Transcranial Doppler ultrasound detection of microemboli as a predictor of cerebral events in patients with symptomatic and asymptomatic carotid disease: a systematic review and meta-analysis

Authors

Lawrence M J Best[1]* *BSc*, **Andrew C Webb[2]** *BSc*, **Kurinchi S Gurusamy[1]***MRCS PhD*, **Suk F Cheng[1]***MD*, **Toby Richards[1]***MD FRCS*

Division of Surgery and Interventional Science UCL[1]

74 Huntley Street

London

WC1E 6AU

University College London Medical School[2]

*Corresponding author:

Mr Lawrence M J Best

Division of Surgery and Interventional Science UCL

74 Huntley Street

London

WC1E 6AU

lawrence.best.11@ucl.ac.uk

Category for submission: Review

Word Count: 3,505 (Excluding author information, tables, appendices and references)

Abstract

Introduction – Identification of patients who will benefit from carotid endarterectomy is not entirely effective primarily utilising degree of carotid stenosis. We aimed to determine if microembolic signals (MES) detected by transcranial Doppler ultrasound (TCD) can provide clinically useful information regarding stroke risk in patients with carotid atherosclerosis.

Methods – We performed a meta-analysis of prospective studies. Three analyses were proposed investigating MES detection as a predictor of: stroke or TIA, stroke alone, and stroke or TIA but with an increased positivity threshold. Subgroup analysis was used to compare pre-operative (symptomatic or asymptomatic) patients and peri- or post-operative patients.

Results – 28 studies reported data regarding both MES status and neurological outcome. Of these, 22 papers reported data on stroke and TIA as an outcome, 19 on stroke alone, and 8 on stroke and TIA with increased positivity threshold. At the median pre-test probability of 3.0%, the post-test probabilities of a stroke after a positive and negative TCD were 7.1% (95% CI 5 to 10.1) and 1.2% (95% CI 0.6 to 2.5) respectively. In addition, the sensitivities and specificities of each outcome showed that increasing the threshold for positivity to 10 MES per hour would make TCD a more clinically useful tool in peri- and post-operative patients.

Conclusion – TCD provides clinically useful information about stroke risk for patients with carotid disease and is technically feasible in the majority of patients. However, the generally weak level of evidence constituting this review means definitive recommendations cannot be made.

Keywords – Transcranial Doppler ultrasound; microembolic signals; carotid disease; stroke; transient ischaemic attack

Introduction

Management of patients with internal carotid artery stenosis is founded on statistical evidence provided by three trials: The North American Symptomatic Carotid Endarterectomy Trial (NASCET), European Carotid Surgery Trial (ECST) and Veterans Affairs Cooperative Study (VACS). All used degree of internal carotid artery stenosis as the indicator of stroke risk [(1)]. Results showed definitive benefit for carotid surgery in symptomatic patients with a 70% or greater stenosis [(2)]. This forms the basis of current clinical recommendations; however not all of these patients will benefit from surgicb;lal intervention. Improved quantification of an individual's risk of future stroke would allow better patient selection for intervention.

First established in 1982 [(3)], transcranial Doppler ultrasound (TCD) is an imaging technique used to detect the presence of small particles which may dislodge from an atherosclerotic plaque and flow into cerebral vessels. These microemboli reflect ultrasound more effectively than the surrounding cells giving a characteristic high intensity short duration signal on TCD. It is proposed that the presence of microemboli indicates an unstable or 'vulnerable' carotid plaque which may lead to rupture, thrombus formation or occlusion of the carotid artery resulting in a stroke [(4)]. Data suggest that microembolic signals (MES) recorded by TCD correlate with stroke risk. A potential link between the two has been known about for a long time, resulting in a significant amount of data. None of the studies performed so far have been definitive and therefore summation of the available evidence by meta-analysis will provide a better picture of the current evidence on the degree of correlation between MES on TCD and stroke risk. We performed a formal meta-analysis based on Cochrane methodological standards.

A common criticism of TCD is that increased temporal bone thickness inhibits scanning in a certain proportion of patients. Therefore, we also investigated the incidence of this in the papers selected for meta-analysis.

Objectives

To determine the prognostic accuracy for stroke and/or TIA of MES recorded by TCD ultrasound in patients with carotid atherogenic disease.

To determine the feasibility of TCD ultrasound in patients with carotid disease by quantifying the temporal bone window availability in studies selected for the primary objective.

Materials and Methods

Ethical approval was not required for this paper. We conducted this review in accordance with PRISMA and Cochrane reporting guidelines.

Study selection

A multiple electronic health database search was performed using Medline (PubMed), Embase and The Cochrane Database. This included all prospective studies between 1990 and September 2015 describing the use of TCD and the detection of MES in patients with carotid atherosclerosis.

Search terms used were:
(High intensity transient signals OR microembolic signal OR embolic signal OR transcranial Doppler OR transcranial ultrasound OR transcranial ultrasonography)
AND
(Amaurosis fugax OR transient ischaemic attack OR TIA OR carotid stenosis OR stroke)

Two independent review authors assessed all papers returned by the search using the title and abstract. Any divergence was resolved through discussion. Full articles were selected if the abstract suggested the presence of relevant data. The reference lists of all included studies and previously published reviews were hand searched.

Inclusion criteria

All prospective studies were included, irrespective of blinding, language, publication status or study setting. Any patient with atherosclerosis of the carotid artery, either directly evidenced or suspected as the cause of neurological damage was included in this review.

Data pertaining to microemboli count and stroke and/or TIA was extracted using a physical criteria form. Temporal bone window availability data was extracted where available.

Exclusion criteria

Studies lacking TCD scan results or information of patient cerebrovascular events were excluded. Any papers which indicated the duplication of subjects from previous studies were excluded.

Assessment of methodological quality

Papers were assessed for risk of bias using the QUADAS-2 tool as found in the Revman Cochrane software(5).

Statistical analysis and data synthesis

Three analyses were proposed, all of which assessed the detection of MES by TCD in the middle cerebral artery. These investigated MES detection as a predictor of:

1. Stroke or TIA;
2. Stroke alone; and
3. Stroke or TIA, with a higher positivity threshold (greater than ten microemboli)

Subgroup analysis was proposed to compare pre-operative (symptomatic or asymptomatic) patients and peri- or post-operative patients. Due to the data collected, this was only possible in the stroke or TIA and the stroke only group. Division of patients into symptomatic and asymptomatic groups was also considered, however it would have likely meant that meta-analysis could not be performed because of the repeated division of results by category.

Data was managed using the Cochrane systematic review software, Revman 5.2. Analysis was performed using the METADAS procedure in SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). We used the bivariate random effects model for all analyses. This process was used to produce meta-analysis of data sensitivity, specificity, positive likelihood ratio and negative likelihood ratio. The likelihood ratio expresses the discriminatory value of a diagnostic test. A positive likelihood ratio of greater than five indicates that the test has high discriminatory value, whereas when the positive likelihood ratio approaches one, the test has no diagnostic value. The same is true for the negative likelihood ratio, with a value of 0.2 demonstrating high discriminatory power and a value approaching one representing little to no discriminatory power. The probability of any of the patients included in each analysis suffering an event (the pre-test probability) was calculated and multiplied by the positive and negative likelihood ratio to generate post-test probabilities. A positive post-test probability indicates the percentage chance of a cerebrovascular event in a patient with a positive TCD test for MES. A perfect test has a positive and negative post-test probability of 100 and 0 respectively. We compared pre- and post-test probabilities in order to determine how useful the test is at identifying high risk and low risk patients. Extracted temporal bone window availability data was averaged across all patients scanned.

Results

Selected studies

Three thousand two hundred and twenty-three papers were identified by the original search. This was reduced to 509 on abstract screening and 62 on full text assessment. A total of 28 studies provided data for meta-analysis. A flow diagram representing this can be found in figure 1. Of these, 22 papers, including 3720 patients, reported stroke or TIA as their target condition. Nineteen papers, with 5570 patients, reported stroke as their target condition. Eight papers, with 1414 patients, reported stroke or TIA with a higher positivity threshold as their target condition. Several papers reported data for more than one of the three analyses in the same individuals. Since direct comparison of the different outcomes was not performed, the same data was used in multiple analyses. The characteristics of studies included for meta-analysis can be found in table 1 and table 2.

Methodological quality of included studies

The results of QUADAS-2 assessment of papers are shown in figures 2 and 3. The quality of the evidence was generally low. Over 50% of studies had a high risk of bias for both patient selection and flow and timing sections of the QUADAS-2 protocol. In addition, there is unclear risk of bias for all studies with regards to the reference standard.

Review authors' judgements about each domain presented as percentages across included studies. This graph summarizes the general quality of evidence with over 50% of selected papers at high risk of patient selection and flow and timing bias. Every paper had an unclear risk of bias with regards to the reference standard which is occurrence of stroke with or without TIA. Almost all papers were thought to be applicable to the review question.

Findings

There were three analyses performed. These were of TCD detection of MES as a predictor of: stroke or TIA, stroke alone, and stroke or TIA with increased positivity threshold.

Stroke or TIA

Twenty-two studies reported stroke or TIA as an outcome along with data for TCD recording of microembolic signals with a total of 3720 individual patients (6–26). The sensitivity and specificity were 79.87 (95% CI 63.39 to 90.09)* and 67.07 (95% CI 56.56 to 76.11)* respectively (* = P<0.05). The positive and negative likelihood ratios were 2.43 (95% CI 1.85 to 3.18)* and 0.30 (95% CI 0.16 to 0.55)* respectively. The median pre-test probability for these studies was 6.7%. The corresponding positive and negative post-test probabilities were 14.8% (95% CI 11.7 to 18.6)* and 2.1% (95% CI 1.2 to 3.8)* respectively. The results of the statistical analysis are detailed in table 3. Figure 4 shows how a positive and negative TCD test change the chance of a patient suffering stroke or TIA with a range of pre-test probabilities.

Subgroup analysis stroke or TIA

The same analysis was performed separately for pre-operative patients and peri- and post-operative patients.

For the preoperative group the sensitivity and specificity were 68.73 (95% CI 50 to 82.85) and 79.96 (95% CI 72.24 to 85.95)* respectively. The positive and negative likelihood ratios were 3.43 (95% CI 2.42 to 4.87)* and 0.39 (95% CI 0.23 to 0.66)* respectively. At the median pre-test probability of 6.7%, the post-test probabilities of a positive and negative test were 19.8% (95% CI 14.8 to 25.9)* and 2.7% (95% CI 1.6 to 4.5)* respectively. The full results are summarised in Summary of findings table 1.

For the peri- and postoperative group the sensitivity and specificity were 89.61 (95% CI 70.8 to 96.84)* and 46.38 (95% CI 35.27 to 57.85) respectively. The positive and negative likelihood ratios were 1.67 (95% CI 1.34 to 2.08)* and 0.22 (95% CI 0.07 to 0.67)* respectively. At the median pre-test probability of 6.7%, the post-test probabilities of a positive and negative test were 10.7% (95% CI 8.8 to 13)* and 1.6% (95% CI 0.5 to 4.6)* respectively. The full results are summarised in Summary of findings table 1.

The differences between subgroups were found to be significant with a Chi squared value of 0.001* derived from the differences in log likelihood ratios.

Stroke

Nineteen studies, with a total of 5570 individual patients, reported stroke as an outcome along with data for TCD recording of microembolic signals (7–10,13,16,18–20,23,27–34). The sensitivity and specificity were 73.14 (95% CI 48.16 to 88.86) and 70.27 (95% CI 58.61 to 79.78)* respectively. The positive and negative likelihood ratios were 2.46 (95% CI 1.69 to 3.59)* and 0.38 (95% CI 0.18 to 0.81)* respectively. At the median pre-test probability of stroke of 3.0%, the post-test probabilities of a positive and negative TCD were 7.1% (95% CI 5 to 10.1)* and 1.2% (95% CI 0.6 to 2.5)* respectively.

The full results are summarised in table 4 with a graphical illustration of the corresponding post-test probabilities for various pre-test probabilities shown in figure 5.

Subgroup analysis stroke

The same analysis was performed separately for pre-operative patients and peri- and post-operative patients.

For the preoperative group the sensitivity and specificity were 71.27 (95% CI 41.49 to 89.67) and 83.72 (95% CI 76.61 to 88.98)* respectively. The positive and negative likelihood ratios were 4.38 (95% CI 2.99 to 6.4)* and 0.34 (95% CI 0.15 to 0.81)* respectively. At the median pre-test probability of 3.0%, the post-test probabilities of a positive and negative test were 12% (95% CI 8.6 to 16.7)* and 1.1% (95% CI 0.5 to 2.5)* respectively. The full results are summarised in Summary of findings table 2.

For the peri- and postoperative group the sensitivity and specificity were 78.86 (95% CI 44.75 to 94.5) and 47.43 (95% CI 35.69 to 59.46) respectively. The positive and negative likelihood ratios were 1.5 (95% CI 1.12 to 2.02)* and 0.45 (95% CI 0.15 to 1.35) respectively. At the median pre-test probability of 3.0%, the post-test probabilities of a positive and negative test were 4.5% (95% CI 3.4 to 5.9)* and 1.4% (95% CI 0.5 to 4) respectively. The full results are summarised in Summary of findings table 2 .

The differences between subgroups were found to be significant with a Chi squared value of less than 0.001 derived from the differences in log likelihood ratios.

Stroke or TIA High MES Count

Eight studies, with a total of 1414 individual patients, reported stroke or TIA as an outcome along with data for TCD recording of microembolic signals with high MES counts defined as positive(13,17–19,21,32,33,35). The sensitivity and specificity were 52.38 (95% CI 30.59 to 73.29) and 90.07 (95% CI 83.72 to 94.12)* respectively. The positive and negative likelihood ratios were 5.27 (95% CI 2.73 to

10.17)* and 0.53 (95% CI 0.33 to 0.85)* respectively. At the median pre-test probability of 3.1%, the post-test probabilities of a positive and negative TCD were 14.4% (95% CI 8 to 24.5)* and 1.7% (95% CI 1.0 to 2.7)* respectively. The full results are summarised in table 5 with a graphical illustration of the corresponding post-test probabilities for various pre-test probabilities shown in figure 6.

Temporal Bone Window

Thirteen studies reported data relating to temporal bone window availability with a total of 2400 patients. These papers showed an average of 89.0% of patients had a thin enough temporal bone for scanning.

Discussion

This review investigates whether TCD examination could play a clinically useful role in assessing the risk of stroke in patients with carotid disease. To do so it must differentiate between patients at high and low risk of future events.

Quality of Evidence

The general quality of the evidence was low. There were methodological issues with patient selection because of the observational nature of the data. Technical issues resulted in exclusions of patients which affected both patient selection and flow and timing (figure 2 and 3). For every study the risk of bias arising from the reference standard was unclear because it was generally unclear if the test was interpreted with or without knowledge of whether the patient suffered a stroke or TIA. Spence et al. 2005, Spence et al. 2010 and Siebler et al. 1995 used two microemboli as positivity rather than one, and Sun et al. 2014 had TCD recordings for 30 minutes rather than an hour [5-8]. Whilst unlikely to skew the data it should be taken into account when interpreting results. Because of these issues the quality of evidence is low which should be considered when interpreting the results.

Stroke or TIA

The results are all statistically significantly different from a test which provides no useful information, i.e. a ‘fifty/fifty’ guess, therefore TCD does provide clinically useful information. As stated earlier the

low quality of evidence means these findings should be viewed cautiously. In addition, the important question is how much information is gained and whether this is enough to recommend its use. The nature of available evidence does not provide appropriate data for answering this question. To definitively quantify how useful a test is direct comparison with all alternative tests should be performed.

The differences between studies with and without the covariate were found to be significant with a Chi squared value of 0.00045* derived from the differences in log likelihood ratios. This means that TCD has a different ability to predict stroke or TIA in preoperative patients and peri or postoperative patients. Recording done in peri or postoperative patients has superior sensitivity however the specificity is reduced. This is unsurprising as MES counts tend to be very high during surgery and in the immediate postoperative period because of the physical stress exerted on the plaque as well as iatrogenic sources of emboli. In this period the baseline number of microemboli that indicates high risk of plaque rupture is raised. This will result in fewer false negatives but more false positives as more patients will have microemboli. To take into account the differences between these two groups of patients it may be preferable to raise the baseline for positivity by requiring a certain microemboli rate before defining a peri- or post-operative patient as microemboli positive.

Stroke

TCD's specificity for predicting stroke was shown to be statistically significant. Sensitivity had a confidence interval which included 50 and therefore did not provide useful information in this regard. Further investigation is required to conclusively prove the utility of TCD in predicting stroke alone. This result is particularly important because prediction of stroke is clinically much more important than predicting stroke or TIA, as TIA is itself the gold standard for stroke prediction. What will actually save lives and brain function is the prediction of stroke not the prediction of TIA. Further investigation with stroke as the outcome alone is important.

Subgroup analysis again revealed that TCD has a statistically significantly different ability to predict stroke in preoperative compared to peri or postoperative patients with a chi squared value less than

0.001. The same pattern emerges with decreased specificity in peri or postoperative patients but increased sensitivity, which provides validation of the data analysed because of the logical explanation for this repeated pattern.

Stroke/TIA with high MES count

Stroke or TIA with a high MES count for positivity threshold had a low sensitivity but high specificity (summary of findings table 3). The low sensitivity but high specificity is unsurprising due to the high baseline number of MES required for positivity meaning some patients with a few MES but not enough to be considered positive who have a stroke or TIA may be missed, however when a patient does have enough MES to be considered positive they are highly likely to suffer an event. It may be hypothesised that raising the baseline for MES positivity is most effective in peri- and post-operative patients. Unfortunately subgroup analysis was not possible for this outcome because the fixed effects bivariate model was considered inappropriate and using a random effects model makes covariate analysis unreliable.

Strengths and weaknesses of the review

King & Markus 2009 is the main review for comparison [(36)]. There is general overall agreement in both stroke and TIA and stroke as outcomes being predicted by MES presence. For the high MES threshold analysis King and Markus included papers with widely varying definitions of high microemboli rate and therefore included considerably more papers than the current review. This enabled them to find statistical significance in all subgroups. The heterogeneity which would be expected when included such a diverse number of studies may have been masked by the fact that the majority of papers reported no false positives which will cause the results to produce statistically similar odds ratios.

The interval between MES recording and start of symptoms has not been taken into account in the analysis. This may provide further useful information when interpreting TCD results, however it was not considered within the scope of this study. Anti-platelet therapy may provide an additional confounder, as it is hypothesised that it may impact the number of MES. It was not investigated as

current evidence indicates that number of MES may not be changed by antiplatelet therapy(37), however if this were to change, the implications for use of TCD will be significant.

Applicability of findings to the review question

This review included a wide variety of patients. The evidence proves that TCD is predictive of stroke and TIA in both preoperative and peri and postoperative patients separately. TCD provides predictive information for stroke and for preoperative patients. There is not enough evidence to demonstrate that TCD provides predictive information for stroke in peri and postoperative patients because of a low specificity. It is unclear if there is genuinely too low a specificity for TCD to provide useful information in these patients. The low quality of evidence and number of studies means more high quality studies are required to explore this further.

Conclusions

This review demonstrates that TCD provides useful clinical evidence for the prediction of stroke and TIA. The weakness of the current evidence base means that more work is necessary in order to incorporate TCD into assessment of patients with carotid disease.

The low level of evidence means large scale randomised control trials are required to establish TCD as an effective adjunct indicator of stroke along with carotid stenosis. Until clinical benefit over current predictors can be conclusively proved and quantified TCD cannot be adopted into clinical guidelines and therefore will not be universally applied. Future carotid trials need to establish a series of indicators which can be compiled into an accurate risk score of future stroke for each patient. Such indicators would include stenosis, TCD and physical plaque characteristics. An effective risk score for all patients with carotid disease will expedite the stroke response pathway which currently requires multidisciplinary collaboration because of the qualitative nature of alternative risk factors besides stenosis. Fast and effective risk assessment will enable a decrease in time from symptoms to surgery, ensuring the best possible patient outcome.

Acknowledgements

Professor Martin Brown and Dr Anne Huibers.

There are no sources of funding for the research discussed in the study .

There is no conflict of interest.

Abbreviations and symbols

* statistical significance at the 95% confidence level when compared to random chance

< indicates a number which whilst it rounds to a non-significant value the number itself is actually significant i.e. if the significance threshold is 1 0.99 will round up to 1.0 however it is still significant to a 95% confidence level.

References

1. Imparato a M, Riles TS, Mintzer R, Baumann FG. The importance of hemorrhage in the relationship between gross morphologic characteristics and cerebral symptoms in 376 carotid artery plaques. Ann Surg [Internet]. 1983 Feb;197(2):195–203. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1353109&tool=pmcentrez&rendertype=abstract
2. Rothwell PM, Eliasziw M, Gutnikov S a, Fox a J, Taylor DW, Mayberg MR, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet [Internet]. 2003 Jan 11;361(9352):107–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12531577
3. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg [Internet]. Journal of Neurosurgery Publishing Group; 1982 Dec 8 [cited 2014 Mar 16];57(6):769–74. Available from: http://thejns.org/doi/abs/10.3171/jns.1982.57.6.0769?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
4. Lusis AJ. Atherosclerosis. Nature. 2000;407(6801):233–41.
5. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med

[Internet]. American College of Physicians; 2011 Oct 18 [cited 2014 Sep 5];155(8):529–36. Available from: http://annals.org/article.aspx?articleid=474994

6. Abbott AL, Chambers BR, Stork JL, Levi CR, Bladin CF, Donnan GA. Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: a multicenter prospective cohort study. Stroke [Internet]. 2005 Jun [cited 2013 Nov 10];36(6):1128–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15879327

7. Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol. 2010;9:663–71.

8. Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. Stroke. 1999;30:1440–3.

9. Orlandi G, Fanucchi S, Sartucci F, Murri L. Can microembolic signals identify unstable plaques affecting symptomatology in carotid stenosis? Stroke. 2002/07/10 ed. 2002;33(7):1744–6.

10. Siebler M, Nachtmann A, Sitzer M, Rose G, Kleinschmidt A, Rademacher J, et al. Cerebral microembolism and the risk of ischemia in asymptomatic high-grade internal carotid artery stenosis. Stroke [Internet]. 1995/11/01 ed. 1995;26(11):2184–6. Available from: http://stroke.ahajournals.org/content/26/11/2184.long

11. Spence JD, Tamayo A, Lownie SP, Ng WP, Ferguson GG. Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis. Stroke [Internet]. 2005 Nov [cited 2013 Nov 10];36(11):2373–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16224084

12. Zhang C, Qu S, Li H, Li G, Chen G, Wang J, et al. Microembolic signals and carotid plaque characteristics in patients with asymptomatic carotid stenosis. Scand Cardiovasc J. 2009/10/30 ed. 2009;43(5):345–51.

13. Censori B, Partziguian T, Casto L, Camerlingo M, Mamoli a. Doppler microembolic signals predict ischemic recurrences in symptomatic carotid stenosis. Acta Neurol Scand [Internet]. 2000 May;101(5):327–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10987322

14. Liu X, Xu Y, Wang J, Zhu Y, Ma X. Analysis on the clinical value of general combined epidural anesthesia in esophageal cancer surgery. [Chinese]. Anti-Tumor Pharm [Internet]. 2013;3(6):455–8. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/700/CN-00979700/frame.html

15. Markus HS, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. Stroke. 2005/04/09 ed. 2005;36(5):971–5.

16. Valton L, Larrue V, Pavy Le Traon A, Geraud G. Cerebral microembolism in patients with stroke or transient ischaemic attack as a risk factor for early recurrence. J Neurol Neurosurg Psychiatry. 1998/01/07 ed. 1997;63(6):784–7.

17. Ackerstaff RG, Jansen C, Moll FL, Vermeulen FE, Hamerlijnck RP, Mauser HW. The significance of microemboli detection by means of transcranial Doppler ultrasonography monitoring in carotid endarterectomy. J Vasc Surg. 1995/06/01 ed. 1995;21(6):963–9.

18. Ogasawara K, Suga Y, Sasaki M, Chida K, Kobayashi M, Yoshida K, et al. Intraoperative microemboli and low middle cerebral artery blood flow velocity are additive in predicting development of cerebral ischemic events after carotid endarterectomy. Stroke. 2008/08/09 ed. 2008;39(11):3088–91.

19. Wolf O, Heider P, Heinz M, Poppert H, Sander D, Greil O, et al. Microembolic signals detected by transcranial Doppler sonography during carotid endarterectomy and correlation with serial diffusion-weighted imaging. Stroke. 2004/09/25 ed. 2004;35(11):e373–5.

20. Laman DM, Wieneke GH, van Duijn H, van Huffelen AC. High embolic rate early after carotid endarterectomy is associated with early cerebrovascular complications, especially in women. J Vasc Surg. 2002/08/10 ed. 2002;36(2):278–84.

21. Abbott AL, Levi CR, Stork JL, Donnan GA, Chambers BR. Timing of clinically significant microembolism after carotid endarterectomy. Cerebrovasc Dis. 2007/02/03 ed. 2007;23:362–7.

22. Gao MY, Sillesen HH, Lorentzen JE, Schroeder T V. Eversion carotid endarterectomy generates fewer microemboli than standard carotid endarterectomy. Eur J Vasc Endovasc

Surg. 2000/08/16 ed. 2000;20(2):153–7.

23. Levi CR, Roberts AK, Fell G, Hoare MC, Royle JP, Chan A, et al. Transcranial Doppler microembolus detection in the identification of patients at high risk of perioperative stroke. Eur J Vasc Endovasc Surg. 1997/11/05 ed. 1997;14(3):170–6.

24. Tytgat SH, Laman DM, Rijken AM, Klicks R, Voorwinde A, Ultee JM, et al. Emboli rate during and early after carotid endarterectomy after a single preoperative dose of 120 mg acetylsalicylic acid--a prospective double-blind placebo controlled randomised trial. Eur J Vasc Endovasc Surg. 2005/01/15 ed. 2005;29(2):156–61.

25. Altaf N, Kandiyil N, Hosseini A, Mehta R, MacSweeney S, Auer D. Risk factors associated with cerebrovascular recurrence in symptomatic carotid disease: a comparative study of carotid plaque morphology, microemboli assessment and the European Carotid Surgery Trial risk model. J Am Heart Assoc. England; 2014 Jun;3(3):e000173.

26. Droste DW, Ritter M, Kemeny V, Schulte-Altedorneburg G, Ringelstein EB. Microembolus detections at follow-up in 19 patients with acute stroke: correlation with stroke etiology and antithrombotic treatment. Cerebrovasc Dis. 2000/07/06 ed. 2000;10(4):272–7.

27. Madani A, Beletsky V, Tamayo A, Munoz C, Spence JD. High-risk asymptomatic carotid stenosis: Ulceration on 3D ultrasound vs TCD microemboli. Neurology. 2011;77:744–50.

28. Spence JD, Coates V, Li H, Tamayo A, Muñoz C, Hackam DG, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. Arch Neurol [Internet]. 2010 Feb;67(2):180–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20008646

29. Liu WS, Zhu SF, Liu WF, Li GL, Jiang HQ. Relationship between microemboli in the internal carotid artery and the occurrence of ischemic stroke after transient ischemic attack. J Clin Neurosci. 2013/07/23 ed. 2013;20(10):1366–70.

30. van Zuilen E V, Moll FL, Vermeulen FE, Mauser HW, van Gijn J, Ackerstaff RG. Detection of cerebral microemboli by means of transcranial Doppler monitoring before and after carotid endarterectomy. Stroke. 1995/02/01 ed. 1995;26(2):210–3.

31. Ackerstaff RG, Moons KG, van de Vlasakker CJ, Moll FL, Vermeulen FE, Algra A, et al. Association of intraoperative transcranial doppler monitoring variables with stroke from carotid endarterectomy. Stroke. 2000/08/06 ed. 2000;31(8):1817–23.

32. Golledge J, Gibbs R, Irving C, Clayton G, Bond D, Greenhalgh RM, et al. Determinants of carotid microembolization. J Vasc Surg. 2001/12/18 ed. 2001;34(6):1060–4.

33. van der Schaaf IC, Horn J, Moll FL, Ackerstaff RG. Transcranial Doppler monitoring after carotid endarterectomy. Ann Vasc Surg. 2005/02/17 ed. 2005;19(1):19–24.

34. Sun DJ, Zhuang AX, Zeng QH, Jiang YL, Jiang JD, Feng SQ, et al. A study of microemboli monitoring of atherosclerotic thrombotic cerebral infarction and artery stenosis. Genet Mol Res. 2014 Jan;13(3):6734–45.

35. Saedon M, Dilshad A, Tiivas C, Virdee D, Hutchinson CE, Singer DRJ, et al. Prospective validation study of transorbital Doppler ultrasound imaging for the detection of transient cerebral microemboli. Br J Surg. England; 2014 Nov;101(12):1551–5.

36. King A, Markus HS. Doppler embolic signals in cerebrovascular disease and prediction of stroke risk: a systematic review and meta-analysis. Stroke. 2009/10/24 ed. 2009;40(12):3711–7.

37. de Borst GJ, Hilgevoord AA, de Vries JP, van der Mee M, Moll FL, van de Pavoordt HD, et al. Influence of antiplatelet therapy on cerebral micro-emboli after carotid endarterectomy using postoperative transcranial Doppler monitoring. Eur J Vasc Endovasc Surg. 2007/05/25 ed. 2007;34(2):135–42.

38. Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium. Basic identification criteria of Doppler microembolic signals. Stroke. 1995; 26: 1123.

39. MP Spencer, GI Thomas, SC Nicholls, LR Sauvage. Detection of middle cerebral artery emboli during carotid endarterectomy using transcranial Doppler ultra-sonography. Stroke, 21 (1990), pp. 415–423.

40. Ringlestein EB, Droste DW, Babikian VL, Evans DH, Grosset DG, Kaps M, Markus HS, Russell D, Siebler M. International Consensus Group on Microembolus Detection. Consensus on

microembolus detection by TCD. Stroke. 1998;29:725–729.

41. Markus HS, Molloy J. The use of a decibel threshold in the detection of embolic signals. Stroke. 1997;28:692–695.

42. Ackerstaff R, Babikian V, Georgiadis D, Russell D, et al. (1995). Basic identification criteria of Doppler microembolic signals. Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium. Stroke 26: 1123