Perspectives in Medicine (2012) 1, 100—103

ELSEVIER
URBAN & FISCHER

Bartels E, Bartels S, Poppert H (Editors):
New Trends in Neurosonology and Cerebral Hemodynamics — an Update.
Perspectives in Medicine (2012) 1, 100—103

journal homepage: www.elsevier.com/locate/permed

Optimized prevention of stroke: What is the role of ultrasound?

Dirk Sander [a,b,*]

[a] *Department of Neurology, Benedictus Krankenhaus Tutzing, Germany*
[b] *Department of Neurology, Klinikum rechts der Isar, Technische Universität München, Germany*

KEYWORDS
Stroke prevention;
Ultrasound;
Carotid stenosis;
Ankle—brachial index

Summary Major cardio- and cerebrovascular events often occur in individuals without known preexisting cardiovascular disease. The prevention of such events, including the accurate identification of those at risk, remains a serious public health challenge. Scoring equations to predict those at increased risk have been developed using cardiovascular risk factors, but they tend to overestimate the risk in low-risk populations and underestimate it in high-risk populations. This overview discusses the possible role of ultrasound for an optimized prevention of stroke and focusses on (1) the importance of embolic signals in asymptomatic carotid stenosis, (2) the detection of unstable carotid plaques using duplex ultrasonography, and (3) the role of the ankle—brachial index for the stroke risk prediction in the acute stage and for secondary prevention.

Introduction

Despite the improvements in acute stroke therapy as well as effective secondary prevention measures, stroke remains the most important disease for permanent disability and is the second frequent cause of death worldwide [1]. The risk factors for stroke are well known and were subdivided into non-modifiable (e.g. age, sex, genetic predisposition) and modifiable catergories (e.g. hypertension, smoking, diabetes). The INTERSTROKE study [2] shows that 5 risk factors (history of hypertension or blood pressure >160/90 mm Hg, smoking, waste-to-hip ratio, physical inactivity and diet-risk score) explain 83.4% of the stroke risk in the population.

However, major cardio- and cerebrovascular events often occur in individuals without known preexisting cardiovascular disease. The prevention of such events, including the accurate identification of those at risk, remains a serious public health challenge [3]. Scoring equations to predict those at increased risk have been developed using cardiovascular risk factors, but they tend to overestimate the risk in low-risk populations and underestimate it in high-risk populations [4]. An important prerequisite for the use of surrogate parameters for risk prediction particularly in the primary care setting is that these parameters add substantial incremental value in risk prediction beyond the traditional Framingham-type risk scores or give a better estimate to select high-risk patients for invasive procedures, e.g. carotid endarterectomy (CEA). This overview discusses the possible role of ultrasound for an optimized prevention of stroke and focusses on (1) the detection of unstable carotid plaques using duplex ultrasonography, (2) the importance of embolic signals in asymptomatic carotid stenosis (ACS), and (3) the

* Corresponding author at: Department of Neurology, Benedictus Krankenhaus Tutzing & Feldafing, Dr.-Appelhans-Weg 6, 82340 Feldafing, Germany. Tel.: +49 8157 28140; fax: +49 8157 28141.
E-mail address: D.Sander@mac.com

2211-968X
doi:10.1016/j.permed.2012.02.029

role of the ankle—brachial index for the stroke risk prediction in the acute stage and for secondary prevention.

Detection of embolic signals in asymptomatic carotid stenosis

Due to the improvements of medical management in patients with high-grade ACS, there is uncertainty as how to best manage these patients. New studies demonstrate, that a well-treated patient with ACS has an annual risk of ipsilateral stroke of only 0.3% [5]. Therefore, 80 patients with an ACS must be treated by a CEA to prevent one disabling stroke. Consequently, the cost-effectiveness of CEA in patients with ACS has been questioned [6]. Nevertheless, ACS accounts for a large burden of stroke, and the majority of ipsilateral strokes are unheralded [7]. Identification of the group of ACS patients at higher risk would improve both risk-benefit and cost-benefit ratios for CEA. Several methods to identify such a high-risk group have been suggested, including ultrasonic detection of asymptomatic embolization. If clinical embolism is a good predictor of the subsequent stroke risk, asymptomatic cerebral emboli might also predict clinical stroke risk [8]. Transcranial Doppler ultrasound (TCD) is a non-invasive technique that can be used to detect circulating emboli. Several studies evaluated the association between detection of embolic signals and new ischemic events in patients with ACS [9—11] and reported different results. Recently a large prospective and multi-center study (ACES, Asymptomatic Carotid emboli Study) evaluated the relationship between asymptomatic emboli and stroke risk in 467 patients with an ACS of at least 70% [8]. The detection of emboli was associated with an increased risk for ipsilateral TIA and stroke (HR 2.54, 95% CI 1.2—5.36) and in particular for ipsilateral stroke (HR 5.57, 95% CI 1.61—19.32) during 2 years of follow-up even after adjusting for antiplatelet therapy, degree of stenosis, and other risk factors. The absolute annual risk of ipsilateral stroke or TIA between baseline and 2 years was 7.13% in patients with embolic signals and 3.04% in those without, and for ipsilateral stroke was 3.62% in patients with embolic signals and 0.70% in those without. The authors performed a meta-analysis with all studies available including 1144 patients. The hazard ratio for the risk of ipsilateral stroke for those with embolic signals compared with those without was 6.63 (95% CI 2.85—15.44) with no heterogeneity between studies ($p = 0.33$).

If TCD is to be used as a clinical tool for risk stratification, improved methods of automated detection of embolic signals are needed [8]. TCD recording itself is simple, non-invasive, and widely used in clinical practice worldwide. However, review of data for the presence of embolic signals is time consuming and relies on trained observers. Automated systems have been developed that have high sensitivity and specificity for detecting the higher intensity embolic signals seen in patients with symptomatic stenosis [12]. However, these systems were less sensitive to the lower intensity embolic signals found in ACS [13]. Therefore new systems are needed that enable an automatic detection of emboli even at lower signal intensity levels with an improved sensitivity and specificity.

Conclusion

- Detection of asymptomatic embolization on TCD can be used to identify patients with ACS who are at a higher risk of stroke and TIA.
- Assessment of the presence of embolic signals on TCD might be useful in the selection of patients with ACS who may benefit from CEA.
- Better systems are needed that enable an automatic detection of emboli even at lower signal intensity levels with an improved sensitivity and specificity.

Unstable plaque

A number of prospective studies have examined associations between ultrasonic plaque characteristics and stroke risk in ACS. Associations have been detected with a number of features including texture heterogeneity, echolucency, and surface irregularities [14]. A limited number of studies have used a simple measure of echolucency and these have shown conflicting results. More recently, data from ACES demonstrated that plaque morphology assessed using a simple visual rating scale predicts ipsilateral stroke in ACS [14]. 435 subjects with ACS $\geq$ 70% were included and followed-up for 2 years. A 4-point visual rating scale was applied to the plaques and they were classified as echolucent (37.7%) or echogenic. Plaque echolucency at baseline was associated with an increased risk of ipsilateral stroke alone (HR 6.43, 95% CI 1.36—30.44). A combination of plaque echolucency and ES positivity at baseline was associated with an increased risk of ipsilateral stroke alone (HR 10.61, 95% CI 2.98—37.82). The combination of ES detection and plaque morphology allows a greater prediction than either measure alone and identifies a high-risk group with an annual stroke risk of 8%, and a low-risk group with a risk of <1% per year. These data show that the combination of 2 measures of plaque instability may identify a high-risk group of patients with ACS that may benefit from a CEA.

Conclusion

- Plaque morphology assessed using a simple and clinically applicable, visual rating scale predicts ipsilateral stroke risk in ACS.
- The combination of asymptomatic emboli detection and plaque morphology allows a greater prediction than either measure alone and identifies a high-risk group with an annual stroke risk of 8%.

Ankle-brachial index (ABI)

Peripheral arterial disease (PAD) is increasingly recognized as a clinically important marker of atherosclerotic disease due to its association with cardiovascular disease incidence and mortality. Determination of the ABI, which is the ratio of systolic pressure at the ankle to that in the arm, is quick, easy to measure and a noninvasive method used to establish the presence of PAD. The equipment is inexpensive — a handheld Doppler sonograph costs less than 400 EUR. The procedure is simple, taking less than 10—15 min, and can

Table 1 Meta-analysis for the association between an pathological ABI (<0.9) and new vascular events according to [21].

Outcome	Age- and sex-adjusted risk		
	No. of studies	Relative risk (95% CI)	Test for heterogenicity
Overall mortality	14	4.0 (3.7—4.3)	$P = 0.002$
Vascular events	11	2.8 (2.6—3.1)	$P < 0.001$
Stroke/TIA	8	2.3 (2.0—2.7)	$P = 0.025$
CHD	8	2.4 (2.1—2.7)	$P < 0.001$

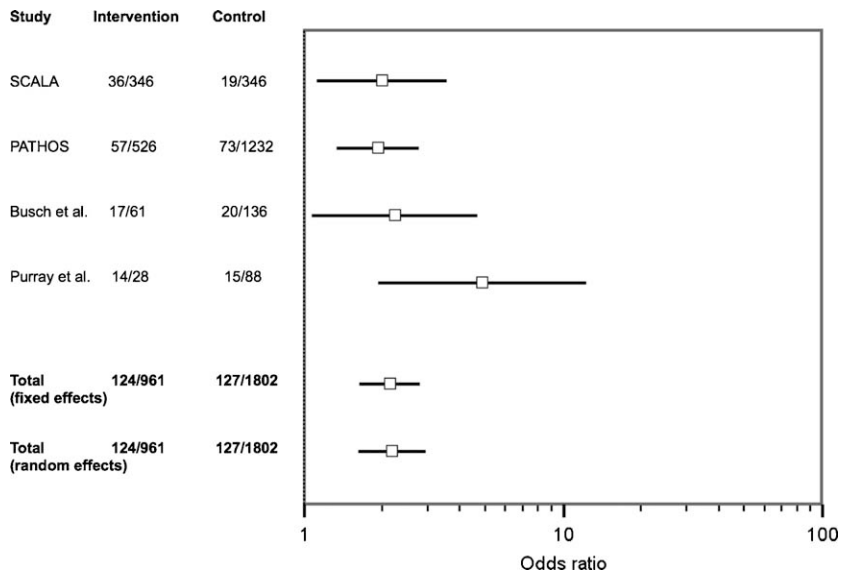

Figure 1 Meta-analysis of four trials showing the predictive value of low ABI (<0.9) for new cardiovascular events (stroke, MI or death) in patients with acute stroke.

be performed by a suitably trained nurse or health care professional.

A reduced ABI has been shown to identify patients at risk for cardiovascular events (Table 1). Patients with stroke or transient ischemic attack often had PAD. However, it is still unclear whether PAD is also a good predictor for future cerebrovascular disease. A recent meta-analysis demonstrated a pooled multivariate adjusted relative risk of 1.35 (95% confidence interval, CI 1.10—1.65) for stroke in patients with an ABI < 0.9 [15].

Meves et al. [16] analyzed the association between PAD, either symptomatic or asymptomatic (defined as an ABI < 0.9), and the future stroke risk in 6880 patients from the German Epidemiological Trial on Ankle—Brachial Index (getABI), a large and prospective cohort study of a typical primary care sample of unselected elderly patients. During the 5-year follow-up period, 183 patients had a stroke. In patients with PAD ($n = 1429$) compared to those without PAD ($n = 5392$), the incidence of all stroke types, with the exception of hemorrhagic stroke, was about doubled (for fatal stroke tripled). The corresponding adjusted hazard ratios were 1.6 (95% CI 1.1—2.2) for total stroke, 1.7 (95% CI 1.2—2.5) for ischemic stroke, 0.7 (95% CI 0.2—2.2) for hemorrhagic stroke, 2.5 (95% CI 1.2—5.2) for fatal stroke and 1.4 (95% CI 0.9—2.1) for nonfatal stroke. Lower ABI categories were associated with higher stroke rates. Besides high age, previous stroke and diabetes mellitus, PAD was a significant independent predictor for ischemic stroke. The stroke risk was similar in patients with symptomatic ($n = 593$) as compared to asymptomatic ($n = 836$) PAD.

Interestingly, recent studies that analyzed the prognostic impact of low ABI values (<0.9) on stroke recurrence and cardiovascular events in acute stroke patients revealed comparable results (Fig. 1). Purroy et al. [17] observed an increased stroke recurrence rate (32.1 vs. 13.6%, $p < 0.001$) and more vascular events (50 vs. 70%, $p < 0.001$) in patients with low ABI values. Similar results were seen in the SCALA trial [18] that examined 852 patients from 85 neurological stroke units throughout Germany as well as the PATHOS study [19] from Italy with 755 acute stroke patients. Busch et al. [20] described an increased risk for stroke, myocardial infarction or death in acute stroke patients with a low ABI < 0.9 (relative risk 2.2; 95% CI 1.1—4.5).

Conclusion

- An ABI < 0.9 is an independent predictor of stroke recurrence in acute stroke.
- The detection of PAD defined as an ABI < 0.9 identifies high-risk patients for further vascular events; the vascular

risk including stroke is clearly increased even in subjects with asymptomatic PAD.

- Elderly patients in the primary care setting should be screened for (asymptomatic) PAD to enable consequent treatment of modifiable cardiovascular risk factors to reduce the risk of ischemic stroke and other vascular events; however, whether this screening is cost-effective remains to be established.

References

[1] Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:517—84.

[2] O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case—control study. The Lancet 2010;376:112—23.

[3] Greenland P, Smith SCJ, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. Circulation 2001;104:1863—7.

[4] Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. Heart 2006;92:1752—9.

[5] Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. Stroke 2010;41:e11—7.

[6] Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke 2009;40:e573—83.

[7] Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 2000;342:1693—700.

[8] 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.

[9] King A, Markus HS. Doppler embolic signals in cerebrovascular disease and prediction of stroke risk: a systematic review and meta-analysis. Stroke 2009;40:3711—7.

[10] 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 2005;36:2373—8.

[11] 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 2005;36:1128—33.

[12] Cullinane M, Reid G, Dittrich R, Kaposzta Z, Ackerstaff R, Babikian V, et al. Evaluation of new online automated embolic signal detection algorithm, including comparison with panel of international experts. Stroke 2000;31:1335—41.

[13] Cullinane M, Kaposzta Z, Reihill S, Markus HS. Online automated detection of cerebral embolic signals from a variety of embolic sources. Ultrasound Med Biol 2002;28:1271—7.

[14] Topakian R, King A, Kwon SU, Schaafsma A, Shipley M, Markus HS, et al. Ultrasonic plaque echolucency and emboli signals predict stroke in asymptomatic carotid stenosis. Neurology 2011;77:751—8.

[15] Heald CL, Fowkes FG, Murray GD, Price JF. Risk of mortality and cardiovascular disease associated with the ankle—brachial index: systematic review. Atherosclerosis 2006;189: 61—9.

[16] Meves SH, Diehm C, Berger K, Pittrow D, Trampisch HJ, Burghaus I, et al. Peripheral arterial disease as an independent predictor for excess stroke morbidity and mortality in primary-care patients: 5-year results of the getABI study. Cerebrovasc Dis 2010;29:546—54.

[17] Purroy F, Coll B, Oro M, Seto E, Pinol-Ripoll G, Plana A, et al. Predictive value of ankle brachial index in patients with acute ischaemic stroke. Eur J Neurol 2010;17:602—6.

[18] Weimar C, Goertler M, Rother J, Ringelstein EB, Darius H, Nabavi DG, et al. Predictive value of the Essen Stroke Risk Score and Ankle Brachial Index in acute ischaemic stroke patients from 85 German stroke units. J Neurol Neurosurg Psychiatry 2008;79:1339—43.

[19] Agnelli G, Cimminiello C, Meneghetti G, Urbinati S. Low ankle—brachial index predicts an adverse 1-year outcome after acute coronary and cerebrovascular events. J Thromb Haemost 2006;4:2599—606.

[20] Busch MA, Lutz K, Rohl JE, Neuner B, Masuhr F. Low ankle—brachial index predicts cardiovascular risk after acute ischemic stroke or transient ischemic attack. Stroke 2009;40:3700—5.

[21] Banerjee A, Fowkes FG, Rothwell PM. Associations between peripheral artery disease and ischemic stroke: implications for primary and secondary prevention. Stroke 2010;41:2102—7.