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Review Article

Meta-analysis of the diagnostic accuracy of transesophageal echocardiography for assessment of atherosclerosis in the ascending aorta in patients undergoing cardiac surgery

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Background: Stroke after cardiac surgery may be caused by emboli emerging from an atherosclerotic ascending aorta (AA). Epiaortic ultrasound scanning (EUS), the current 'gold' standard for detecting AA atherosclerosis, has not gained widespread use because there is a lack of optimized ultrasound devices, it lengthens the procedure, it endangers sterility, and there is a false belief by many surgeons that palpation is as sensitive as EUS. Furthermore there is no clear evidence proving that the use of epiaortic scanning changes outcome in cardiac surgery. Various researchers investigated the ability of transesophageal echocardiography (TEE) to discriminate between the presence and absence of AA atherosclerosis. It is acknowledged that TEE has limited value in this, but it has never been supported by a meta-analysis estimating the true diagnostic accuracy of TEE based on all quantitative evidence. We aimed to do this using state-of-the-art methodology of diagnostic meta-analyses.
Methods: We searched multiple databases for studies comparing TEE vs. EUS for detection of atherosclerosis. A random-effects bivariate meta-regression model was used to obtain summary estimates of sensitivity and specificity, incorporating the correlation between sensitivity and specificity as well as covariates to explore heterogeneity across studies.
Results: We extracted six studies with a total of 346 patients, of whom 419 aortic segments were analyzed, including 100 segments with atherosclerosis [median prevalence 25% (range 17–62%)]. Summary estimates of sensitivity and specificity were 21% (95% CI 13–32%) and 99% (96–99%), respectively.
Conclusions: Because of the low sensitivity of TEE for the detection of AA atherosclerosis, a negative test result requires verification by additional testing using epiaortic scanning. In case of a positive test result, AA atherosclerosis can be considered as present, and less manipulative strategies might be indicated.

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Key words: Meta-analysis; diagnostic accuracy; transesophageal echocardiography; atherosclerosis; ascending aorta.

NEUROLOGICAL complications, such as ischemic stroke, occur in 3% of all cardiac operations, accounting for 20% of post-operative deaths after cardiac surgery (1–3). Prevention of stroke after cardiac surgery saves on average $13,019 for mild ischemic strokes and $20,346 for severe ischemic strokes per patient, in direct medical costs of the first 30 days (4). This does not even account for savings after the first 30 days in case of disabling strokes. Peri-operative stroke may be caused by emboli emerging from atherosclerosis in the ascending aorta (AA) to the brain, as the AA is manipulated during cardiac surgery for placement of the aortic cannula and (de)clamping, as well as by the 'sand-blasting' effect due to the aortic cannula flow.

Epiaortic ultrasound scanning (EUS) is the 'gold' standard for detecting atherosclerosis in the AA. Its use, combined with appropriate modification of operative technique when severe atherosclerosis is present, can effectively reduce the incidence of post-operative stroke (5–9). However, EUS has not gained widespread use because there is a lack of optimized ultrasound devices, it would lengthen the surgical procedure, it may endanger the steri-

lity of the surgical field, and there is a false belief by many surgeons that palpation is as sensitive as EUS (10, 11). Finally, there is no clear evidence proving that the use of epiaortic scanning changes outcome in cardiac surgery. Moreover, as it is applied during the operation, decisions regarding surgical strategy are to be made at a late stage. Preferably, such decisions are to be made pre-operatively (12).

Transesophageal echocardiography (TEE) is a minimally invasive and widely available tool that can be used pre-sternotomy and may overcome these limitations (13). However, the distal section of the AA is poorly visualized due to interposition of the trachea between the esophagus and the AA, the so-called 'blind spot'. Various researchers thus investigated the ability of TEE to discriminate between the presence and absence of AA atherosclerosis (10, 14–19). Accordingly, it is often acknowledged that TEE has limited value in this, but it has never been supported by a systematic review or meta-analysis estimating the true diagnostic accuracy of TEE based on all available quantitative evidence. We aimed to do this using state-of-the-art methodology of diagnostic meta-analyses, incorporating the correlation between sensitivity and specificity as well as covariates to explore heterogeneity across studies.

Methods

Search strategy and study selection

Medline (Pubmed), Embase, the Cochrane library, the Database of Abstracts of Reviews of Effectiveness (DARE), and Medion (a database of diagnostic test reviews) were searched from 1966 through January 2006 for publications. We used 'EUS,' and 'TEE' as keywords (see Appendix 1 for search filters) without language restrictions.

We explicitly used EUS as the reference standard, because it is most widely accepted as the best available per-operative diagnostic for the detection of AA atherosclerosis. Magnetic resonance imaging (MRI) and computer-aided tomography scanning (CT scanning) are believed to be superior to TEE in the detection of AA atherosclerosis. Despite extensive search efforts, only one study was found that (quantitatively) compared the accuracy of CT scanning with that of EUS (20). Hence, these modalities could not be included in our meta-analysis. Furthermore, MRI and CT have as yet limited application and availability in the routine care of cardiac surgery patients because they are not capable of providing real-time images of the AA to direct immediate changes in surgical strategy.

Based on titles and abstracts, all studies evaluating TEE for assessment of the AA in cardiac surgery patients were selected. Reference lists from these retrieved studies and related articles identified by MEDLINE were scanned to identify any additional studies. We contacted the authors of the retrieved studies for additional published or non-published studies. Hand searching of topic-specific journals and conference proceedings was not performed. Non-English publications were assessed by observers who had command of the language to allow data extraction from those studies. We eventually included studies comparing TEE with EUS for the assessment of AA atherosclerosis in patients undergoing cardiac surgery that reported the number of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN), and studies from which these numbers could be inferred in our analysis.

Quality assessment

The methodological quality of included studies was independently assessed by two observers (B. v. Z., A. P. N.), and in case of doubt by a methodologist (K. G. M. M.), using the QUADAS-tool in a slightly adapted version (see Table 1 for quality criteria) (21).

The selected items of the QUADAS-tool enabled us to examine potential sources of bias and variation (22). We did not calculate summary scores estimating the overall quality of included studies because it has been shown that their interpretation is problematic and may be misleading (23).

Data extraction

The two observers independently extracted the raw data from the included studies to construct two-by-two contingency tables. Other elements that were extracted included the year of publication, sample size, patient's mean or median age, proportion of male subjects, prevalence of atherosclerosis, and the cut-off point used for TEE and EUS to determine the presence of (clinically relevant) atherosclerosis. Data were considered missing if they were not mentioned explicitly in the text. Discrepancies were resolved by discussion or, if agreement could not be reached, by consultation of a third reviewer (K. G. M. M.).

Table 1

Summary of methodological quality of seven studies on the diagnostic accuracy of transesophageal echocardiography for assessing the ascending aorta for atherosclerosis.

Authors	Cohort study design	Prospective data collection	Consecutive recruitment	Representative patient sample	Selection criteria clearly described	Adequate reference standard	Cross-sectional design	Complete verification of diagnosis	Number of differential verification	Adequate index-test description	Adequate reference-test description	Blinding of index-test results	Blinding of reference test results	Clinical data available as in practice	Uninterpretable/intermediate results reported	Withdrawals explained
Sylivris (14)	+	+	+	+	+	+	+	+	+	−	+	?	?	?	?	+
Davila-Roman (15)	+	+	−	+	−	+	+	+	+	+	+	+	+	−	?	?
Royse (16)	+	+	?	+	−	+	+	+	+	−	−	?	?	?	?	+
Konstadt (18)	+	+	?	+	−	+	+	−	+	+	+	?	?	?	?	?
Konstadt (10)	+	+	?	+	−	+	+	+	+	+	+	+	+	?	+	?
Wilson (19)	+	+	+	+	+	+	+	+	+	+	+	+	+	?	?	?

Columns 4–16 represent 13 of the 16 QUADAS criteria (+, Yes; ?, Unclearly reported; −, No).

To reach a more precise description of the location of atherosclerosis in the AA, the AA is often divided into different segments. This can range from a simple division between the proximal and the distal AA to more complex divisions with multiple (up to 12) different segments. If studies presented multiple two-by-two tables for different segments of the thoracic aorta, we included the data concerning the AA only. When studies provided a per-segment analysis instead of a per-patient analysis, we attempted to contact the first authors of these studies to obtain the original data on a patient level if this could not be inferred from the paper. If authors did not respond or could not provide the data, we included the segmental data in our analysis.

Analysis

We used sensitivity and specificity as our primary measures of association. Sensitivity was calculated by dividing TP by (TP+FN) and specificity by dividing TN by (FP+TN). We first used forest plots to display the precision [95% confidence interval (CI)] by which sensitivity and specificity had been measured in each study, and to illustrate the variation in the estimates between studies. The exact binomial method was used to calculate the 95% CIs of the sensitivity and specificity. We calculated the inconsistency (I^2), which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. This measure may range from 0% to 100%, where 0% means no variation is due to heterogeneity, and 100% means all variation can be explained by heterogeneity.

Until recently, the summary Receiver Operating Characteristic (sROC) was the method of choice for the meta-analysis of studies reporting pairs of sensitivity and specificity. The sROC approach converts each pair of sensitivity and specificity into a single measure of accuracy, the diagnostic odds ratio (DOR). The disadvantage of converting sensitivity and specificity into a single measure of diagnostic accuracy is that it does not discriminate between nor provide insight anymore into the sensitivity and specificity of a test. Distinguishing between these two measures of accuracy is important to determine the optimal use of the test under investigation in clinical practice. With the introduction of the bivariate model it has become possible to meta-analyze estimates of sensitivity and specificity directly, hereby taking into account the inherent correlation between sensitivity and specificity within studies as a result of differences in threshold

(24–26). We thus applied the bivariate model, a random effects model as known from therapeutic meta-analysis, to obtain a valid summary estimate for both sensitivity and specificity of TEE (with 95% CI) (SAS statistical packages version 9.1) (26). Two studies reported only test results per segment, and not a two-by-two table on the patient level (15, 19). By using these segmental data, the 95% CI appears narrower than it should be. Therefore we adjusted these 95% CIs by dividing the standard errors of sensitivity and specificity by the number of segments used.

Finally, we intended to include the following covariates in the model to explore the heterogeneity between studies in sensitivity, specificity, or both: sample size, year of publication, patient mean age, prevalence of atherosclerotic disease, cut-off point of TEE for the presence of atherosclerosis, whether or not a segmental analysis was performed, and the methodological criteria from the adapted QUADAS-tool.

Assessment of publication bias

The validity of a meta-analysis largely depends on minimizing the bias in the identification and selection of the relevant studies. Meta-analytical results will be compromised by publication bias if the retrieved studies have results that significantly differ from relevant studies that are missed (27). To explore the effect of small studies and the possibility of publication bias, we constructed a funnel plot by plotting the natural logarithm of the DOR (lnDOR) against the inverse of the square root of the effective sample size ($1/ESS^{1/2}$), and applied the effective sample size regression test for asymmetry as recommended by Deeks et al (27). The effective sample size regression test uses regression of lnDOR with the $1/ESS^{1/2}$ weighted by ESS to show asymmetry of the funnel plot. A significant test indicates a potential for the presence of publication bias (27).

Results

Search results

Our searches located 310 potentially eligible articles (Fig. 1). After screening titles, 263 studies were excluded. After reviewing the abstracts of the remaining 47 studies, 14 studies remained. Reading these papers and applying the in- and exclusion

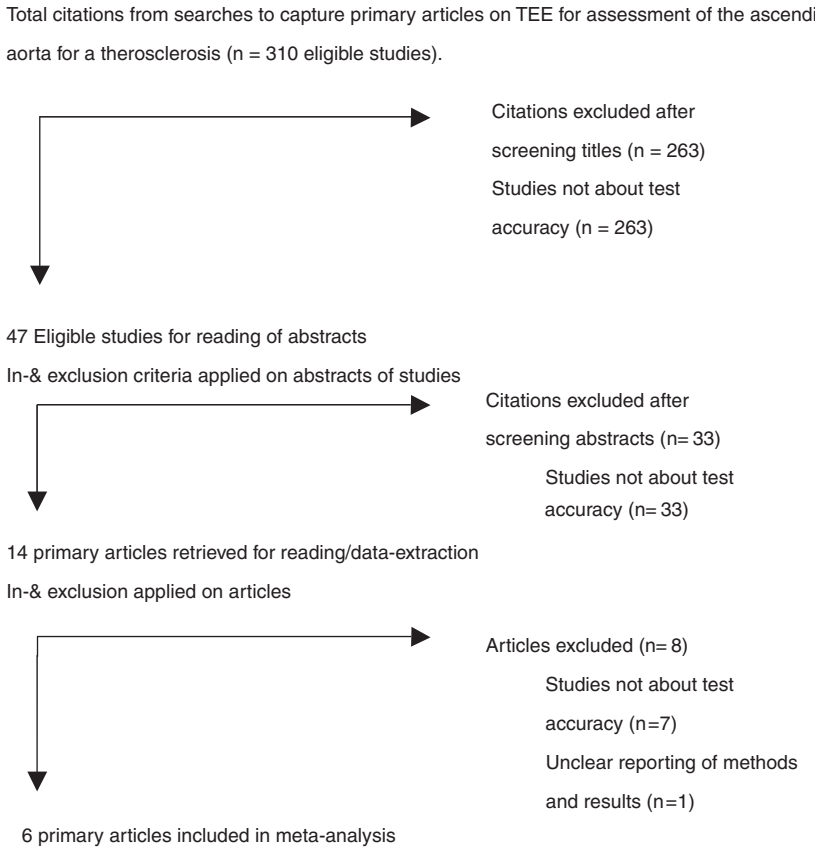

Fig. 1. Flowchart of search results and study inclusion.

criteria yielded seven studies for analysis. One of the seven studies lacked sufficient reporting of major methodological features and was therefore also excluded (Fig. 1) (17). All included studies were published in the English language (10, 14–16, 18, 19). The mean sample size and the number of studied segments of the studies were 52 and 70, respectively. The meta-analysis comprised a total of 346 patients, of whom 419 aortic segments were analyzed, including 100 with atherosclerosis [median prevalence 25% (range 17–43%)]. The mean age across all studies was 68 years and the proportion of male subjects was 72%. Table 1 lists the methodological characteristics and Table 2 lists the demographic characteristics of the included studies. None of the included studies fulfilled all quality criteria. All studies used a prospective cross-sectional cohort design, an adequate reference standard, and a representative patient sample. A clear description of selection criteria was found in only two studies. In the majority of the studies it remained unclear if the observers were blinded to the index-test results, the reference-test results, or the clinical data.

Meta-analysis

All studies divided the thoracic AA in two or more segments. Two studies reported the test result only per-segment and not by a two-by-two table on the patient level (15, 19). The authors of both studies could not provide us the original data to reconstruct a per-patient two-by-two table. Therefore, we included the per-segment data into our analysis for these two studies.

Figure 2 shows the sensitivities and specificities of TEE for the detection of clinically relevant atherosclerosis (as defined by the authors of the included studies) in the distal AA with their 95% CIs. The I^2 was 31.3% and 0.0% for sensitivity and specificity, respectively, showing small heterogeneity of the included studies, for both sensitivity and specificity. Furthermore, Fig. 2 shows that sensitivity varied more across studies and had a lower precision than specificity did.

The bivariate model yielded a summary estimate for the sensitivity of 21% (95% CI 13–32%), and specificity of 99% (96–99%). Figure 3 represents the sensitivity and specificity combination data of the six original studies and the summary estimates of sensitivity and specificity with a 95% confidence ellipse. The 95% confidence ellipse around the summary estimate of sensitivity–specificity shows

Table 2

Demographic characteristics of included studies.

Authors	Year of publication	Number of patients	Mean age (Year)	Male (%)	Pre-valence (%)	Number of segments in analyses	Location of TEE	Location of EUS	Cut-off Point	True positive	False positive	False negative	True negative
Sylivris (14)	1997	100	69	75	28	1	?	PAA/DAA	Intimal thickening >4 mm	3	0	25	72
Davila-roman (15)	1996	44	69	70	25	2	PAA/DAA	PAA/DAA	–	3	0	19	66
Royse (16)	1998	70	66	76	20	1	AA	AA	Intimal thickening >4 mm	4	0	10	56
Konstadt (18)*	1994	29	67	70	43	1	?	?	Intimal thickening >3 mm	0	0	6	8
Konstadt (10)	1995	81	64	70	17	1	AA	AA	Intimal thickening >3 mm	4	1	10	66
Wilson (19)	2000	22	66	73	24	3	?	PAA/DAA	Intimal thickening >2 mm	5	1	11	49

*Partial verification

AA, ascending aorta; DAA, distal ascending aorta; EUS, epiaortic ultrasound scanning; PAA, proximal ascending aorta; TEE, transesophageal echocardiography.

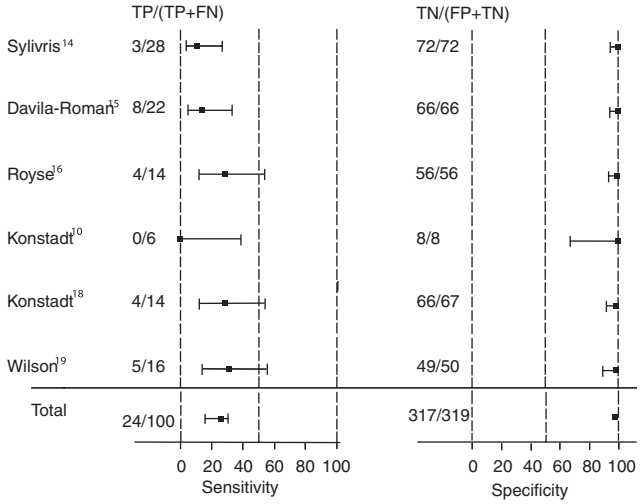

Fig. 2. Forest plot of sensitivities and specificities with 95% confidence interval for transesophageal echocardiography for the detection of ascending aorta atherosclerosis.

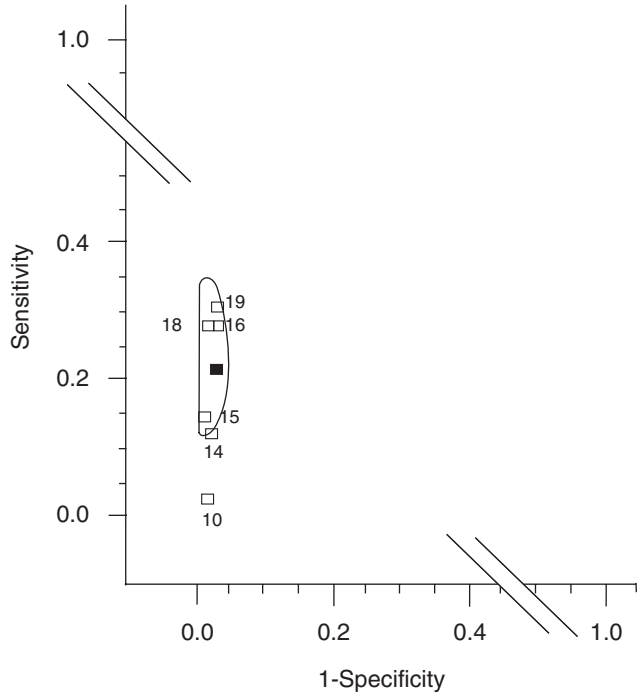

Fig. 3. Sensitivity and specificity of individual studies plotted in receiver operating characteristic space. Black square represents the summary estimate of sensitivity and specificity with the 95% confidence ellipse from the bivariate model. Numbers represent the reference numbers.

the region that contains (with 95% confidence) the true but unknown mean sensitivity and specificity of TEE for the detection of atherosclerosis. The analysis of the impact of study features on diagnostic accuracy was hampered by poor reporting and by the low number of included studies. Therefore, we could only include whether or not a segmental analysis was performed and the cut-off point of the test as a covariate into our bivariate analysis. This did not significantly change the diagnostic accuracy of TEE, yielding the same overall summary estimates for sensitivity and specificity.

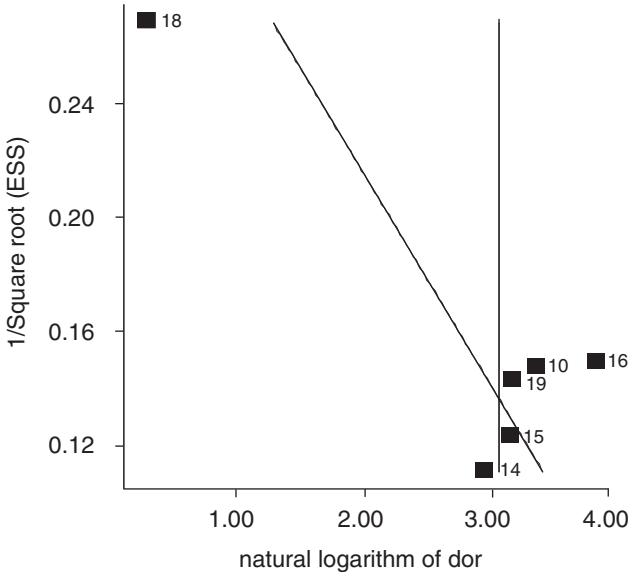

Fig. 4. Funnel plot of the natural logarithm of the diagnostic odds ratio (lnDOR) against the inverse of the square root of the effective sample size ($1/ESS^{1/2}$) of included studies. Regression line (deviation from vertical) is used as a measure of asymmetry. Numbers represent the reference numbers.

Publication bias

If publication bias is absent in a systematic review, it is expected that the lnDor and $1/ESS^{1/2}$ points of the individual studies are evenly distributed around the crude mean DOR (vertical line in Fig. 4), i.e. a symmetric funnel plot. Figure 4 shows that four of the six included studies are at the right side of the crude mean DOR. This is an indication for an asymmetric funnel plot. The diagonal line in the figure indicates the regression line as obtained with the effective sample size regression test. The difference between the two lines is an indication for the presence of some form of sample size effect, most likely due to publication bias (27–29). The *P*-value of the effective sample size regression test was <0.001, confirming possible publication bias. If the outlier in the left upper corner was excluded from the analysis for publication bias, the test remained significant ($P<0.001$), although the line changed in direction. Exclusion of this study from

the bivariate model, however, did not change the overall sensitivity or specificity.

Discussion

We summarized all available quantitative evidence on the diagnostic accuracy of TEE for the detection of clinically relevant atherosclerosis in patients undergoing cardiac surgery, with EUS as the reference standard. In most diagnostic meta-analysis, results are summarized using the DOR or a sROC curve, but such measures are hard to translate or apply to practice. By using the bivariate approach we directly obtained an overall estimate of the (clinically better understood) sensitivity and specificity of TEE for the detection of AA atherosclerosis.

We found that the overall sensitivity of TEE for detection of atherosclerosis of the AA in patients undergoing cardiac surgery was 21% (95% CI 13–32%) and the specificity 99% (96–99%). Hence, routine use of TEE would lead to a false negative test result in 79% of patients with atherosclerosis of the AA. Accordingly, almost all negative results require additional testing with EUS to determine the 'true' presence or absence of AA atherosclerosis. As such, TEE cannot simply replace EUS, although it could be used as a screening or triage tool to detect or include AA atherosclerosis. If TEE is positive, atherosclerosis is almost certain to be present (given the specificity of 99%). The low sensitivity of TEE is most likely due to TEE being unable to show the entire AA because of the so-called 'blind spot' (18). The use of TEE as a screening tool in all patients is only effective when the incidence of atherosclerosis is high enough. We found that the incidence of significant atherosclerosis of the aorta has been reported to vary widely from 1.2% to 28% of the cardiac surgical population, depending on the definition of 'significant' pathology and on the sensitivity of the diagnostic methods. On average, the incidence will be approximately 10–15%; this will be a sufficient incidence to establish some form of screening (EUS or some alternate technology), certainly when taken into account the devastating complications that might be prevented (5, 30–35).

The variation in specificity was small between studies, but the variation in sensitivity was considerable. These variations could partly be explained by the low number of patients with clinical significant atherosclerosis in the studies but could not be attributed to specific study features. Incomplete reporting and the small number and size of the studies hampered the latter analysis.

Limitations of the included studies

The result of a meta-analysis largely depends on the quality of the included studies. Using the QUADAS criteria, we found that the overall methodological quality and reporting of the included studies was fair to poor. Reporting was often incomplete or confusing with respect to study design, patient characteristics, and study outcomes. This severely limited our efforts to introduce covariates into the bivariate model to explain the difference in diagnostic accuracy across the included studies. Sub-optimal methodological quality and incomplete reporting are not unique for the studies we retrieved for our review and occur frequently in diagnostic research (22, 36–39). The STAndards for Reporting of Diagnostic accuracy (STARD) steering committee has proposed guidelines for the conduct and reporting of diagnostic research to improve the quality of diagnostic studies (36). Future studies on diagnostic accuracy should adhere to this concept, if only to facilitate the performance of systematic reviews and meta-analyses and to avoid premature dissemination of diagnostic tests based on over-optimistic results from poorly designed studies (40).

Limitations of the review process

Our review has several limitations. We recognize that our search was limited by the fact that we did not hand-search journals or conference proceedings. As in therapeutic reviews, this could have led to an overestimation of the diagnostic accuracy of TEE. However, there is no empirical data available, specific for diagnostic studies, that shows this overestimation. Our review might also be limited by publication bias or small sample size effects because the test for asymmetry of the funnel plot (Fig. 4) showed a significant result. This asymmetry can be due to various reasons as long as they are related to both sample size and the observed diagnostic accuracy parameters (sensitivity and specificity). The most important reason is publication bias: i.e. in general, small studies with a high estimate of sensitivity and specificity are more likely to be published than large studies with less promising results. Other reasons may be an inadequate search strategy, differences in study

population, poor study quality, and a small number of included studies (41). We are confident that we have minimized the influence by publication bias, by searching multiple databases, and contacting the authors of all included papers. The significant result of the test for asymmetry is therefore more likely to be related to a combination of factors, like the between-study variation, the low number of included studies, and study quality. The fact that the slopes with and without the study outlier are both significant and in a different direction is most likely due to between-study variation and the low number of studies. This was also confirmed by the small I^2. Finally, for two studies we included the per-segment rather than patient data in our analysis. However, we believe that this only had a small effect on our results. There was no significant relation between the use of segmental data and the sensitivity or specificity, as indicated by the non-significant change in sensitivity and specificity when the use of segmental data was included in the bivariate model as a covariate. Furthermore, inclusion of segmental data will lead to a narrower 95% CI. We tried to adjust the 95% CI by dividing the standard error by the number of segments used to overcome this limitation.

Conclusion

We formally meta-analyzed all available evidence on the accuracy of TEE in the detection of AA atherosclerosis. Because of the low sensitivity, a negative TEE result requires verification by additional testing using epiaortic scanning. In case of a positive test result, AA atherosclerosis can be considered as present, and less manipulative surgical strategies such as off-pump surgery might be indicated. Eventually this may reduce the incidence of post-operative stroke.

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Appendix 1: Search filters

Table A1

Search filters

Database	Search filter
Medline 1966 to 2005/11	(epiaort* [tiab] OR 'epicardial' [tiab]) AND ('Echocardiography, Transoesophageal' [MeSH] OR 'TEE' [tiab] OR 'transoesophageal echocardiography' [tiab] OR (Echocardiography [tiab] AND ultraso* [tiab]) OR (intraoperative ultraso* [tiab]))
Embase 1966 to 2005/09	epiaort* AND ('transoesophageal echocardiography' OR TEE OR echocardiography OR (intraoperative AND ultraso*))
Medion 5/11/2005	Circulatory [Icpc_Name] AND Medical imaging [Signs_Name]