Role of transcranial colour-coded duplex sonography in stroke management

Review article

Richard B. Olatunji[1], Godwin I.Ogbole[1], Omolola M. Atalabi[1], Abiodun O. Adeyinka[1], Ikeola Lagunju[2] Alexander Oyinlade[2],Olufunmilola Ogun[3], Mayowa O. Owolabi[4], Oluremi A.Ogunseyinde[1], Adesola Ogunniyi[4].

[1]*Department of Radiology, University of Ibadan, Nigeria,* [2]*Department of Paediatrics, University of Ibadan, Nigeria* [3]*Department of Medicine, University of Ibadan, Nigeria,* [4]*Department of Ophthalmology , University of Ibadan, Nigeria.*

Abstract

The development of transcranial colour-coded duplex sonography (TCCS) has resurrected the hope of safe, real time bedside brain imaging beyond childhood. This review article provides an overview of the role of TCCS in the management of patients with stroke. The objective is to stimulate interest in the field of neurosonology as a potential means of improving neurological outcome for stroke patients and a area for stroke research endeavors in Africa. Literature search was done on MEDLINE, Cochrane library, and Google Scholar databases with the following keywords: transcranial colour Doppler, Transcranial duplex sonography, transcranial colour-coded Doppler sonography, stroke, infarct and haemorrhage. We also identified relevant articles from the references section of studies produced by our literature search. We discussed the roles of TCCS to discriminate ischaemic from haemorrhagic forms; unravel the mechanism of stroke; monitor temporal evolution of stroke and predictors of stroke outcome; and promote better understanding of the epidemiology of stroke. Its emerging role as a potent point-of-care imaging modality for definitive treatment in ischaemic stroke within and outside the hospital setting is also highlighted. Comparison of TCCS with alternative modalities for neuroimaging in stroke is also discussed. A root cause analysis of the untenable high cost of neuroimaging for stroke patients in Africa is presented vis-à-vis the potential economic relief which widespread adoption of TCCS may provide. We advocate capacity building for TCCS and suggest some action plans required to achieve safe, cheap, affordable and reliable ultrasound based neuroimaging for stroke patients in resource limited areas of Africa.

Corresponding Author
Godwin I. Ogbole
Department of Radiology, University of Ibadan, Nigeria
Email: gogbole@yahoo.com

Keywords: Transcranial Sonography, Stroke, Ultrasound, Doppler, Resource Poor setting, Transcranial Colour Doppler,

Introduction

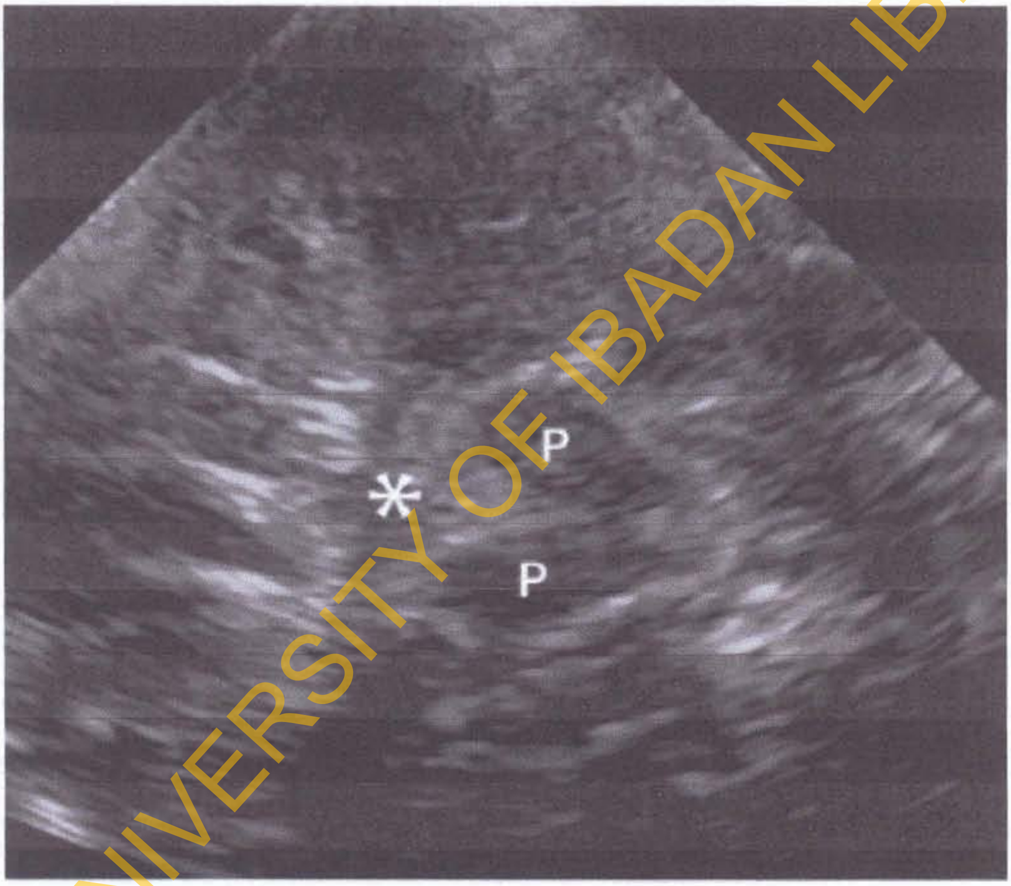
The successful insonation of intracranial blood vessels via the skull was reported by Aaslid and coworkers in 1982 when the term transcranial Doppler (TCD) was introduced into the literature.[1] TCD entails the application of low frequency ultrasound (US) wave through a thin aspect of the skull and at various depths of insonation to obtain Doppler signals from the blood vessels at the skull base. Further improvements in the technology of TCD enabled its wide range of application as seen in clinical practice today.[2] The limitations of TCD such as its reliance on indirect parameters to identify blood vessels, poor spatial resolution, non-visualization of anatomical landmarks, inaccurate blood velocity metrics, and misclassification of specific blood vessels in the presence of normal anatomical variants formed the basis for the invention of TCCS.[3]

Brightness mode (B-mode) and Doppler US capabilities were added to the conventional TCD by Schoning et al in the late 1980s to overcome some of the known shortcomings of TCD.[4] In its earliest documented application, TCCS was successfully done on 49 out of 52 adult subjects examined by Bogdahn et al in 1990- the group widely credited as the first to use TCCS in adults[3]. The image quality of TCCS has been enhanced greatly since then by technological advancement in transducer design, computational capabilities; better sonographic contrast materials; and recent introduction of molecular imaging.[5,6] A low frequency (2-to 3-MHz) linear transducer applied to the pterion is recommended by the American institute of ultrasound in medicine (AIUM) to produce good transtemporal sonograms of the brain (figure 1,2).[7]

TCCS has therefore emerged as a safe, cheap, non-invasive, fast, portable, bedside real-time neuroimaging modality for the evaluation and follow-up monitoring of many neurological diseases such as acute stroke, neurodegenerative diseases and brain tumours among others. It is also used in intensive care units for many reasons which include the diagnosis of brain death and raised intracranial pressure. Neurosonology has been applied in stroke imaging only in pediatric sickle cell patients in Nigeria, to the best of our knowledge first by Lagunju *et al* (TCD) and later by Tabari *et al* (TCCS).[8,9] The other mention of TCCS in the literature in sub-Saharan Africa was its use to evaluate cerebral haemodynamics in patients with eclampsia in South Africa.[10] There however exists a gap in our knowledge of intracranial haemodynamics and intracranial vascular architecture among patients with stroke in indigenous Africans as alluded to by Owolabi et al and the INTERSTROKE study.[11,12]

This article therefore provides an overview of the role of TCCS in the management of patients with stroke aimed at stimulating its clinical application and research utilities particularly in resource poor settings where access to conventional neuroimaging modalities remains limited. The target is to improve neurologic outcome for poor patients with stroke through expedited but inexpensive neuroimaging availed them by TCCS.

Figure 1. *Transtemporal gray-scale image showing the cerebral peduncles (P) with the echogenic basilar cistern (*) located just anteriorly.*[7]



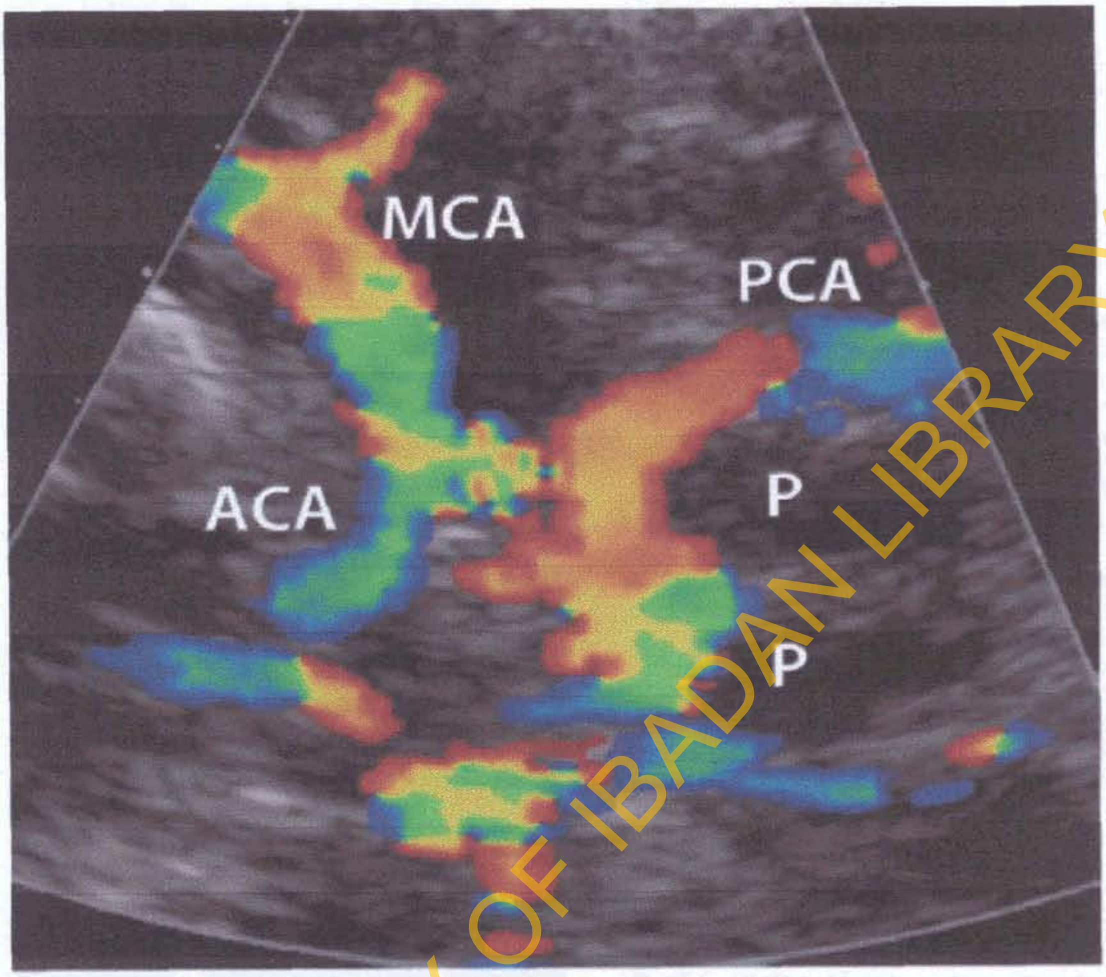
Learning objectives:

- Identify the clinical uses of TCCS in diagnosis, treatment and follow up of patients with stroke.
- Appreciate the comparative advantage of TCCS over other neuroimaging modalities in management of stroke.
- Identify the potential challenges and latent prospects for the clinical use of TCCS in managing stroke patients in resource challenged settings.

Role of TCCS in management of Haemorrhagic Stroke

Haemorrhagic stroke constitutes 5-15% of all strokes in Caucasians though the proportion is about twice that in Africa[12] and has a 30-day mortality rate of 25-43% with overall worse prognosis than ischaemic stroke.[13,14] Brain haematoma appears on TCCS as an echo-dense parenchymal lesion in the acute phase, with progressive decrease in the echogenicity of its central region as time passed (figure 3). Spontaneous subarachnoid haemorrhage (SAH) appears as marked increase in the echogenicity of the basal cisterns on TCCS. TCCS can thus be used for bedside classification of haemorrhagic stroke into either intracerebral or subarachnoid subtypes while awaiting further imaging. It is also a dependable alternative stand- alone imaging modality where computed tomography (CT) and magnetic resonance imaging (MRI) services are not accessible for any reason as is common in most developing and resource poor environments.

Figure 2. *Transtemporal color Doppler image of the circle of Willis showing the MCA with flow directed toward the transducer. The ACA flow is directed away from the transducer. The PCA is seen coursing around the cerebral peduncles (P).*[7]

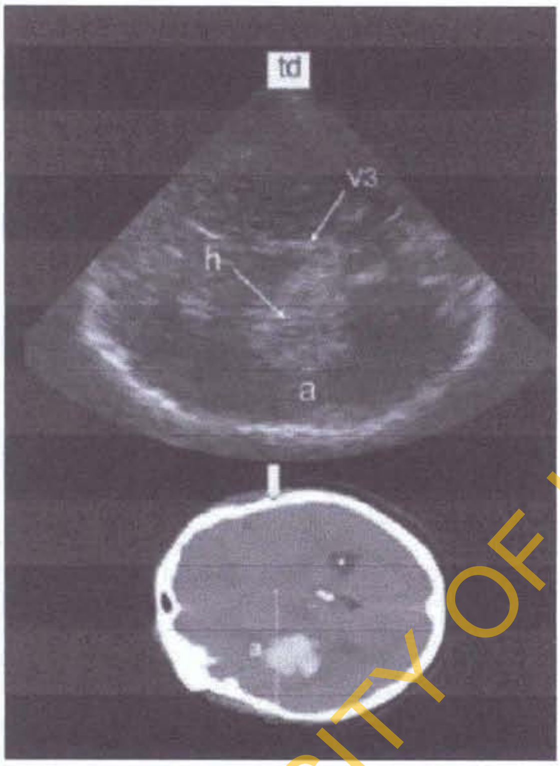


TCCS may be used to answer pertinent clinical questions such as the site and size of intracranial haematomas with accuracies comparable to those obtainable from CT.[15-19] TCCS via an adequate trans-temporal acoustic window detects haematomas in the supratentorial compartment excellently when the volume is at least 1ml.[15,16] All infratentorial intracranial haemorrhages (ICH), located in the trans-temporal blind spot, were also detected in a recent TCCS study via the trans-temporal window.[17] These workers were further able to detect a significant proportion of associated intraventricular haemorrhage (IVH) even in the fourth ventricle.[17] Other workers reported an excellent correlation between TCCS and CT measurements for haematoma diameters (longitudinal: r=0.91, p=<0.001; sagittal: r=0.85, p=0.002; coronal: r=0.79, p=0.022) and for total haematoma volume (r=0.82, p=0.001) in the patients who had demonstrable ICH on both TCCS and CT scans.[18] Maurer *et al*[19] reported that TCCS has a sensitivity of 94%, specificity of 95%, positive predictive value (PPV) of 91%, and negative predictive value (NPV) of 95% when CT was used as the reference standard for the diagnosis of ICH.

Besides the site and size of ICH, there are several other factors associated with poor prognosis in intracerebral haemorrhagic stroke.[20,21] The presence of poor prognostic factors such as haematoma expansion and associated mass effect are easily unraveled by TCCS. The usefulness of TCCS to detect early haematoma expansion was recently and extensively studied by Ovesen *et al.*[22] These workers documented the entire expansion profile of ICH by serial measurement of its volume on TCCS performed in 25 patients who were recruited within 4.5 hours of onset of symptoms.

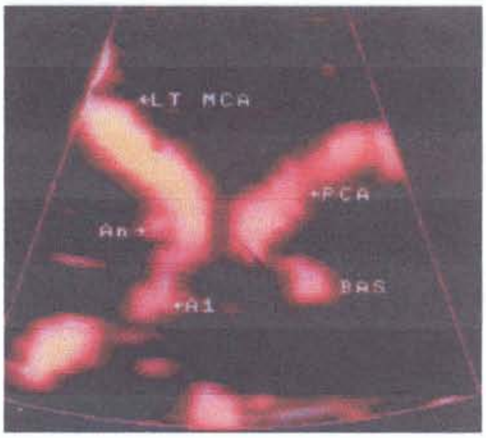
Their findings confirmed the preliminary observations of others[18,23] and validated TCCS as a reliable tool for bedside monitoring of haematoma progression.
Midline shift (MLS) is an evidence of mass effect and an independent predictor of poor outcome in haemorrhagic stroke.[24-26]

FIGURE 3: *B-mode transcranial ultrasound shows acute intracerebral haemorrhage (h) as an echodense parenchymal lesion compared with the cranial computed tomographic (CT) image of the same lesion in the lower image. V3 is the echogenic line that represents the third ventricle which is displaced as an evidence of midline shift. Adapted from Kiphuth IC et al*[26].



The fact that the third ventricle is remarkably easy to identify on TCCS as the prominent echogenic midline (figure 3), regardless of the insonation window, allows confident detection of MLS. Stolz *et al*[24] found no significant difference in measurements of MLS by TCCS and CT scans. Tang *et al*[25] reported a very high correlation between these modalities for MLS measurement ($r=0.91$, $p<0.01$). Other specific utilities of MLS as determined by TCCS in acute ICH have been described by Kiphuth *et al.*[26] These authors observed from Receiver Operating Characteristic (ROC) curve analysis that MLS of ≥4.5 -7.5 mm detected on TCCS indicated an impending failure of conservative therapy. A MLS of ≥12 mm at any time indicates mortality with a sensitivity of 69%, specificity 100%, positive predictive value (PPV) and negative predictive value (NPV) of 100 and 74% respectively. They also observed that a cut-off MLS of >5 mm within 24 hours identifies patients with re-bleeding with a sensitivity of 100%.
TCCS can aid the bedside detection of SAH; elucidate the probable cause as an aneurysm or arterio-venous Malformations (AVM); and help monitor patients for early detection of complications such as cerebral vasospasm. Even in its infancy, TCCS was recommended as an alternative imaging modality for screening or diagnosing intracranial aneurysm when computed tomography angiography (CTA)/ magnetic resonance angiography (MRA) is not readily available. This is because 85% of saccular aneurysms occur in the circle of Willis,[27] a region imaged excellently on contrast enhanced power mode TCCS (figure 4). In a large prospective multicenter blinded study,[28] power mode TCCS had an accuracy of 85% (Sensitivity= 78%, Specificity=90%, PPV= 85%, NPV= 84%) for detecting aneurysms in 157 patients who also underwent intra-arterial digital subtraction angiography (DSA) examination. Other studies reported sensitivities that ranged between 40 and 91% depending on the sample size, prevalence of aneurysm, average size of aneurysm, mode of image acquisition, experience of operator and use of contrast agent. There was also no significant difference in the performance of TCCS for detecting larger aneurysms (>5mm) compared with CTA and MRA, although it is the least sensitive among them.

FIGURE 4: *A small terminal left internal carotid artery aneurysm (An) on power mode transcranial Duplex ultrasound. A1 is pre-communicating segment of the anterior cerebral artery, Lt MCA is the left middle cerebral artery, PCA is the posterior*



communicating artery, and BAS is the basilar artery. Adapted from White PM et al[28].

AVMs appear on TCCS as a heterogeneous echo-dense lesion with focal accumulations of vascular networks which have turbulent flow, low impedance, mixed arterial and venous flows. AVM detection rates of 96.7% and 70% by contrast enhanced and native TCCS respectively with DSA as the reference modality have been reported.[29] TCCS imaging of AVMs is however limited by its inability to detect the draining veins.

Symptomatic cerebral vasospasm occurs in 12-57% of patients with subarachnoid haemorrhage (SAH), is essentially an 'ischaemic transformation' of the haemorrhagic stroke because delayed ischaemic neurologic deficit ensues, and is associated with poor prognosis.[30,31] TCCS is the only safe non-invasive test of proven reliability for detecting and monitoring post SAH cerebral vasospasm. The questionable accuracy of conventional TCD for monitoring this complication, [32,33] underscores the importance of TCCS as a great improvement in this clinical context. TCCS derived peak systolic velocity in the middle cerebral artery and the Lindegaard index (Vmca:Vica ratio) have similar utility for the detection and monitoring of vasospasm when DSA is the gold standard.[34]

Role of TCCS in management of Ischaemic Stroke

Ischaemic stroke is the more common form globally, and the second most common cause of mortality in developed countries.[35] The rising prevalence and higher morbidity associated with ischaemic stroke in the low-to-middle income countries (LMIC) makes rapid affordable neuroimaging a crucial factor for improving treatment outcome.

TCCS has the inherent capability to evaluate the brain parenchyma and the patency of blood pipes in the acute phase of stroke. The applications of TCCS in acute ischaemic stroke (AIS) cover diagnosis, screening, treatment and prognostication. The pertinent diagnostic clinical questions in AIS, which include the type- thrombotic or embolic, small vessel or large vessel; and severity- stenosis or occlusion, can all be resolved partially or totally by TCCS.

TCCS has an important role for neurovascular evaluation in AIS to detect or exclude intracranial stenosis or occlusion. This has huge potential to positively impact management of AIS in Africa since intracranial atherosclerotic disease is more prevalent in the black race.[36] In a groundbreaking work, Baumgartner et al pioneered the use of TCCS for detection of intracranial stenosis, and published velocity-based criteria which were correlated with DSA findings.[37] They concluded that TCCS may provide a reliable and non-invasive assessment of patients with symptomatic intracranial stenosis, and supply the information needed to initiate adequate medical treatment.

The multicenter work in Germany and Switzerland termed the DIAS study (Duplex-Sonography in Acute Stroke) evaluated the intracranial vasculature with respect to the presence of blood clots; stenosis or occlusion within 6 hours of onset of AIS.[38] TCCS was found useful to detect abnormalities in the intracranial circulation in AIS. TCCS was also used in the Neurosonology in Acute Ischemic Stroke (NAIS) study to systematically determine the pattern of stenosis and occlusion of the intracranial arteries in AIS.[39] The multicenter Italian ELIGIBLE study discovered that TCCS allows identification of the presence and site of clots in the intracranial vessels in AIS.[40] Other workers have also used TCCS to determine the prevalence of intracranial carotid atherosclerotic disease (ICAD) in their population and screen for ICAD in patients with CVD[41]. The performance of TCCS for detection of intracranial arterial stenosis (sensitivity=88.9%, specificity=94.8%, PPV=51.1%, NPV=99.3%) also compare favorably with that of CTA (sensitivity=81.5%, specificity=98.7%, PPV=78.6%, NPV=98.6%) when DSA was the reference standard.[42] Tang *et al* in Taiwan published velocity criteria and diagnostic validity tables for various grades of MCA stenosis derived from TCCS examination of 193 patients.[43] They concluded that TCCS has high reliability for detection of MCA stenosis almost similar to MRA.

The adequacy of collateral circulation in AIS, which is a known factor affecting treatment outcome, is currently being assessed with TCCS. Leading experts in the field recently released the Chinese consensus statement on the evaluation and intervention of collateral circulation for AIS.[44] A main recommendation by this group of experts, who also acknowledged the superiority of TCCS, is that "TCD or TCCS can be used as screening tools for primary evaluation of collateral circulation in stroke patients".

Perfusion imaging is another fascinating application of TCCS in AIS. It aims to determine perfusion of the cerebral microvasculature, estimate the size of the infarct and ischemic penumbra with implications for therapeutic clinical decisions. The legacy means of carrying out perfusion imaging such as MRI, CT, positron emission tomography (PET) and single photon emission computed tomography (SPECT) are not easily done by the bedside among many of their limitations. Ultrasound perfusion imaging (UPI) depends on tissue harmonic imaging and infusion of echo-amplifying ultrasound contrast media. Weismann *et al* [45] published reports of their landmark work in healthy human subjects to demonstrate feasibility of the novel approach to cerebral perfusion imaging in the year 2000. Many studies[46-48] have since been done on clinical uses of

UPI in stroke with impressive results which often agree with MRI yardstick. Eyding et al concluded that perfusion anomalies and dysfunctional but viable tissues at risk are reliably detected by UPI, which can give alternative supplementary information to perfusion-weighted MRI.[47]

Sonothrombolysis is one of the therapeutic applications of TCCS. The combination of focused continuous insonation of an identified blood clot, administration of an echo-amplifying contrast medium, and ultrasound guided infusion of a thrombolytic agent has been credited with higher recanalization rate than blind thrombolytic therapy or spontaneous recanalization alone.[49,50] A faster rate of recanalization is also achieved without any significant increase in complication such as haemorrhagic transformation of AIS.[51] Patients so treated have been shown to recover more speedily with better long term prognosis compared with those treated by invasive techniques of any degree.[52] Sonothrombolysis is now advocated as the non-invasive method of choice to achieve recanalization within and even beyond the prescribed window period, with a shift in the paradigm from 'time is brain' to 'physiology is brain'. Ultrasound guided targeted delivery of microbubbles laden with thrombolytic agent is another evolving therapeutic application of TCCS in AIS.[53] Monitoring of reperfusion with the thrombolysis in brain ischemia index (TIBI) during and after recanalization is also better done with TCCS.[54]

The diagnostic utility of TCCS in AIS at the pre-hospital level has been evaluated[55-57]. The International Prehospital Stroke Project (IPSP)[56] provides ample evidence and experience of this. The IPSP team established the feasibility of using portable TCCS device for emergency assessment of intracranial arteries shortly after arrival of the emergency team at the patient's site.[55] Pre-hospital brain ultrasound scan in the emergency phase of AIS was done with high diagnostic accuracy even during patient's transport via air or road ambulance. Reports from the second phase of the IPSP suggest a bright outlook for TCCS as the stethoscope of the stroke neurologist/neuroradiologist in the field[57]. Preliminary reports also indicate that TCCS can guide the pre-hospital initiation of definitive thrombolytic management of AIS, and is a way to recruit many patients within the golden window period when they can benefit from thrombolysis.

Limitations

Insufficient acoustic window is the major factor that may hinder TCCS in adults. This factor is more common in the elderly, women and non-Caucasian races. It accounts for 10-20% of inconclusive examinations prior to the introduction of echo-amplifying ultrasound contrast agents.[58] The use of contrast agents has reduced the drop-out rate to fewer than 7%.[58] Supplementary acoustic windows such as the transorbital and transforaminal routes are also advocated to improve inclusion for TCCS. It is known than 20% of stroke patients are unable to undergo MRI because of sundry contraindications and such services are rarely available round the clock.[59] The drop-out rate of TCCS, if interpreted in the light of the foregoing, may be of negligible clinical significance. The other limitation is that TCCS is operator dependent. This can be mitigated by adequate training of personnel to improve dexterity and allow confident TCCS based diagnosis and intervention.

Implications for stroke care in Africa

TCCS offer new rays of hope for neuroimaging to the typical patient with stroke in Africa. The endemic poverty in most African nations implies that the majority of patients with stroke are unable to afford the cost of neurovascular diagnosis with the few available CT and MR facilities.[60] This often leads to delay in accurate diagnosis of stroke and initiation of treatment. It is also one of the reasons why thrombolytic agents are not used for treatment of AIS in many developing nations.[61] Inadequate power infrastructure and high temperatures in most African nations also predisposes the expensive CT and MR equipment to break down frequently. These, in addition to the paucity of qualified biomedical engineers results in high cost of maintenance of the few available neuroimaging modalities which are ultimately transferred to the patient.

In contrast to CT and MRI, Ultrasound based imaging, wherever applicable in the human body, is widely acknowledged to be cheaper, safer and more affordable for the end users. It is known to be easier to maintain and require less fastidious electricity supply to operate. Ultrasound has therefore been the bedrock of cross-sectional imaging for most African nations. Its ubiquitous presence in our imaging ecosystem is implicit evidence of easy adaptation to the tropical environment. Though there is dearth of literature on the cost analysis of TCCS in stroke care, anecdotal evidence suggest that it is a far cheaper alternative to the pre-existing neuroimaging modalities.

The funds conserved from a cheaper means of neurovascular imaging may be available to the patients to offset care related bills, and generally improve physical, psychosocial and financial wellness given the prevalent 'out of pocket' model of healthcare financing in Africa. The time saved in making accurate diagnosis of stroke and its subtypes more rapidly by TCCS will encourage faster initiation of definitive treatment with positive impact on prognosis. The portable form of TCCS scanners, which can be battery-powered, will insulate stroke care from the unreliable utility power supply and facilitate community based

interventions such as screening for ICAD.
Investment in training of manpower is the prime requirement in order to benefit from the technology of TCCS which is remarkably operator dependent. The radiologist, neurologist and sonographers need to be well trained and certified in neurosonography to guarantee reliable reports of brain ultrasound scans. These personnel will then transfer knowledge and skills to others thereafter. A feasibility study on the adequacy of transcranial insonation in indigenous African populations will be necessary to determine the proportion to augment with ultrasound contrast media.

Conclusion

There appears to be sufficient evidence for the inclusion of TCCS in a standard stroke imaging protocol, especially in resource poor settings. Its ability to provide complementary information on cerebral architecture cum vasculature in stroke serves as a veritable alternative to CT/MRI for the critically ill patient. This technology competes fairly well with the more developed CT/MR technologies. Therefore no stroke patient would be denied a form of neuroimaging even in the LMIC when TCCS is added to the diagnostic toolbox for stroke care.

Teaching points:

- TCCS is a non-invasive ultrasound examination used to image the brain parenchyma, visualize the intracranial blood vessels, measure blood flow velocity, and observe cerebral hemodynamics in real time on brightness or Duplex modes as an improvement on non-image guided (blind) transcranial Doppler.
- TCCS can be used to distinguish haemorrhagic from ischaemic forms of stroke and identify poor prognostic factors such as haematoma expansion and mass effect.
- The circle of Willis, where 85% of saccular aneurysms are found, is better evaluated in real time on TCCS.
- Narrowing or occlusion of intracranial vessels in post-haemorrhagic vasospasm, intracranial atherosclerotic disease and embolic phenomenon can be reliably detected on TCCS.
- Ultrasound contrast medium is indicated in TCCS if the transcranial acoustic window is inadequate; for perfusion imaging to diagnose viable neural tissue at risk of infarction in acute ischaemic stroke; and for vessel recanalization purpose in sonothrombolyis.
- Diagnosis and definitive treatment of stroke can be commenced in the pre-hospital phase with the aid of TCCS which saves time, money and life where this relatively low-cost technology and technical expertise is available.

References

1. Aaslid R, Markwalder T-M, Nornes H. Noninvasive transcranial Doppler ultrasound recording of fow velocity in basal cerebral arteries. J Neurosurg 1982; 57:769-772.
2. Sloan MA, Alexandrov AV, Tegeler CH, Spence MP, Caplan LR, Feldmann E. et al., Assessment: Transcranial Doppler ultrasnongraphy: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2004; 62:1468-1481.
3. Bogdahn U, Becker G, Winkler J, Greiner K, Perez J, Meurers B. Transcranial Colour-Coded Sonography in Adults. Stroke 1990; 21(12):1680-1688.
4. Schoning M, Grunert D, Stier B. Transcranielle Real-Time-Sonographie bei Kindern und Jugentlichen: Ultraschall-anatomie des Gehirns. Ultraschall 1988; 9:286-292.
5. Holscher T. Prehospital use of portable ultrasound for stroke diagnosis and treatment initiation. AirRescue 2012; 2:64-67.
6. Alonso A, Della Martina A, Stroick M, Fatar M, Griebe M, Pochon S. et al., Molecular imaging of human thrombus with novel abciximab immunobubbles and ultrasound. Stroke 2007; 38:1508-1514.
7. AIUM practice guideline for the performance of transcranial Doppler ultrasound examination for adults and children. AIUM 2012: pp 1-12.
8. Lagunju I, Sodeinde O, Telfer P. Prevalence of transcranial Doppler abnormalities in Nigerian children with sickle cell disease. Am J Hematol 2012; 87:544-547.
9. Tabari A, Ismail A. Doppler ultrasound velocimetry of middle cerebral arteries of patients with sickle cell disease at Aminu Kano Teaching Hosptal: a preliminary report. Ultrasound Q 2013; 29:61-65.
10. Naidu K, Moodley J, Corr P, Hoffmann M. Single photon emission and cerebral computerised tomographic scan and transcranial Doppler sonographic findings

in eclampsia. Br J Obstet Gynecol 1997; 104:1165-1172.

11. Owolabi MO, Agunloye AM, Ogunniyi A. The relationship of flow velocities to vessel diameters differs between extracranial carotid and vertebral arteries of stroke patients. J Clin Ultrasound 2014; 42:16-23.

12. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chim SL, Rao-Melacini P. et al., Risk factors for ischaemic stroke and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010; 376:112-123.

13. Meyer-White K, Sallusti F, Kern R. Diagnosis of Intracerebral Haemorrhage with Transcranial Ultrasound. Cerebrovascular Dis 2009; 27:40-47.

14. Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB. et al., Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. JAMA 2006; 296:2939-2946.

15. Seidel G, Kaps M, Dorndorf W. Transcranial colour-coded duplex sonography of intracerebral haematomas in adults. Stroke 1993; 24:1519-1527.

16. Becker G, Hofmann E, Winkler J, Bogdahn U. Differentiation between ischaemic and haemorrhagic stroke by transcranial colour-coded real-time sonography. J Neuroimaging 1993; 3:42-47.

17. Kukulska-Pawluczuk B, Ksiazkiewicz B, Nowaczewska M. Imaging of spontaneous intracerebral haemorrhages by means of transcranial colour-coded sonography. Eur J Radiol 2012; 81:1253-1258.

18. Perez ES, Delgado-Mederos R, Rubiera M, Delgado P, Ribo M, Maisterra O et al., Transcranial duplex sonography for monitoring hyperacute intracerebral haemorrhage. Stroke 2009; 40: 987-990.

19. Maurer M, Shambal S, Berg D, Woydt M, Hofmann E, Georgiadis D. et al., Differentiation between intracerebral haemorrhagic and ischaemic stroke by transcranial color-coded duplex sonography. Stroke 1998; 29:2563-2567.

20. Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Gracia M. et al., Stroke Project, Cerebrovascular Disease Group of the Spanish Neurological Society. Early neurologic deterioration in intracerebral haemorrhage: predictors and associated factors. Neurology 2004; 63:461-467.

21. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G: Volume of intracerebral haemorrhage: a powerful and easy-to-use predictor of 30-day mortality. Stroke 1993; 24:987-993.

22. Ovesen C, Christensen AF, Krieger DW, Rosenbaum S, Havsteen I, Christensen H. Time course of early postadmission hematoma expansion in spontaneous intracerebral haemorrhage. Stroke 2014; 45: 994-999.

23. Matsumoto N, Kimura K, Iguchi Y, Aoki J. Evaluation of cerebral haemorrhage volume using transcranial colour-coded duplex sonography. J Neuroimaging. 2011; 21(4):355-8.

24. Stoltz E, Gerriets T, Fiss I, Babacan SS, Seidel G, Kaps M. et al., Comparison of Transcranial colour-coded duplex sonography and cranial CT measurements for determining third ventricle midline shift in space-occupying stroke. AJNR Am J Neuroradiol 1999; 20:1567-1571.

25. Tang SC, Huang SJ, Jeng JS, Yip PK. Third ventricle midline shift due to spontaneous intracerebral haemorrhage evaluated by transcranial colour-coded sonography. J Ultrasound Med 2006; 25:203-209.

26. Kiphuth IC, Huttner HB, Breuer L, Schwab S, Kohrmann M. Sonographic monitoring of midline shift predicts outcome after intracerebral haemorrhage. Cerebrovasc Dis 2012; 34:297-304.

27. Gasparotti R, Liserre R. Intracranial aneurysms. Eur Radiol 2005; 15:441-447.

28. White PM, Wardlaw JM, Teasdale E, Sloss S, Cannon J, Easton V, Power transcranial Doppler ultrasound in the detection of intracranial aneurysms. Stroke 2001; 32:1291-1297.

29. Wang LS, He W, Wang H, Zhao YL, Tian FL, Ning B. et al., Comparison of transcranial colour-coded real-time sonography and contrast-enhanced colour-

coded sonography for detection and characterization of intracranial arteriovenous malformations. J Ultrasound Med 2014; 33:273-280.

30. Dorsch NWC, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage, part I: incidence and effects. J Clin Neurosci 1994; 1:19-26.

31. Kirsch JD, Mathur M, Johnson MH, Gunabushanan G, Scout LM. Advances in transcranial Doppler US: Imaging Ahead. Radiographics 2013; 33:E1-E14.

32. Lysakowski C, Walder B, Contanza MC, Tramer MR. Transcranial Doppler versus angiography in patients with vasospasm due to ruptured cerebral aneurysm: a systematic review. Stroke 2001; 32:2292-2298.

33. Mariak Z, Krezja J, Swiercz M, Kordecki K, Lewko J. Accuracy of transcranial colour Doppler ultrasonography in the diagnosis of middle cerebral artery spasm determined by receiver operating characteristic analysis. J Neurosurg 2002; 96:323-330.

34. Krezja J, Kochanowicz J, Mariak Z, Lewko J, Melhem ER. Middle cerebral artery spasm after subarachnoid haemorrhage: Detection with transcranial colour-coded duplex US. Radiology 2005; 236:621-629.

35. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol 2007; 6:182-187.

36. Rincon F, Sacco RL, Kranwinkel G, Xu Q, Paik MC, Boden-Albala B. et al., Incidence and risk factors of intracranial atherosclerotic stroke: The Northern Manhattan Stroke Study. Cerebrovasc Dis 2009; 28:65-71.

37. Baumgartner RW, Mattle HP, Schroth G. Assessment of ≥50% and <50% intracranial stenosis by transcranial colour-coded duplex sonography. Stroke 1999; 30:87-92.

38. Gerriets T, Postert T, Goertler M, Stolz E, Schlachetzki F, Sliwka U et al. DIAS I: Duplex-Sonographic assessment of the cerebrovascular status in acute stroke: A useful tool for future stroke trials. Stroke 2000; 31:2342-2345.

39. Allendoerfer J, Goertler M, von Reutern GM. Neurosonology in acute ischemic stroke study group: Prognostic relevance of ultra-early Doppler sonography in acute ischaemic stroke: a prospective multicenter study. Lancet Neurol 2006; 5:835-840.

40. Malferrari G, Bertolino C, Casoni F, Zini A, Sarra VM, Sanguigni S. et al., The Eligible study: Ultrasound assessment in acute ischemic stroke within 3 hours. Cerebrovasc Dis 2007; 24:469-476.

41. Logallo N, Naess H, Waje-Andreassen U, Thomassen L. Prevalence of intracranial stenosis in a Norwegian ischemic stroke population. J Stroke Cerebrovasc Dis 2014; 23:1611-5.

42. Roubec M, Kuliha M, Jonszta T, Prochazka V, Fadrna T, Filip M. et al., Detection of intracranial arterial stenosis using transcranial colour-coded duplex sonography, computed tomographic angiography, and digital subtraction angiography. J Ultrasound Med 2011; 30:1069-1075.

43. Tang SC, Jeng JS, Yip PK, Lu CJ, Hwang BS, Lin WH. et al., Transcranial colour-coded sonography for the detection of middle cerebral artery stenosis. J Ultrasound Med 2005; 24:451-457.

44. Liu LP, Xu AD, Wong KS, Zang DZ, Wang YJ. et al., Chinese consensus statement on the evaluation and intervention of collateral circulation for ischaemic stroke. CNS neurosci Ther 2014; 20:202-208.

45. Weismann M, Seidel G. Ultrasound perfusion imaging in human brain. Stroke 2000; 31:2421-2425.

46. Kern R, Diels A, Pettenpohl J, Kablau M, Brade J, Hennerici G. et al., Real-time ultrasound brain perfusion imaging with analysis of microbubble replenishment in acute MCA stroke. Journal of cerebral blood flow and metabolism 2011; 31:1716-1724.

47. Eyding J, Krogias C, Schollhammer M, Eyding D, Wilkening W, Meves S. et al., Contrast-enhanced ultrasound parametric perfusion imaging detects dysfunctional tissue at risk in acute MCA stroke. Journal of cerebral blood flow and metabolism 2006; 26:576-582.

48. Meyer K, Wiesmann M, Albers T, Seidel G. Harmonic imaging in acute stroke: detection of a cerebral perfusion deficit with ultrasound and perfusion MRIA. J Neuroimaging 2003; 13:166-168.

49. Perren F, Loulidi J, Poglia D, Landis T, Sztajzel R. Microbubble potentiated transcranial duplex ultrasound enhances IV thrombolysis in acute stroke. J Throm Thrombolysis 2008; 25:219-223.

50. Molina CA, Ribo M, Rubiera M, Montaner J, Santamarina E, Delgado-Mederos R. et al., Microbubble administration accelerates clot lysis during continuous 2-MHz ultrasound monitoring in stroke patients treated with intravenous tissue plasminogen activator. Stroke 2006; 37:425-429.

51. Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J. et al., for the CLOTBUST investigators. Ultrasound systemic thrombolysis for acute ischaemic stroke. N Engl J Med 2004; 351:2170-2178.

52. Egger J, Konig IR, Koch B, Handler G, Seidel G. Sonothrombolysis with transcranial colour-coded sonography and recombinant tissue-type plasminogen activator in acute middle cerebral artery main stem occlusion: results from a randomized study. Stroke 2008; 39:1470-1475.

53. Tiukinhoy-Laing SD, Huang S, Klegerman M, Holland CK, McPherson DD. Ultrasound-facilitated thrombolysis using tissue plasminogen activator-loaded echogenic liposomes. Throm Res 2007; 119:777-784.

54. Eggers J, Seidel G, Koch B, Konig IR. Sonothrombolysis in acute ishaemic stroke for patients ineligible for rt-PA. Neurology 2005;`64:1052-1054.

55. Holscher T, Schlachetzki F, Zimmerman M, Jakob W, Ittner KP, Haslberger J. et al., Transcranial ultrasound from diagnosis to early stroke treatment- Part 1. Feasibility of prehospital cerebrovascular assessment. Cerebrovasc Dis 2008; 26:659–663.

56. Herzberg M, Boy S, Holscher T, Ertl M, Zimmerman M, Ittner KP. et al., Prehospital stroke diagnostics based on neurological examination and transcranial ultrasound. Critical Ultrasound Journal 2014; 6:3.

57. Schlachetzki F, Herzberg M, Holscher T, Ertl M, Zimmerman M, Ittner KP. et al., Transcranial ultrasound from diagnosis to early stroke treatment- Part 2. Prehospital neurosonography in patients with acute stroke- The Regensburg stroke mobile project. Cerebrovasc Dis 2012; 33:262–271.

58. Gerriets T, Goertler M, Stolz E, Postert T, Sliwka U, Schlachetzki F. et al., Feasibility and validity of transcranial duplex sonography in patients with acute stroke. J Neurol Neurosurg Psychiatry 2002; 73:17-20.

59. Singer OC, Sitzer M, du Mesnil de RR, Neumann-Haefelin T. Practical limitations of acute stroke MRI due to patient-related problems. Neurology 2004; 62:1848-1849.

60. Kolapo KO, Ogun SA, Danesi MA, Osalusi BS, Odusote KA. Validation of the Siriraj stroke score in African Nigerians and evaluation of the discriminant values of its parameters-a preliminary prospective CT scan study. Stroke 2006; 37:1997-2000.

61. Ghandehari K. Barriers of thrombolysis therapy in developing countries. Stroke Res Treat 2011. doi: 10.4061/2011/686797.

Acknowledgements
This work was carried out with the support and guidance of the NIH grant (1RN25NS080949) on "Improving Neurologic Outcome Measurement for Interventional Research in Ibadan, Nigeria"

Conflict of interest
The authors disclose that they have no conflict of interest in their participation in this work.