed that TEE is not needed for uncomplicated IE and those with good response to treatment (strength of evidence: II C)[11, 13].

An intraoperative Echo examination for IE patients requiring surgery is recommended by 3 out of 9 guidelines (class of recommendation: I, level of evidence: B-C), and brought up with no formal recommendation by BASC 2011[17]. Moreover, BASC/BHRS 2014 mentioned that patients after IECD removal also need follow-up Echo to identify persisting vegetations (level of evidence: C)[15].

At the completion of antibiotic therapy, TEE is recommended by 6 out of 9 guidelines (class of recommendation: I-IIa, level of evidence: C).

The controversial processing steps in different guidelines' algorithms were shown in Figure 4, and it can be seen that 7 out of 9 guidelines include the recommendation on the first-line modality of suspected IE. Besides, most of the guidelines (6 out of 7) agreed that TTE should be the first choice (class of recommendation: I, level of evidence: B-C) except that SSID 2007 recommended TEE instead[11] (class of recommendation: I, level of evidence: B).

In the case that an initial TEE showed a negative result, as per the recommendation by 6 out of 9 guidelines, a subsequent TEE should be conducted within a given time limit stipulated by different guidelines when suspicion exists without diagnosis of IE (class of recommendation: I, level of evidence: B-C). However, the maximum time limit given by different guidelines varied from 5 to 10 days.

Regarding whether a TEE is needed for suspected IE with a positive TTE, guidelines' replies are based on varied target population features. For example, BASC 2011 suggested that a positive TTE should be considered as the indication for a subsequent TEE (no formal recommendation formulated)[17]. While ESC 2015 and JCS 2015 excluded the unequivocal isolated right-sided native valve IE (class of recommendation: IIa, level of evidence: C)[14, 16]. In the meantime, NHAM 2017 and AHA 2015 advised that TEE was necessary for patients under the concern for complications. NHAM 2017 mentioned that worsening clinical course and high predisposing risk should be included as the indications for TEE (AHA 2015 is with strength of recommendation of I B, and no formal recommendation is formulated in NHAM 2017)[12, 13]. Besides, SSID 2007 and NHAM 2017 recommended not to use a TEE after a positive TTE for the patients with uncomplicated native valve endocarditis (NVE) and low predisposing risk, as well as the patients who have prompt response to treatment (SSID 2007 is with strength of recommendation of IIIc, no formal recommendation is formulated in NHAM 2017)[11, 12].

Discussion

It has been the first time that the controversies among recommendations on the appropriate use of Echo were evaluated combined with AGREE II score of guidelines.

In the 9 guidelines, NHAM 2017 and BHRS 2014 mentioned in the methodology part that the entire content was compiled based on the AGREE II principle, and both of them received a score higher than 60% [12, 15]. However, compared with other guidelines which failed to involve some certain AGREE II items and thus got deducted scores, the superior score of NHAM 2017 largely owes to a more general coverage of items rather than a higher grade of each item. The description referred to Item 19 (facilitators and barriers to the application) and Item 20 (the potential resource) in NHAM 2017 is rather perfunctory without any in-depth content. Though AGREE II items are encouraged to get generally involved during developing guidelines, there is still criticism saying that comprehensive coverage of quantity is just as important as quality.

It should also be noted that, some studies showed that the exposure to information provided directly by pharmaceutical companies had been found to be associated with higher prescribing frequency, higher costs and lower prescribing quality. Therefore, disclosure of Potential COI could be very necessary [19, 20]. Yet it is found that there is no correlation between the proportion of RWI and the AGREE II score involved in the study. This could happen for a variety of reasons, i.e., some guidelines were found to have a high RWI thanks to a more thorough and accomplished disclosure process and less underreporting. For example, ESC has a very detailed COI appendix [14]. On the contrary, it is only mentioned in NHAM 2017 that there is no potential conflict of interest to disclose, and no further detailed relevant content to present. In that case, it cannot be ruled out that the actual RWI proportion of its guideline committee members was concealed and underreported.

Based on the comparison of recommendations and viewpoints of different guidelines, it is found that the algorithms of echocardiography usage given by these guidelines are roughly the same in most cases. Differentiated recommendations are mainly given on more specific clinical scenarios, which are not conflict to each other, but a complement.

As is shown in Figure 4, there are also 3 issues for conflicting views.

The first issue relates to the first-line modality of suspected IE. It was found in a cost-effectiveness analysis that the initial use of TEE was the optimal diagnostic strategy for most suspected patients [21]. SSID 2007 recommended TEE as the first choice for vegetations and complications due to its cost efficiency and higher sensitivity [11], while TTE was recommended by all other guidelines. However, these guidelines recommended TTE for different reasons. AHA 2015 proposed that although TEE was a better choice with higher sensitivity, it was not always available immediately (since a patient did not fast for the preceding 6 hours or the medical institution did not have 24-hour TEE service), therefore a TTE is recommended to be conducted as soon as possible, nonetheless it remains a suboptimal alternative [13]. In addition, there are also other guidelines, like JCS 2017, which recommended TTE for the evaluation of

valve dysfunction and hemodynamics based on its value as well as its feature of non-invasiveness and repeatability[16]. Actually, with the technological progress of echocardiography, TTE was proved to have a sufficient negative predictive value of NVE for in-patients with low to intermediate risk when strict negative criteria are applied[22, 23]. For these low risk patients stratified based on clinical judgment with negative TTE, although few recommendations was made, guidelines proposed in the context or in the algorithm that a TEE was not required[10-14, 16, 17, 24], and this have been verified by the recently published Meta-analyses[25, 26]. In this case, the claim of SSID 2007 is outdated, which says that TEE is better and more cost-effective than TTE as the first-line examination. and SSID was blamed for recommending overuse of TEE as well as citing studies based on obsolete echocardiography methods and lack of hand-on knowledge about echo [27].

For a first-line negative TTE with undiagnosed but high suspicion of IE, a follow-up TEE is fully agreed. However, the maximum time limits given by different guidelines vary from 5 to 7 days. It is known that the severity of pathology distinguished by echocardiography is helpful for the determination of the following management strategy[28]. As per the research, early (<4 days) definitive echocardiography is associated with less embolic events than the later one does[29]. Therefore, time delays to diagnostic Echo should be avoided.

For the most controversial issue of whether a subsequent TEE is mandatory in uncomplicated NVE with initial positive TTE, as is shown in figure 4, NHAM 2017, SSID 2007 and AHA 2015 recommended TEE for all patients expect isolated right-sided NVE[11, 12, 13] while ESC 2015, JCS 2017 and BASC 2011 recommended TEE examination only for those with suspected complications[14, 16, 17]. Therefore, for the patients (with the exception of isolated-right-sided NVE) with no or low risk of complications, which are not uncommon in clinical practice, it is confusing whether TEE examination is necessary. On the one hand, TEE is helpful in evaluating the presence of intracardiac complications, offering prognostic information and helping developing treatment plan. On the other hand, in the case that an initial TTE presents the vegetation clearly, and the probability of complications is low (presented as a small aortic vegetation, mild aortic regurgitation, and normal left ventricular size and function), a subsequent TEE then seems to make no incremental value for the treatment strategy[25], which may lead to the overuse of TEE. However, the recommendation that suggested a subsequent TEE over a positive TTE seems to be less evidence-based and convincing with a recommendation class of IIa which indicates that weight of evidence and opinion is in favor of usefulness and/or effectiveness, and an evidence level of C which refers to only consensus of opinion. Similarly, the evidence strength given by SSID 2007 which explicitly recommended that there was no need to repeat TEE is of C III, which manifests that the evidence to support the recommendation is weak. Therefore, it can be concluded that neither side has sufficient evidence for this issue, and more researches with high evidence level are needed in the future. Besides, for the following reasons, the isolated right-side NVE was excluded from the adapted population recommended by NHAM 2017, SSID 2007 and AHA 2015 who requires a subsequent TEE examination, i.e., the right-sided structure is located anteriorly, which is closer to the TTE transducer than transoesophageal transducer, and hence allows TTE to offer more valuable information. And it was also

because that a subsequent TEE was found to have no additional value for providing new information in isolated right-sided NVE patients[30].

Conclusion

According to AGREE II and compared with guidelines marked with “recommended with modification”, those guidelines marked with “strongly recommended” was more rigorously developed, the recommendations involved in these guidelines could be identified to have better quality. Clinicians could rely on the guideline quality score when evaluating the recommendations for clinical decision making. Besides, it is also expected that later updating of guidelines will lead to a better performance in the domain of “stakeholder involvement”. The main controversy arose from the views of the SSID 2007 with the lowest AGREE II score among all the guidelines may be mainly due to its outdated concepts. For the most contentious issue, i.e., whether a subsequent TEE is mandatory in uncomplicated NVE with initial positive TTE, related studies are rarely seen. Therefore, more researches on this issue, especially those with high evidence level are desired in the future.

Abbreviations

Echo: Echocardiography; IE: Infective endocarditis; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography; AGREE II: APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION II; COI: Conflicts of Interest; RWI: the proportion of panel members with an industry relationship; ICED: Implantable cardiac electronic device; LCED-LI: Implantable cardiac electronic device lead infection; LCED-IE: Implantable cardiac electronic device associated native or prosthetic valve endocarditis.

Declarations

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Authors' contributions

Peihan Xie: Conceptualization, Resources, Writing Original Draft. Xiaodong Zhuang: Conceptualization, Methodology, Formal analysis, Investigation, Supervision. Menghui Liu: Data curation, Writing- Original draft preparation. Shaozhao Zhang: Data curation, Writing- Original draft preparation. Jia Liu: Writing- Original draft preparation. Donghong Liu: Project administration, Supervision. Xinxue Liao: Validation, Supervision, Writing - Review & Editing. All authors read and approved the final manuscript.

PHX, XDZ, and XXL contributed to the study design. PHX and XDZ reviewed the guidelines, DDL re-examined the results, SZZ and MHL performed the statistical analysis, PHX and JL drafted the main manuscript and all authors reviewed and approved the final submitted manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and supplementary information files.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest or personal relationships.

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Figures



Figure 1

Flow diagram of inclusion/exclusion processes for the guidelines



Figure 2

Rader charts of guidelines' AGREE II scores distribution of 6 domains, guidelines were divided into different charts by scale of aggregate score. AGREE II, appraisal of Guidelines for research & evaluation. (right) Guidelines of "strongly recommended" (left) guidelines of "recommended with modification"



Figure 3

Box plot of the AGREE II score distribution comparison between "guidelines strongly recommended" and "guidelines recommended with modification" in different domains. ns: no significant difference. *: significant difference ($P < 0.05$).



Figure 4

Flowcharts for the controversial clinical scenarios. The dotted box presents the recommendations of the dispute. The ratio marked on the arrow represents the number of guidelines made the pointing recommendation. The level of recommendation is indicated in brackets. The darker the background color in the box, the higher the average score of the guidelines that made the recommendation.

Supplementary Files

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