Transcranial Doppler versus Transthoracic Echocardiography for the Detection of Patent Foramen Ovale in Patients with Cryptogenic Cerebral Ischemia: A Systematic Review and Diagnostic Test Accuracy Meta-analysis

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Objective: Patent foramen ovale (PFO) can be detected in up to 43% of patients with cryptogenic cerebral ischemia undergoing investigation with transesophageal echocardiography (TEE). The diagnostic value of transthoracic echocardiography (TTE) in the detection of PFO in patients with cryptogenic ischemic stroke or transient ischemic attack has not been compared with that of transcranial Doppler (TCD) using a comprehensive meta-analytical approach.
Methods: We performed a systematic literature review to identify all prospective observational studies of patients with cryptogenic cerebral ischemia that provided both sensitivity and specificity measures of TTE, TCD, or both compared to the gold standard of TEE.
Results: Our literature search identified 35 eligible studies including 3,067 patients. The pooled sensitivity and specificity for TCD was 96.1% (95% confidence interval [CI] = 93.0–97.8%) and 92.4% (95% CI = 85.5–96.1%), whereas the respective measures for TTE were 45.1% (95% CI = 30.8–60.3%) and 99.6% (95% CI = 96.5–99.9%). TTE was superior in terms of higher positive likelihood ratio values (LR+ = 106.61, 95% CI = 15.09–753.30 for TTE vs LR+ = 12.62, 95% CI = 6.52–24.43 for TCD; $p = 0.043$), whereas TCD demonstrated lower negative likelihood values (LR−

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= 0.04, 95% CI = 0.02–0.08) compared to TTE (LR− = 0.55, 95% CI = 0.42–0.72; $p < 0.001$). Finally, the area under the summary receiver operating curve (AUC) was significantly greater ($p < 0.001$) in TCD (AUC = 0.98, 95% CI = 0.97–0.99) compared to TTE studies (AUC = 0.86, 95% CI = 0.82–0.89).
Interpretation: TCD is more sensitive but less specific compared to TTE for the detection of PFO in patients with cryptogenic cerebral ischemia. The overall diagnostic yield of TCD appears to outweigh that of TTE.

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Patent foramen ovale (PFO) can be detected in up to 43% of patients with cryptogenic cerebral ischemia undergoing investigation with transesophageal echocardiography (TEE).[1] PFOs discovered in patients with cryptogenic stroke are more likely to be etiologically associated to the index event, probably via paradoxical embolism, if the patient is younger and without conventional vascular risk factors.[2] Many discovered PFOs, however, are incidental.

Transthoracic echocardiography (TTE) is commonly used in the evaluation and management of cerebrovascular ischemic events. However, there is a great concern that investigation with TTE can fail to identify probable causes of cardioembolism in the majority of patients with ischemic stroke (IS) or transient ischemic attack (TIA).[3] Transcranial Doppler ultrasonography (TCD) is a noninvasive, inexpensive, easily repeatable investigation of the cerebral blood flow that has also been evaluated as a potential screening tool for the detection of a right-to-left shunt (RLS) at the bedside.[4,5]

To the best of our knowledge, the diagnostic yield of TTE in the detection of PFO in patients with cryptogenic IS or TIA has not been compared with that of TCD using a comprehensive meta-analytical approach. We conducted a comprehensive systematic review and meta-analysis using standardized methodology[6,7] that sought to critically compare the diagnostic value of TCD and TTE for PFO detection in patients with cryptogenic cerebral ischemia against the gold standard of TEE.

Materials and Methods

The present systematic review and meta-analysis has adopted the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[8] and was written according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) proposal.[9]

Eligible prospective observational studies that provided both sensitivity and specificity measures of TTE, TCD, or both compared to the gold standard of TEE in the examination of patients with IS or TIA were identified by searching the MEDLINE and SCOPUS databases. The following combination of search strings was used in both database searches: "transesophageal echocardiography", "transthoracic echocardiography", "transcranial Doppler", "ischemic stroke", "transient ischemic attack", and "cerebral ischemia". No language or other restrictions were imposed. The last literature search was conducted on February 23, 2015. Reference lists of all articles that met the inclusion criteria and of relevant review articles were examined to identify studies that may have been missed by the initial database search. All retrieved studies and reference lists were scanned independently by 2 reviewers (A.H.K. and G.T.). Studies were excluded from further evaluation if they were case reports, case series, or retrospective studies, or if they included non-IS/TIA patients as the majority of the study population.

As recommended by the Cochrane Collaboration, the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used to assess the risk of bias of each study that reported both sensitivity and specificity measures.[10,11] Two reviewers (A.H.K. and G.T.) independently evaluated QUADAS-2 items, and all emerging conflicts were resolved by consensus. In each eligible study, true positives, false negatives, true negatives, and false positives of TCD/TTE compared to TEE were independently extracted by the 2 investigators who performed the literature search (A.H.K. and G.T.).

Data Synthesis and Statistical Analysis

Based on the frequencies of true-positive, false-positive, true-negative, and false-negative results in the individual studies, the pooled sensitivity, specificity, diagnostic odds ratio (DOR), and positive (LR+) and negative (LR−) likelihood ratios, as well as the area under the summary receiver operating curve (sROC), with their 95% confidence intervals (CIs), were separately estimated for TCD and TTE (vs TEE, which was treated as the gold standard procedure regarding both techniques). The estimation was based on a generalized linear mixed-model approach to bivariate meta-analysis of sensitivity and specificity.[12,13] Afterward, the DOR and the area under the sROC values were compared between TCD and TTE using the appropriate z tests; the level of statistical significance was set at 0.05.

All statistical analyses were performed with Review Manager (RevMan) version 5.3 software (Copenhagen, Denmark, Nordic Cochrane Centre, Cochrane Collaboration, 2014) and STATA/SE version 13 (Stata Corp, College Station, TX).

Results

Study Selection and Study Characteristics

MEDLINE database search yielded 271 results and SCOPUS database search 470 results. Excluding 182 duplicate studies, the remaining 559 studies were screened for eligibility criteria. Potentially eligible studies for the meta-analysis (n = 43) were retained, after screening both the titles and abstracts of all studies. After retrieving the full-text version of the aforementioned 43

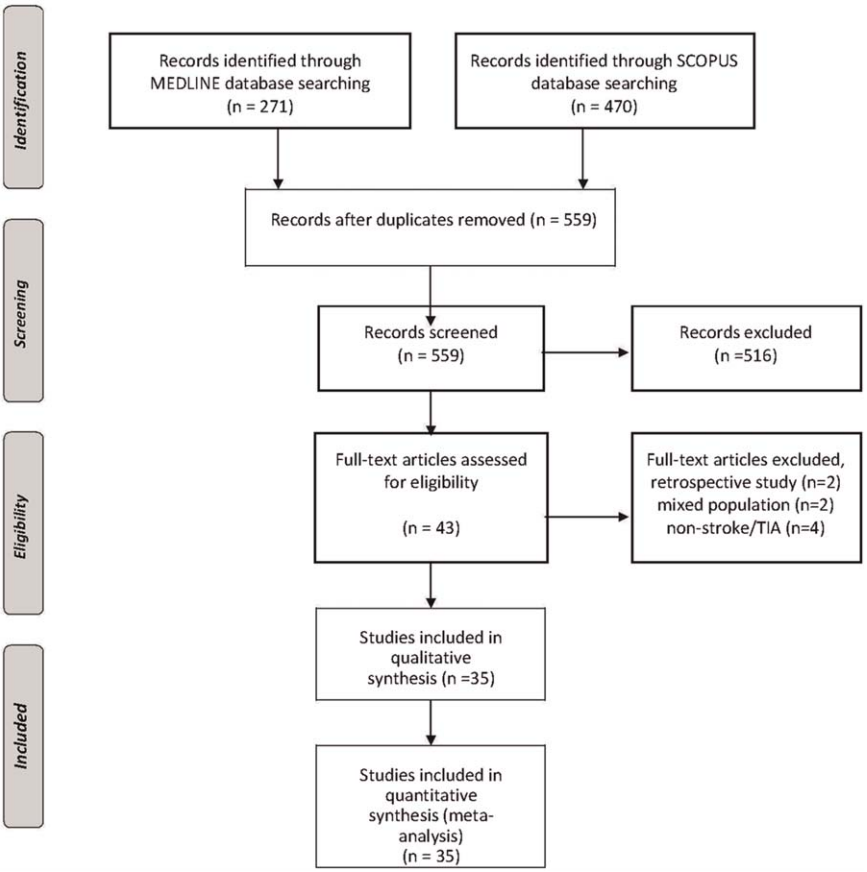

FIGURE 1: Flow chart diagram presenting the selection of eligible studies. TIA = transient ischemic attack.

studies, 8 studies were excluded because they were retrospective cohort studies,[14,15] included mixed population (non-IS/TIA patients as the majority of study population),[16–19] or evaluated exclusively nonstroke patients.[20,21] The remaining 35 studies, comprising 3,067 total patients (89.7% with cryptogenic IS/TIA, mean age = 50 years, 57.3% males), were included in both the qualitative and quantitative synthesis (Fig 1). The characteristics of the included studies are summarized in Table 1,[22–56] and the technical information for the imaging methods used in the included studies are presented in the Supplementary Table.

Quality Assessment

The quality assessment of included studies using QUADAS-2 is presented in Figures 2 and 3. In 20 (57%) of the study protocols, consecutive IS/TIA patients were enrolled, with no inappropriate exclusions after initial recruitment. The risk of bias in patient selection was unclear in the remaining 15 studies, as they did not explicitly report consecutive patient recruitment. In 12 (34%) of the studies, investigators performing the index test (TCD or TTE) were blinded to the results of the reference standard test (TEE). Conversely, investigators performing TEE, as the reference standard, were unaware of the index test results (TCD or TTE) in 21 (60%) of the study protocols. Double blinding in imaging assessment was reported in 12 (34%) of the studies. Risk of bias on flow and timing between the index test and reference standard was categorized as unclear in 26 (74%) of the protocols that did not explicitly state successful investigation with both index and reference tests in all included patients. Regarding applicability, low concerns were found for patient selection, index test, and reference standard.

Quantitative Analysis

From the included study protocols, 24 used TCD as the index test examination, 9 used TTE as the index test examination, and 2 used both TCD and TTE with TEE as reference standard (see Table 1). The sensitivity and specificity values—with the corresponding 95% CIs—were calculated for all included studies. From the visual inspection of the forest plots, no significant heterogeneity was found across different studies for both TCD sensitivity and TTE specificity; however, there was considerable heterogeneity across studies for TCD specificity and TTE sensitivity (Fig 4).

The sROC curves for TCD and TTE are depicted in Figure 5A and B, respectively. The pooled sensitivity

TABLE 1. Characteristics of Included Studies in the Meta-analysis

Authors	Year	Imaging Method	Total Patients	IS/TIA Patients	Mean Age, yr	Males
Albert et al[22]	1997	TCD	69	69	44.0	41%
Belkin et al[23]	1994	TTE	38	31	45.0	61%
Belvís et al[24]	2006	TCD	110	110	56.7	61%
Blersch et al[25]	2002	TCD	40	40	47.9	58%
Caputi et al[26]	2009	TCD	100	80	46.0	41%
de Bruijn et al[27]	2006	TTE	231	231	N/A	N/A
Devuyst et al[28]	1997	TCD	37	37	46.0	62%
Di Tullio et al[29]	1993	TCD/TTE	49	49	63.6	55%
Droste et al[30]	1999	TCD	54	46	44.0	70%
Droste et al[31]	1999	TCD	46	46	47.0	43%
Droste et al[32]	2002	TCD	64	63	47.0	72%
Droste et al[33]	2002	TCD	81	81	48.7	62%
González-Alujas et al[34]	2011	TCD	134	119	46.4	56%
Ha et al[35]	2001	TTE	136	136	59.0	N/A
Hamann et al[36]	1998	TCD	44	44	34.7	41%
Hausmann et al[37]	1992	TTE	198	122	N/A	N/A
Heckmann et al[38]	1999	TCD	45	45	41.4	53%
Horner et al[39]	1997	TCD	45	45	41.0	47%
Jauss et al[40]	1994	TCD	50	40	54.3	74%
Job et al[41]	1994	TCD	137	137	36.0	55%
Karnik et al[42]	1992	TCD	36	30	61.0	55%
Klötzsch et al[43]	1994	TCD	111	111	58.9	69%
Kuhl et al[44]	1999	TTE	111	111	56.0	58%
Madala et al[45]	2004	TTE	71	39	N/A	56%
Maffè et al[46]	2010	TCD	75	75	49.0	37%
Mesa et al[47]	2003	TTE	90	90	38.8	46%
Nemec et al[48]	1991	TCD/TTE	32	20	50.0	44%
Nygren & Jogestrand[49]	1998	TCD	23	23	56.0	70%
Orzan et al[50]	2010	TCD	68	68	49.0	56%
Rahmouni et al[51]	2008	TTE	189	117	59.0	54%
Sastry et al[52]	2009	TCD	39	33	39.0	46%
Serena et al[53]	1998	TCD	208	208	64.8	75%
Siostrzonek et al[54]	1991	TTE	150	99	52	59%
Souteyrand et al[55]	2006	TCD	107	107	56.0	63%
Venketasubramanian et al[56]	1993	TCD	49	49	62.7	55%

IS = ischemic stroke; N/A = not applicable; TCD = transcranial Doppler ultrasonography; TIA = transient ischemic attack; TTE = transthoracic echocardiography.

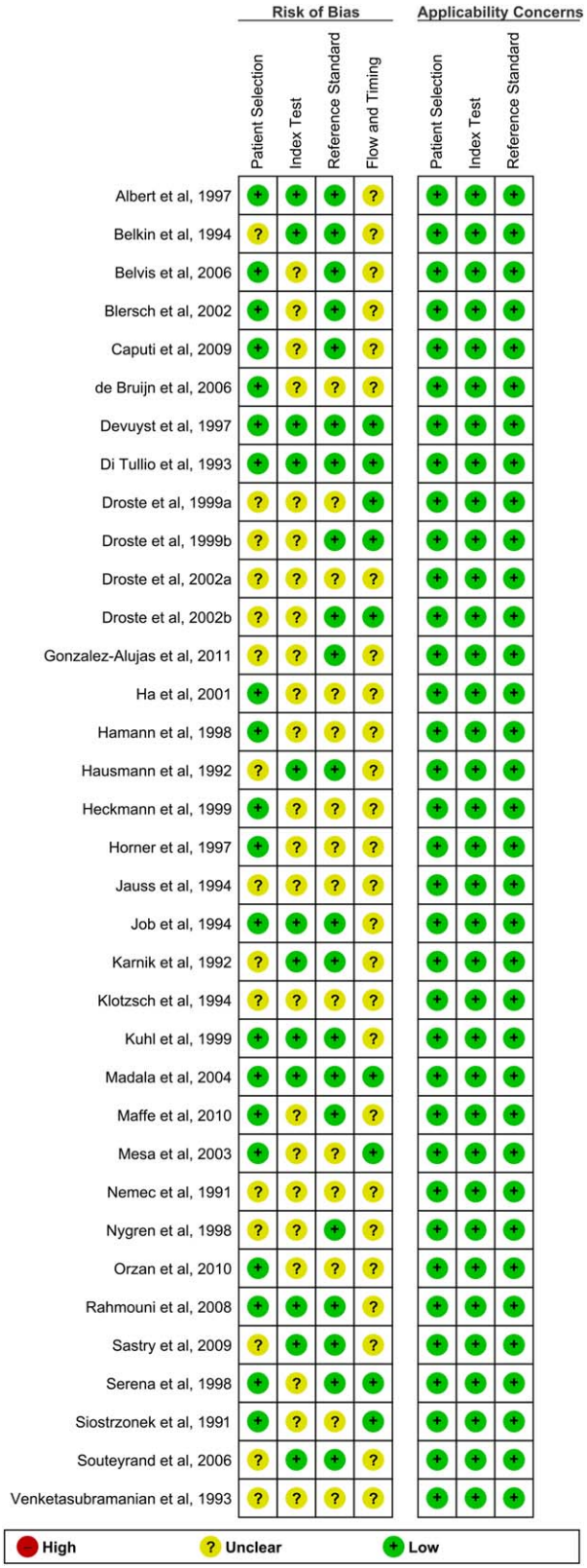

FIGURE 2: Risk of bias and applicability concerns: summary. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

and specificity for TCD were 96.1% (95% CI = 93.0–97.8%) and 92.4% (95% CI = 85.5–96.1%), respectively, whereas the corresponding accuracy parameters for TTE were 45.1% (95% CI = 30.8–60.3%) and 99.6% (95% CI = 96.5–99.9%), respectively. The pooled diagnostic odds ratio for TCD (DOR = 297.97, 95% CI = 131.18–676.83) and TTE (DOR = 193.44, 95% CI = 30.38–1231.67) did not significantly differ between the two techniques (z value = 0.418, p = 0.676; Table 2). Nevertheless, TTE was superior in terms of higher positive likelihood ratio values (LR+ = 106.61, 95% CI = 15.09–753.30 for TTE vs LR+ = 12.62, 95% CI = 6.52–24.43 for TCD; p = 0.043), which is in accordance with the higher specificity values for TTE. Conversely, TCD yielded lower negative likelihood ratio values (LR− = 0.04, 95% CI = 0.02–0.08) compared to TTE (LR− = 0.55, 95% CI = 0.42–0.72; p < 0.001), a finding that reflects the higher sensitivity values for TCD. Finally, the area under the sROC curve (AUC) was significantly greater (p < 0.001) in TCD (AUC = 0.98, 95% CI = 0.97–0.99) compared to TTE studies (AUC = 0.86, 95% CI = 0.82–0.89).

After dichotomizing the available TCD studies according to the insonation method that was used (unilateral middle cerebral artery [MCA] insonation vs bilateral MCA insonation), we documented that unilateral MCA insonation did not lower the diagnostic accuracy statistics of TCD (sensitivity, specificity, LR+, 1/LR−, and AUC) in comparison to bilateral MCA monitoring (Table 3).

In the study protocol by de Bruijn et al,[27] TTE without contrast agent was compared to TEE with contrast agent. Because TTE without contrast agent is considered to have lower sensitivity and specificity for detecting PFO than TTE with contrast agent, we performed additional sensitivity analyses on the available TTE studies after excluding the data from this study (7.5% of the total number of patients included in the meta-analysis) to investigate a potential confounding effect of this study on the cumulative results of the meta-analysis. The diagnostic accuracy statistics (sensitivity, specificity, LR+, 1/LR−, and AUC) of TTE in the overall analysis (including 11 studies) did not differ from those of the sensitivity analysis (including 10 TTE studies after exclusion of the study by de Bruijn et al). These additional analyses are presented in detail in Table 4.

Discussion

Our study showed that TCD is more sensitive but less specific compared to TTE for the detection of PFO in patients with cryptogenic IS or TIA. Moreover, TTE has higher LR+ values than TCD, indicating that a positive

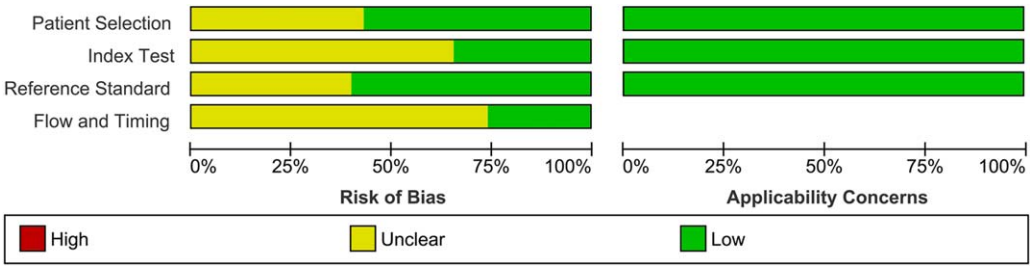

FIGURE 3: Risk of bias and applicability concerns: graph. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

TTE test is reliable in ruling in the diagnosis of PFO. Conversely, significantly lower LR− values were detected in TCD in comparison to TTE, indicating that a negative TCD test is accurate in ruling out the diagnosis of PFO. Taken into account together, the overall diagnostic yield of TCD appears to outweigh that of TTE.

TCD is an established, cost-effective, fast, and valid noninvasive bedside method for the diagnosis and management of

TCD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Albert et al, 1997	25	0	0	33	1.00 [0.86, 1.00]	1.00 [0.89, 1.00]
Belvis et al, 2006	36	0	0	74	1.00 [0.90, 1.00]	1.00 [0.95, 1.00]
Blersch et al, 2002	21	2	2	15	0.91 [0.72, 0.99]	0.88 [0.64, 0.99]
Caputi et al, 2009	61	8	2	29	0.97 [0.89, 1.00]	0.78 [0.62, 0.90]
Devuyst et al, 1997	24	5	0	8	1.00 [0.86, 1.00]	0.62 [0.32, 0.86]
Di Tullio et al, 1993	7	0	2	2	0.78 [0.40, 0.97]	1.00 [0.16, 1.00]
Droste et al, 1999a	18	6	1	29	0.95 [0.74, 1.00]	0.83 [0.66, 0.93]
Droste et al, 1999b	20	10	0	16	1.00 [0.83, 1.00]	0.62 [0.41, 0.80]
Droste et al, 2002a	27	15	0	22	1.00 [0.87, 1.00]	0.59 [0.42, 0.75]
Droste et al, 2002b	29	22	2	28	0.94 [0.79, 0.99]	0.56 [0.41, 0.70]
Gonzalez-Alujas et al, 2011	80	10	2	42	0.98 [0.91, 1.00]	0.81 [0.67, 0.90]
Hamann et al, 1998	6	0	2	36	0.75 [0.35, 0.97]	1.00 [0.90, 1.00]
Heckmann et al, 1999	22	0	4	19	0.85 [0.65, 0.96]	1.00 [0.82, 1.00]
Horner et al, 1997	34	3	1	7	0.97 [0.85, 1.00]	0.70 [0.35, 0.93]
Jauss et al, 1994	14	0	1	35	0.93 [0.68, 1.00]	1.00 [0.90, 1.00]
Job et al, 1994	58	6	7	66	0.89 [0.79, 0.96]	0.92 [0.83, 0.97]
Karnik et al, 1992	13	0	2	21	0.87 [0.60, 0.98]	1.00 [0.84, 1.00]
Klotzsch et al, 1994	42	4	4	61	0.91 [0.79, 0.98]	0.94 [0.85, 0.98]
Maffe et al, 2010	53	1	9	12	0.85 [0.74, 0.93]	0.92 [0.64, 1.00]
Nemec et al, 1991	13	3	0	16	1.00 [0.75, 1.00]	0.84 [0.60, 0.97]
Nygren et al, 1998	10	2	0	9	1.00 [0.69, 1.00]	0.82 [0.48, 0.98]
Orzan et al, 2010	6	15	0	47	1.00 [0.54, 1.00]	0.76 [0.63, 0.86]
Sastry et al, 2009	16	0	0	23	1.00 [0.79, 1.00]	1.00 [0.85, 1.00]
Serena et al, 1998	44	4	0	40	1.00 [0.92, 1.00]	0.91 [0.78, 0.97]
Souteyrand et al, 2006	42	6	0	59	1.00 [0.92, 1.00]	0.91 [0.81, 0.97]
Venketasubramanian et al, 1993	12	0	0	37	1.00 [0.74, 1.00]	1.00 [0.91, 1.00]

TTE

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Belkin et al, 1994	7	2	7	22	0.50 [0.23, 0.77]	0.92 [0.73, 0.99]
de Bruijn et al, 2006	3	0	9	219	0.25 [0.05, 0.57]	1.00 [0.98, 1.00]
Di Tullio et al, 1993	6	0	3	3	0.67 [0.30, 0.93]	1.00 [0.29, 1.00]
Ha et al, 2001	9	0	31	96	0.23 [0.11, 0.38]	1.00 [0.96, 1.00]
Hausmann et al, 1992	15	0	29	154	0.34 [0.20, 0.50]	1.00 [0.98, 1.00]
Kuhl et al, 1999	31	1	20	59	0.61 [0.46, 0.74]	0.98 [0.91, 1.00]
Madala et al, 2004	7	0	2	55	0.78 [0.40, 0.97]	1.00 [0.94, 1.00]
Mesa et al, 2003	4	0	26	60	0.13 [0.04, 0.31]	1.00 [0.94, 1.00]
Nemec et al, 1991	7	1	6	18	0.54 [0.25, 0.81]	0.95 [0.74, 1.00]
Rahmouni et al, 2008	11	3	1	16	0.92 [0.62, 1.00]	0.84 [0.60, 0.97]
Siostrzonek et al, 1991	9	0	21	104	0.30 [0.15, 0.49]	1.00 [0.97, 1.00]

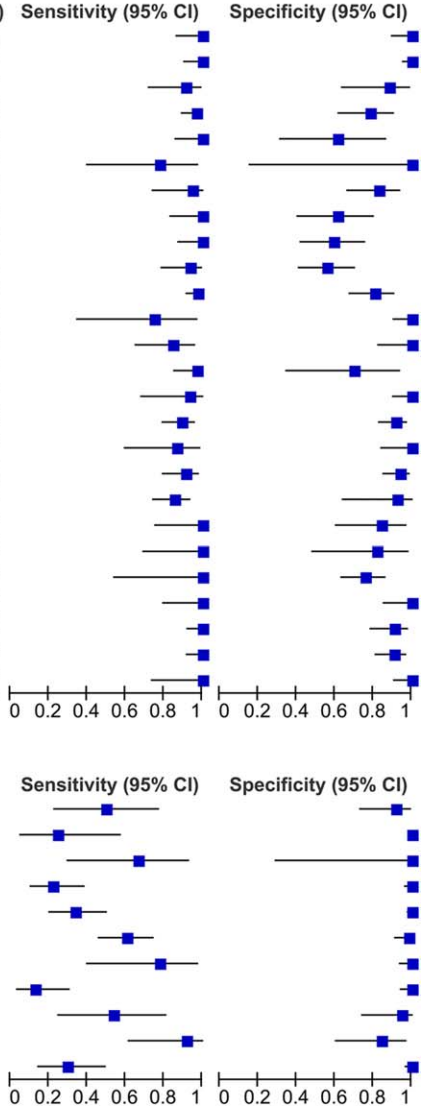

FIGURE 4: Forest plot of individual study results showing estimates of sensitivity and specificity, and exact 95% confidence limits. CI = confidence interval; FN = false negative; FP = false positive; TCD = transcranial Doppler ultrasonography; TN = true negative; TP = true positive; TTE = transthoracic echocardiography. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

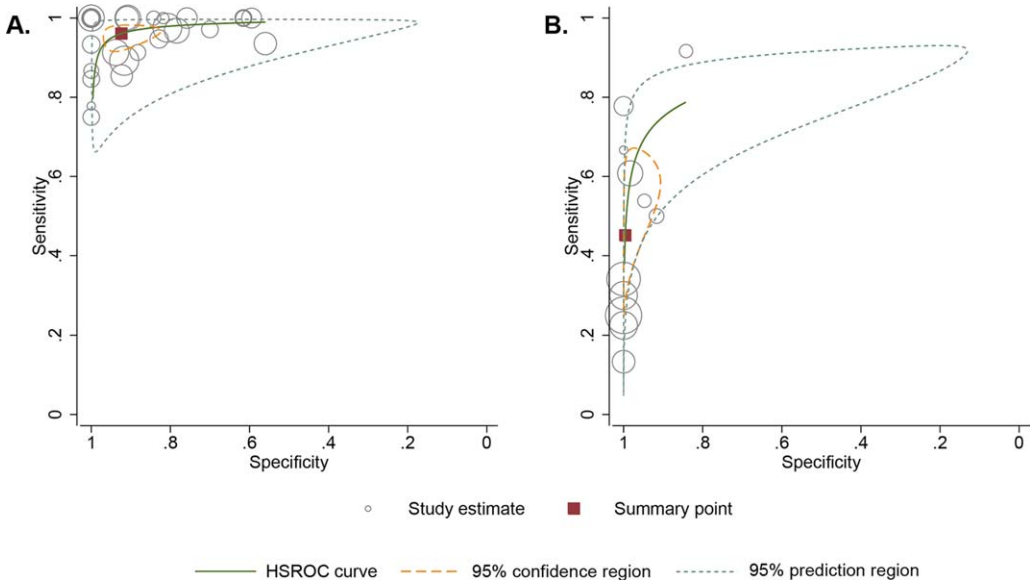

FIGURE 5: Summary receiver operating curve plot of the diagnostic yield of (A) transcranial Doppler and (B) transthoracic echocardiography compared to the gold standard transesophageal echocardiography. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

patients with acute ischemic stroke.[57,58] Not only is TCD examination less expensive than echocardiography, but also patients undergoing TCD detection of RLS can do a calibrated Valsalva maneuver, and the test can be repeated with different body positions.[58] Although there have been scarce reports of ischemic cerebrovascular complications in patients with RLS who underwent TCD bubble study (TCD-BS),[59] a prospective, international, multicenter study reported that TCD-BS was a safe screening test for identification of RLS independent of the presence of cardiac structural abnormalities.[60] Both the International Consensus Criteria (ICC) and the Spencer Logarithmic Scale (SLS) consider RLS present when TCD detects even 1 microbubble, with the SLS criteria having a higher positive predictive value in the detection of large and functional RLS compared to ICC.[61]

Our findings indicate the diagnostic superiority of TCD in comparison to TTE for RLS detection, given that LR+ is >10 both for TCD and TEE, whereas LR− is <0.1 only for TCD but not for TTE. Moreover, the area under the sROC was significantly greater in TCD than in TTE. This finding may be attributed to the following technical advantages of TCD: bedside evaluation in disabled patients, repeat testing in different body positions, increased patient cooperation to perform a calibrated Valsalva maneuver, and high intra- as well as inter-rater reliability for ultrasound detection of RLS.[4,5,59,60] Moreover, the inadequate sensitivity of TTE could also be attributed to poor image quality. Image quality has been improving over the years with technical progress in echocardiographic equipment and as a consequence, more recent studies have reported greater TTE sensitivity than older ones.[62,63] It is thus possible that the differences between TCD and TTE might be reduced when looking at more recent studies, which more closely approach the

TABLE 2. Summary Statistics Regarding the Comparison between TCD (n = 26 Studies) and TTE (n = 11 Studies)

Measure	TCD, Accuracy Parameter (95% CI)	TTE, Accuracy Parameter (95% CI)	*z*	*p*
DOR	297.97 (131.18–676.83)	193.44 (30.38–1,231.67)	0.418	0.676
LR+	12.62 (6.52–24.43)	106.61 (15.09–753.30)	2.027	0.043
LR−	0.04 (0.02–0.08)	0.55 (0.42–0.72)	7.853	<0.001
AUC	0.98 (0.97–0.99)	0.86 (0.82–0.89)	6.461	<0.001

AUC = area under the curve; CI = confidence interval; DOR = diagnostic odds ratio; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; TCD = transcranial Doppler ultrasonography; TTE = transthoracic echocardiography.

TABLE 3. Subgroup Analyses According to the Insonation Method That Was Used in the TCD Studies

Measure	TCD, Unilateral, n = 15, Accuracy Measure (95% CI)	TCD, Bilateral, n = 11, Accuracy Measure (95% CI)	*z*	*p*
DOR	361.57 (126.56–1,033.00)	208.20 (62.23–696.52)	0.676	0.499
LR+	18.32 (8.43–39.82)	6.69 (2.83–15.83)	1.703	0.089
1/LR−	19.73 (10.08–38.63)	31.10 (11.07–87.40)	0.724	0.469
AUC	0.985 (0.970–0.993)	0.982 (0.966–0.991)	0.346	0.729

AUC = area under the curve; CI = confidence interval; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; TCD = transcranial Doppler ultrasonography.

current conditions of PFO detection. Finally, it should be noted that even if RLS is detected by TTE, TEE may still be needed to determine the anatomical lesion responsible for the shunt, as TTE has a low yield in distinguishing between PFO and atrial septal defect, and management options may depend on the TEE clarification of an initially TTE-discovered RLS.[64,65]

Certain limitations need to be taken into consideration for the interpretation of the reported findings. First, although in most studies consecutive patient enrollment was reported, selection bias cannot be ruled out in the studies that used TCD as the index test, due to reports of insufficient temporal window (see Table 1). Apart from operator and interpreter dependency—which are major concerns in all ultrasound examinations—TCD examination is also limited by the absence of temporal "windows," which leads to unsuccessful insonation in 10 to 15% of patients older than 60 years.[66] Second, evidence of possible reporting bias also exists, as double blinding in imaging assessment was reported in only one-third of the protocols that were included in the meta-analysis (see Figs 2 and 3). It should also be noted that TEE is the only diagnostic technique that can accurately discriminate a PFO shunt from an intrapulmonary shunt, as it can directly visualize both the PFO area and the pulmonary veins in real time, that is, while the contrast material is being injected. Both TCD and TTE attempt this distinction on the basis of the timing of appearance of microbubbles in the left atrium/ventricle (TTE) or in the MCA (TCD), a criterion that is tenuous at best and may lead to diagnostic misclassifications.[39,48,67] Moreover, TEE allows exclusion of other causes of ischemic stroke, including atherosclerosis of the aorta, apical thrombus, and more rarely fibroelastomas or atrial myxomas. Third, an adequate Valsalva maneuver is considered crucial for diagnosis of PFO.[68] Although all study protocols reported that all patients underwent Valsalva maneuver during TEE, TTE, or TCD examination, disparities among them were detected in both the duration and the timing of the maneuver across studies. Fourth, the agreement of TCD and TTE with TEE in shunt size quantification was not assessed in the present systematic review/meta-analysis. However, a correct RLS classification can be considered of minor importance, as

TABLE 4. TTE Diagnostic Accuracy Parameters in the Overall Analysis and in the Sensitivity Analysis after Exclusion of the Study by de Bruijn et al[27]

Measure	TTE Overall Analysis,[a] Accuracy Measure (95% CI)	TTE Sensitivity Analysis,[b] Accuracy Measure (95% CI)	*z*	*p*
DOR	193.44 (30.38–1,231.67)	136.83 (26.92–695.40)	0.275	0.783
LR+	106.61 (15.09–753.30)	72.30 (12.69–411.83)	0.291	0.771
1/LR−	1.81 (1.38–2.38)	1.89 (1.40–2.56)	0.208	0.835
AUC	0.86 (0.82–0.89)	0.88 (0.84–0.90)	0.851	0.395

[a]Including all studies (n = 11).
[b]Including the remaining studies (n = 10) after exclusion of the study by de Bruijn et al.[27]
AUC = area under the curve; CI = confidence interval; DOR = diagnostic odds ratio; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; TTE = transthoracic echocardiography.

according to existing data the degree of RLS is not considered to be associated at all—or is associated in a counterintuitive direction—with the risk of future cerebrovascular events in patients with IS/TIA and PFO.[69,70]

In conclusion, TCD appears to be more sensitive but less specific compared to TTE for the detection of PFO in patients with cryptogenic stroke or TIA. Notably, the overall diagnostic yield of TCD appears to outweigh that of TTE and is nearly comparable to that of TEE. Consequently, it is reasonable to use TCD as the initial screening method for RLS detection in patients with cryptogenic cerebral embolism.

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Author Contributions

A.H.K. and G.T. contributed to the conception and design of the study. A.H.K., T.P., T.N.S., and G.T. contributed to the acquisition and analysis of data. All authors contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

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