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RESEARCH ARTICLE

Microalbuminuria could improve risk stratification in patients with TIA and minor stroke

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Abstract

Objective: Transient ischemic attacks (TIA) and minor strokes are important risk factors for recurrent strokes. Current stroke risk prediction scores such as ABCD2, although widely used, lack optimal sensitivity and specificity. Elevated urinary albumin excretion predicts cardiovascular disease, stroke, and mortality. We explored the role of microalbuminuria (using albumin creatinine ratio (ACR)) in predicting recurrence risk in patients with TIA and minor stroke. **Methods**: Urinary ACR was measured on a spot sample in 150 patients attending a daily stroke clinic with TIA or minor stroke. Patients were followed up at day 7, 30, and 90 to determine recurrent stroke, cardiovascular events, or death. Eligible patients had a carotid ultrasound Doppler investigation. High-risk patients were defined as those who had an event within 90 days or had >50% internal carotid artery (ICA) stenosis. **Results**: Fourteen (9.8%) recurrent events were reported by day 90 including two deaths. Fifteen patients had severe ICA stenosis. In total, 26 patients were identified as high risk. These patients had a higher frequency of previous stroke or hypercholesterolemia compared to low-risk patients ($P = 0.04$). ACR was higher in high-risk patients (3.4 [95% CI 2.2–5.2] vs. 1.7 [1.5–2.1] mg/mmol, $P = 0.004$), independent of age, sex, blood pressure, diabetes, and previous stroke. An ACR greater than 1.5 mg/mmol predicted high-risk patients (Cox proportional hazard ratio 3.5 (95% CI 1.3–9.5, $P = 0.01$). **Interpretation**: After TIA or minor stroke, a higher ACR predicted recurrent events and significant ICA stenosis. Incorporation of urinary ACR from a spot sample in the acute setting could improve risk stratification in patients with TIA and minor stroke.

Introduction

Stroke is the third most common cause of death and a leading cause of disability worldwide.[1] Despite, or possibly because of, recent trends in reducing stroke mortality, the healthcare and social support consequences are increasing.[2] Transient ischemic attack (TIA) and minor stroke are the most important risk factors for recurrent stroke and also predict long-term mortality.[3,4] Nearly, a quarter of patients presenting with stroke have a history of TIA in the 3 months prior to the index event, with half of these recurring within the first week.[5] However, this high-risk group represents only 10% of patients who present to TIA clinics.[6,7] Therefore, accurate detection and risk stratification is critical to identify those patients who are at highest risk of stroke in order to appropriately allocate intensive risk-reducing interventions such as urgent carotid endarterectomy, while reassuring those at lower risk.

The majority of patients with TIA/minor stroke present to a primary care physician or the emergency department after resolution of their symptoms. There are several risk stratification tools utilized in these settings such as ABCD2 (awarding points for Age, presenting Blood pressure, Clinical features of unilateral weakness or aphasia, Duration of symptoms and Diabetes),[8] California score[6]

and imaging based scoring systems.[9,10] However, these tools still lack optimal sensitivity and specificity.[11] Further, scores involving imaging are expensive, time consuming, and not available at all centers. Recent studies seeking to identify biomarkers that could predict risk have shown modest association between these markers and high-risk patients, with only interleukin-6 and CRP significantly predicting recurrent stroke.[12] These tests are not routinely or rapidly available for primary care and emergency physicians to risk stratify patients presenting with TIA/minor stroke. The urgent surgical correction of severe internal carotid artery (ICA) stenosis is one of the most effective strategies to reduce the risk of evolution to completed stroke.[10] However, an apparently "low-risk" ABCD2 score <4 could miss up to 40% of patients with severe ICA stenosis.[13] Indeed, some studies suggest patients with an ABCD2 score <4 (considered to be "low risk") have similar 90 day stroke risk as patients with ABCD2 score ≥4 (deemed "high risk").[14] This brings the need for refinement of risk tools or simple bedside tests that allow primary care and emergency physicians to identify high-risk patients needing hospital admission for urgent assessment and imaging.

Increased urinary albumin excretion rate has been shown to predict incident stroke and heart failure in those with diabetes and cardiovascular disease, and mortality post stroke in those without diabetes independent of conventional cardiovascular risk factors such as hypertension, diabetes, and smoking.[15–18] Urinary albumin creatinine ratio (ACR) is a well recognized proxy for urinary albumin excretion rate. It can be assessed using simple and relatively inexpensive point of care equipment. We aimed to determine the feasibility of using urinary ACR to improve risk stratification in patients presenting with TIA or minor stroke.

Methods

Consecutive patients with suspected TIA/minor stroke presenting to the daily stroke clinic in a single large district teaching hospital over a 9-month period were approached and written informed consent was sought. After consent, basic demographics, including age, sex, height, weight, past medical history, and ABCD2 score were recorded. Time from onset of symptoms to assessment and enrollment in the study was documented. A specimen of urine was collected from participants during their visit and ACR was measured using a point of care analyzer (The Afinion™ AS100 Analyzer, Axis Shield, Dundee, UK). This system uses an immunometric membrane flow-through principle for albumin measurement and an enzymatic colorimetric test for creatinine quantification [19] and reports, in approximately 5 min, an ACR in the range 0.1–140 mg/mmol with a coefficient of variance of 4.6–6%.[19] Eligible patients (anterior circulation events and patients fit for surgery) had carotid ultrasound Doppler studies. All carotid ultrasound studies were performed by SVT (*Society of Vascular Technologists*) accredited clinical scientists using Toshiba Aplio MX. The NASCET criteria were used to identify severe ICA stenosis.[20.]

Participants were followed up by telephone on day 7, 30, and 90 for the primary end points of any further cardiovascular event, stroke, and death. Outcome events were verified by an independent clinician, blinded to the ACR, by examination of clinical records if they attended the hospital or by verifying their clinical symptoms from the research records if patients did not seek further medical advice. High-risk patients were defined as those patients who had recurrent vascular events (either cerebro- or cardiovascular) or death within 90 days or had severe ICA stenosis (>50% NASCET). The study protocol was approved by the Southwest Research Ethics Committee (REC Reference 10/H0203/57).

Statistical analysis

Data were treated as continuous variables where appropriate. All normally distributed data are presented as mean ± SD. Skewed data were appropriately log transformed and presented as geometric means (95% CI). Statistical significance for categorical variables was estimated using the chi-squared test, and Student's *t*-test was used for continuous variables. Independence of urinary ACR (as a risk predictor) from diabetes and other measures of the ABCD2 score was assessed using logistic regression. Statistical significance was considered at $P < 0.05$. Statistical analysis was performed using Stata SE 12.1 (Mac version: Statacorp Ltd, Texas). This study was powered to detect a difference of 0.5SD in ACR between high-risk and low-risk patients allowing for 15% drop out with 80% power at a significance of 0.05 by recruiting 150 participants. Prespecified exploratory analyses were dependent on the primary outcome of a difference in ACR between high- and low-risk patients being fulfilled. These included analyses of patients experiencing recurrent events (i.e., excluding those deemed high risk because of ICA stenosis), patients in the "acute phase" (within 7 days of index event), and assessing the independence of findings from the conventional risk score ABCD2.

Results

Five hundred and twenty-three patients attending the daily stroke/TIA clinic in a large district general hospital were screened over 9 months period. Two hundred and

sixty-six patients met the screening criteria for the study, out of these, 150 patients consented to take part in the study. The main reasons why eligible patients did not take part in the study were patient could not produce a urine sample, evidence of UTI on urine test, unable to provide informed consent, personal reasons, and involvement in other clinical trials. Follow-up was completed in all participants to day 90, with no patients lost to follow-up. Seven patients were subsequently excluded after the diagnosis was revised as a stroke mimic. There was an approximately equal distribution of males (56%) and females, and baseline characteristics were representative of the usual clinic population (Table 1). All patients with confirmed diagnosis of TIA/minor stroke were commenced on secondary prevention with antiplatelet or anticoagulants as well as statin therapy unless contraindicated in accordance with the current national guidelines.[21.]

Over the 90 days of the study, 14 out of the 143 patients included in the analysis (9.8%) had further events (12 recurrent strokes/TIA, two cardiac events, and two deaths [two patients had more than one event]). One hundred and thirteen of patients included in analysis had anterior circulation events that warranted urgent carotid ultrasound Doppler assessments of whom 15 had severe ICA stenosis (13%) amenable to urgent surgical intervention. Three of those with recurrent events also had severe ICA stenosis resulting in a total of 26 high-risk patients identified. High-risk patients had a higher incidence of previous stroke and hypercholesterolemia ($P = 0.04$) than lower risk patients, but were otherwise similar (Table 1). Notably, ABCD2 score was statistically not different and numerically lower in the high-risk population. ACR was higher in the high-risk patients compared to the lower risk group 3.4 (95% CI: 2.2–5.2) versus 1.7 (1.5–2.1) mg/mmol, respectively; $P = 0.004$). This remained significant after adjustment for age and sex (adjusted ACR 3.1 [2.1–4.6] vs. 1.8 [1.5–2.2], $P = 0.008$) (Table 2).

Further adjustment to blood pressure, diabetes, previous stroke, and history of hypercholesterolemia, did not alter the results (adjusted ACR 3.4 [2.4–5.0] vs. 1.7 [1.4–2.0] mg/mmol; $P < 0.0001$) (Table 2).

Nine patients had a recurrent event within 7 days of the index event. The only distinguishing feature of these individuals was a higher ACR at presentation (ACR 4.0 [2.0–7.9] vs. 1.9 [1.6–2.3] mg/mmol, respectively, $P = 0.04$).

An ABCD2 score of ≥4 (traditionally regarded as high risk) did not predict subsequent events or the need for carotid endarterectomy. An ABCD2 score of ≥4 was not associated with elevated ACR (2.1 [1.7–2.6] vs. 1.8 [1.4–2.5] mg/mmol for those with ABCD2 < 4; $P = 0.4$). Adjustment for ABCD2 score either as a continuous or categorical variable did not affect the predictive role of ACR (adjusted ACR 3.2 [2.1–4.7] vs. 1.8 [1.5–2.2] mg/mmol, $P = 0.017$; Table 2).

Table 1. Sample characteristics stratified by High-risk and Low-risk patients (High-risk patients defined as recurrent events within 90 days or ICA stenosis >50% (NASCET)).

	High-risk patients	Low-risk patients	Sig (2-tailed)
Number	26	117	
Age (years)	74 ± 10	74 ± 11	0.2
Sex			
Females(%)	12 (46)	51 (44)	0.8
Males(%)	14 (54)	66 (56)	
Height (m)	1.64 ± 0.09	1.68 ± 0.10	0.08
Weight (Kg)	72 ± 19	76 ± 15	0.27
BMI (kg/m^2)	27 ± 5	27 ± 4	0.7
SBP (mmHg)	140 ± 19	141 ± 32	0.8
DBP (mmHg)	74 ± 11	77 ± 16	0.5
MAP (mmHg)	96 ± 12	101 ± 12	0.08
ABCD2	4.3 ± 1.4	4 ± 1.5	0.25
DM (%)	4 (15)	11 (9)	0.37
IHD (%)	6 (23)	20 (17)	0.47
High cholesterol (%)	10 (38)	23 (20)	0.04
Previous stroke (%)	10 (38)	23 (20)	0.04
Retinopathy (%)	0 (0)	3 (3)	0.4
eGFR (ml/min/1.73 m^2)	60 ± 38	68 ± 27	0.16

Figures presented as mean ± SD (except where indicated).
SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; ABCD2 (A = age, B = BP, C = clinical features, D = duration of symptoms + Diabetes); DM, diabetes mellitus; IHD, ischemic heart disease; PVD, peripheral vascular disease; eGFR, estimated Glomerular Filtration Rate.

Table 2. Unadjusted and adjusted albumin creatinine ratio (ACR) (geometric mean (95% CI) mg/mmol) for High-risk and Low-risk patients. (High-risk patients defined as recurrent events within 90 days or ICA stenosis >50% (NASCET)).

	Low-risk patients	High-risk patients	*P*-value
Unadjusted ACR	1.7 (1.5–2.1)	3.4 (2.2–5.2)	0.004
ACR adjusted for age and sex	1.8 (1.5–2.2)	3.1 (2.1–4.6)	0.008
ACR adjusted for age, sex, BP & DM	1.7 (1.4–2.0)	3.4 (2.4–4.9)	<0.0001
ACR adjusted for age, sex, BP, DM, previous stroke & hypercholesterolemia	1.7 (1.4–2.0)	3.4 (2.4–5.0)	<0.0001
ACR adjusted for ABCD2	1.8 (1.5–2.2)	3.2 (2.1–4.7)	0.017

ACR, albumin creatinine ratio; BP, mean arterial blood pressure, calculated from the mean of three readings; DM, confirmed diagnosis of diabetes prior to inclusion in the study; ABCD2, clinically utilized risk stratification risk into low, medium and high risk of a further event within 90 days.

An ACR ≥1.5 had a positive predictive value of 25% (95% CI: 16%–36%) and a negative predictive value of 90% (95% CI: 80–96%) for high-risk patients.

After adjustment for age, sex, ABCD2 score, SBP, DBP, previous stroke, history of cardiovascular disease, eGFR, and hypercholesterolemia, an ACR greater than 1.5 mg/mmol predicted high-risk patients (Cox proportional hazards: 3.5; 95% CI: 1.3–9.5; $P = 0.01$), significant ICA stenosis (Cox proportional hazard: 4.2; 95% CI: 1.14–15.7; $P = 0.03$), and showed a trend for the prediction of recurrent events (Cox proportional hazards: 4.1; 95% CI: .91–18.2; $P = 0.067$). Contrary to ACR, an ABCD2 score ≥ 4 did not predict high-risk patients (Cox proportional hazard ratio: 1.9; 95% CI: 0.7–5.4; $P = 0.22$), severe ICA stenosis (1.2; 95% CI: 0.35–4.2; $P = 0.75$) or recurrent events (5.4; 95% CI: 0.6–45.5; $P = 0.12$).

Discussion

We have demonstrated for the first time the potential utility of a near-patient test for ACR in predicting patients who will go on to have recurrent episodes or benefit from urgent carotid scan assessment and surgical intervention after a minor stroke or TIA. Further, this was independent of a widely accepted risk stratification tool, ABCD2 (which incorporates blood pressure and diabetes, both thought to be determinants of microalbuminuria). ACR is easy to test, can provide an immediate result and is already widely accepted in primary care as a prognostic tool in diabetes. Therefore, if confirmed, the use of ACR could easily be extended to assist with risk stratification and services allocation in people after TIA or minor stroke.

Recently, Kiyohara et al. suggested the ABCD3 (an extra D for "dual" TIA event) or ABCD3-I (I for severe ICA stenosis) are superior to ABCD2 score in predicting stroke in patients with TIA.[10] However, whereas predictive power may be improved, both proposed scores involve further delay. Immediate carotid imaging is often not available to front-line clinicians (family and emergency physicians) to allow them to risk stratify patients with suspected TIA. Simple point of care testing with urinary ACR may improve risk stratification in this circumstance.

Elevated urinary albumin excretion rate is a recognized marker of generalized endothelial and microvascular dysfunction. In the general population, microalbuminuria predicts cardiovascular events including stroke and all-cause mortality.[15,18] It identifies those patients with diabetes who are likely to develop atherosclerotic disease and progression to renal impairment[22] and it has strong association with atherosclerosis.[23] In those with recent myocardial infarction, the urinary albumin excretion is higher, and stratifying by ACR adds valuable prognostic information.[24] Therefore, the predictive value of microalbuminuria in the setting of TIA and severe ICA stenosis is not unexpected.

The mechanism behind the association between microalbuminuria and incident cardiovascular events is thought to reflect its role as a marker of increased vascular permeability and altered homeostasis, coagulation and endothelial function.[25,26] The increased filtration of albumin by the renal glomerulus is thought to be due to changes in the chemical and physical properties of the endothelial barrier and its glycocalyx.[22,27] After acute vascular events such as myocardial infarction, TIA, or minor stroke, increased urinary albumin excretion is associated with endothelial dysfunction,[26] indices of plaque instability in diabetes and acute coronary syndrome[28], and with subclinical atherosclerosis in patients with diabetes or hypertension.[29] Improving systemic inflammation, such as through the pleiotropic effect of statins, has been associated with simultaneous improvements in urinary albumin excretion and CV event rates in patients with elevated high-sensitivity C-reactive protein (hsCRP).[30] In hypertensive patients treated with standard therapy, changes in urinary albumin excretion over time predicted cardiovascular events and patients who remained normo-albuminuric or showed regression in their microalbuminuria had a lower incidence of cardiovascular disease.[31] Further studies are needed to determine whether microalbuminuria represents an easily accessible therapeutic target amenable to treatment, and if reductions in microalbuminuria are associated with reductions in the vascular events they predict.

Study limitations

Our study had limited power to test the independence of confounders such as diabetes and blood pressure. Nevertheless, the difference in ACR between those with future events over 90 days or with ICA stenosis requiring treatment, did remain after adjustment for ABCD2 (which includes a score for the presence of hypertension or diabetes), or diabetes and hypertension in logistic regression models, and the small numerical difference made by adjustment makes residual confounding unlikely. Further, our study had relatively small numbers, therefore a larger study sample may be needed to verify the predictive power of ACR and to identify the most relevant cutoff limit for ACR.

ACR was measured on a single urine sample obtained during the clinic assessment. There is significant, diurnal variability in urinary albumin excretion within individuals, which might limit the generalizability to other populations and studies using overnight or 24-hour

urine collection. However, the pragmatic design makes this study more applicable to general clinic populations.

This study did not attempt to subclassify the events by etiology, such as through the use of TOAST criteria. It is possible that microalbuminuria has different predictive roles in the different subtypes of stroke, and it may be that microalbuminuria is a proxy for the different subtypes which have a poorer prognosis. However, this study is seeking to identify a more practical prognostic tool which can be used at the first assessment of the patient, when the information necessary for accurate TOAST classification will not be routinely available.

Conclusion

We have demonstrated for the first time the potential utility of ACR in patients presenting with TIA and minor stroke as a prediction tool to assist triaging patients into high- and low-risk categories. This performed better than the currently utilized ABCD2 score, and was independent of clinically apparent confounders such as blood pressure, diabetes, and previous stroke. Larger-scale studies are now required to determine whether the use of ACR would provide a clinically significant risk stratification tool for front-line physicians, allowing for better allocation of resources while providing appropriate reassurance for those at lower risk.

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Conflict of Interest

None Declared.

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