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Predicting ischaemic stroke subtype from presenting systolic blood pressure: the BASIC Project

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Abstract. Meurer WJ, Sánchez BN, Smith MA, Lisabeth LD, Majersik JJ, Brown DL, Uchino K, Bonikowski FP, Mendizabal JE, Zahuranec DB, Morgenstern LB (University of Michigan Health System and University of Michigan School of Public Health, Ann Arbor, MI; University of Pittsburgh Medical Center Stroke Institute, Pittsburgh, PA; Texas A&M Medical University and Corpus Christi Neurology, Corpus Christi, TX; USA). Predicting ischaemic stroke subtype from presenting systolic blood pressure: the BASIC Project. *J Intern Med* 2009; **265**: 388–396.

Objective. We hypothesized that low presenting systolic blood pressure (SBP) predicted cardioembolic stroke aetiology.

Design. Active and passive surveillance were used to identify all ischaemic strokes as part of the Brain Attack Surveillance in Corpus Christi (BASIC) population-based study. Multinomial logistic regression was used to examine the association between stroke subtype and first documented SBP in the medical record.

Setting. Nueces County, TX, USA (313 645 residents in 2000). The community is urban with the majority of the population residing in the city of Corpus Christi. The area is served by seven adult acute care hospitals.

Patients. Three hundred and eight cases with completed ischaemic stroke and determined subtype aetiology between January 2000 and December 2002.

Results. Lower presenting SBP was associated with stroke subtype ($P = 0.001$). This association remained significant in the final model adjusted for age and history of coronary artery disease. The odds of cardioembolic versus small vessel occlusion increased by 20% (OR = 1.20, 95% CI: 1.07–1.35) for every 10 mmHg decrease in presenting SBP. Other covariates including race/ethnicity, gender, history of hypertension, and diabetes were neither significant predictors of stroke subtype, nor did they confound the association of SBP and stroke subtype. A 5 year increase in age increased the odds of cardioembolic subtype by 25% (OR = 1.25, 95% CI: 1.07–1.47).

Conclusions. Lower initial SBP and older age at ischaemic stroke presentation were associated with cardioembolic stroke. Suspicion of cardioembolic stroke should be increased in those presenting with low SBP.

Keywords: blood pressure, coronary artery disease, embolism, epidemiology, ischaemic stroke.

Introduction

Identifying the ischaemic stroke subtype is crucial for providing directed secondary stroke prophylaxis.

This study was presented as an abstract at the International Stroke Conference, 20 February 2008, New Orleans, Louisiana.

Internists are commonly the primary in-hospital care providers for acute stroke patients when evaluation of stroke subtype occurs. Early clues to ischaemic stroke subtype may facilitate an expeditious, thorough evaluation for stroke mechanism and allow the clinician to institute proper preventive therapy. Patients with acute ischaemic stroke present to the hospital with a wide range of blood pressures. Worse neurological outcome is associated with either low or markedly elevated blood pressures on presentation [1, 2]. To date, we are aware of no studies in which the presenting blood pressure has been used to attempt to predict the stroke subtype. Prior work has focused on trends in blood pressure during the first 24–48 h after the onset of stroke [3–7]. An association between lower blood pressure and the cardioembolic subtype is suggested by these studies; a possible mechanism is pre-existing heart disease [7].

We assessed the ability of presenting blood pressure to predict modified TOAST subtype classification amongst ischaemic stroke patients in a population-based study [8–10]. We hypothesized that lower presenting systolic blood pressure (SBP) would be an independent predictor of cardioembolic stroke subtype.

Methods

Study setting

The Brain Attack Surveillance in Corpus Christi (BASIC) Project is a population-based stroke surveillance study in Nueces County, TX, USA, which had 313 645 residents in 2000. The community is urban with the majority of the population residing in the city of Corpus Christi. The area is served by seven adult acute care hospitals. The methods utilized to collect patient data and to determine stroke subtype as part of the BASIC project have previously been described [10, 11].

Study cohort

Briefly, both active and passive surveillance were used to identify all strokes amongst those >44 years presenting to any emergency department or hospital. Completed ischaemic strokes, between January 2000 and December 2002, were identified by trained abstractors and validated by board-certified neurologists utilizing source documentation. The first ischaemic stroke event per individual captured by BASIC was utilized.

Data sources

A random sample of validated stroke cases was selected for extended chart review, in which detailed information was collected including medical test results, laboratory results and the discharge summary. First recorded SBP after presentation to the emergency department (or hospital for direct admissions) were abstracted from the medical record.

Stroke subtype classification

Ischaemic stroke cases were classified by two fellowship-trained stroke neurologists according to a previously published [10], modified version of the TOAST criteria. The stroke subtype categories were large artery atherosclerosis, cardioembolic, small-vessel occlusion, stroke of other determined aetiology, stroke of undetermined aetiology and an additional category of nonlacunar stroke of unknown aetiology (NLUE). The NLUE category comprised large artery territory strokes that had insufficient evidence for categorization into large-artery atherosclerosis versus cardioembolic; this categorization has been utilized previously [10, 12]. The neurologists were blinded to age and were unaware of the study question of the relationship of blood pressure to ischaemic stroke subtype. The inter-rater agreement for stroke subtype was high (kappa = 0.80, $P < 0.001$) [10].

Statistical methods

Frequencies, means and other descriptive statistics were calculated for the demographic and clinical characteristics of the patients in the study, both for the overall sample and for the stroke subtype. Chi-square tests, ANOVA F-tests and the Kruskal–Wallis test were used to assess differences in demographic

and clinical characteristics between stroke subtype groups and between patients with a classified stroke subtype and those with an undetermined aetiology. Stroke of other determined aetiology was excluded from further analysis due to low numbers ($n = 5$).

Multinomial logistic regression was used to study the association between stroke subtypes and presenting systolic SBP. Multinomial logistic regression generalizes binary logistic regression by allowing the outcome of interest to be categorized into more than two possible outcomes, in this case, multiple stroke subtypes. In binary logistic regression, the odds of the event versus no event are calculated; in multinomial logistic regression, the odds of one type of event (e.g. cardioembolic) versus a reference type of outcome are computed. We used small vessel occlusion as the referent stroke subtype, as past work has demonstrated this subtype to generally present with the highest SBP [4, 6, 7]. The results from multinomial logistic regression were adjusted for other predictor and confounding variables and were used to calculate adjusted probabilities of each of the possible stroke subtypes. Age, gender, ethnicity and history of hypertension, diabetes and coronary artery disease (CAD) were considered as covariates. Atrial fibrillation was not considered as a covariate because it was used to classify stroke as cardioembolic. Variables were kept in the model whether they were confounders (assessed by the 10% rule of confounding) or independent predictors ($P < 0.05$) of stroke subtype. Deciles of SBP were used to construct Pigeon and Heyse's goodness of fit statistic to test for lack of fit of the multinomial regression models [13]. For the models fitted, the test statistic had a chi-square distribution with 27 degrees of freedom. We decided *a priori* to exclude undetermined cases from the primary analysis as this is a clinically heterogeneous subgroup. However, to be sure that this decision did not affect our results, the multinomial logistic regression was repeated including the undetermined cases.

The estimated models were used to predict the probability of each stroke subtype for a continuous range of values of SBP. The predicted probabilities were then plotted against SBP. In practical situations, categories of SBP may be more useful than continuous changes in SBP. Thus, the models were re-estimated using quartiles of SBP. Bar graphs depicting the odds ratios (OR) for each subtype were constructed based on the model with SBP quartiles. For all calculations, the highest SBP quartile was the referent. The odds of cardioembolic, NLUE and large vessel versus small vessel occlusion (referent stroke subtype) were calculated to depict the association between subtype and quartiles of SBP. Additionally, the odds of small vessel occlusion versus all other stroke subtypes combined were computed to depict the association between small vessel occlusion and increasing SBP.

A sensitivity analysis was conducted to assess the possible effects of misclassification of stroke subtype. Specifically, the NLUE stroke category contained both cardioembolic and large-artery stroke, and therefore, a potential source of misclassification bias, if just the cardioembolic stroke group was considered in the analysis. For the sensitivity analysis, stroke subtypes were dichotomized into two broader categories. One category included cardioembolic and the NLUE stroke groups, whilst the second included large artery and small vessel occlusions. To analyse the dichotomized stroke subtypes binary logistic regression was used.

This project was approved by the University of Michigan Institutional Review Board, the University of Texas at Houston Committee for the Protection of Human Subjects and the Institutional Review Boards of all involved hospitals. The data were analysed using SAS Version 9.1 (SAS Corporation, Cary, NC, USA).

Results

Study enrolment and demographics

Abstractors screened 13 291 possible cerebrovascular events. Of these, 2378 were subsequently validated as stroke. A random sample of 711 patients was selected for extended data abstraction. Two hundred and

ninety-three of these patients with other stroke types were excluded from the analysis [199 transient ischaemic attacks (TIA), 80 intracerebral haemorrhages, 11 subarachnoid haemorrhages and one event in which it was unclear whether it was ischaemic versus haemorrhagic stroke]. Of the 418 remaining ischaemic stroke patients with extended abstraction data, five events for patients with more than one stroke during the study period and 14 patients with no subtype data were excluded from the analysis. Finally, five patients with ischaemic stroke of other determined aetiology were excluded from the analysis. The analytical sample consisted of 308 patients with determined stroke aetiology and 86 patients with ischaemic stroke subtype of undetermined aetiology.

Some differences existed between cases with determined and those with undetermined aetiology. Specifically, those with an undetermined aetiology were more likely to have a history of stroke or TIA (45.9% vs. 32.9%, $P = 0.02$), were less likely to have a history of CAD (25.9% vs. 38.6%, $P = 0.04$) and had a lower National Institutes of Health Stroke Scale (NIHSS) score (median 2 vs. 3, $P = 0.02$) compared with the determined aetiology group.

The demographic and clinical data for the patients are reported in Table 1. Of those with known aetiology, nearly 30% were NLUE, 27% cardioembolic, 24% small vessel occlusion and 19% large artery atherosclerosis.

Results of subtype prediction modelling

In the unadjusted model, presenting SBP was strongly associated with stroke subtype ($P = 0.001$). The model did not show a significant lack of fit ($\chi^2 = 27.2$, $P = 0.44$). The odds of cardioembolic stroke versus small vessel occlusion increased by 20% [OR = 1.20, 95% confidence interval (CI): 1.08–1.34] for every 10 mmHg decrease in presenting SBP. The OR for other stroke subtypes versus small vessel occlusion is given in Table 2. The NLUE aetiology had an intermediate risk between that of cardioembolic and large artery atherosclerosis.

In the adjusted multinomial logistic regression model (lack of fit $\chi^2 = 24.2$, $P = 0.62$), the only other variables included as predictive of subtype were age and history of CAD. Other covariates including race/ethnicity, gender, history of hypertension and diabetes were neither significant predictors of stroke subtype nor did they confound the association of SBP and stroke subtype. The adjusted association between SBP and cardioembolic aetiology did not change and remained significant (Table 3). That is, the odds of cardioembolic versus small vessel occlusion increased by 20% (OR = 1.20, 95% CI: 1.07–1.35) for every 10 mmHg decrease in presenting SBP. The odds of cardioembolic aetiology versus small vessel occlusion increased by 25% for a 5 year increase in age (OR = 1.25, 95% CI: 1.07–1.47), but were not significantly changed versus the other subtypes. Similarly, the odds of cardioembolic versus small vessel occlusion more than tripled for those with CAD compared to those without (OR = 3.12, 95% CI: 1.56–6.24). The odds of any other subtype versus small vessel occlusion did not differ between those with and without CAD. Repeating the multinomial logistic regression including the undetermined cases did not significantly alter the relationship between stroke subtype and presenting blood pressure.

Probabilities of stroke subtype over range of SBP

The age-adjusted probabilities of stroke subtype over a range of presenting SBP were calculated for patients (i) overall, and those (ii) with and (iii) without history of CAD, and are depicted graphically in Fig 1. As an example, a 73 year patient (average age in the sample) with a presenting SBP of 100 mmHg had approximately a 44% probability of cardioembolic stroke (Fig 1a) . If the patient had a history of CAD, this probability increased to 55% (Fig 1c).

The OR of the analysed subtypes were also calculated for each quartile of presenting SBP, and is presented in Fig. 2. For example, within the first quartile of presenting SBP (<140 mmHg), the odds of cardioembolic stroke were four times larger than the odds of small vessel occlusion.

Table 1 Demographics, risk factors and clinical characteristics of patients with determined versus undetermined subtype

Stroke subtype	Overall determined $N = 308$	Cardioembolic $N = 84$ (27.3%)	NLUE $N = 91$ (29.5%)	Large artery $N = 56$ (18.2%)	Small vessel $N = 77$ (25.0%)	Undetermined $N = 86$
Demographics						
Gender (%female)	179 (58)	185 (60)	169 (55)	188 (61)	179 (58)	179 (58)
Race/ethnicity (%MA)	151 (49)	183 (60)	132 (43)	154 (50)	136 (44)	147 (48)
Age, mean (SD)	73 (11)	78 (11)	72 (12)	70 (11)	72 (10)	72 (12)
Smoking status(%)						
Never	217 (71)	238 (77)	232 (75)	201 (65)	189 (61)	213 (69)
Former	48 (16)	31 (10)	47 (15)	47 (15)	66 (21)	61 (20)
Current	43 (14)	39 (13)	29 (9)	59 (19)	53 (17)	34 (11)
Health insurance(%)	293 (95)	301 (98)	284 (92)	302 (98)	288 (94)	301 (98)
Clinical characteristics						
History of hypertension(%)	233 (76)	235 (76)	217 (70)	246 (80)	240 (78)	210 (68)
Diabetes(%)	139 (45)	125 (41)	136 (44)	162 (53)	140 (46)	123 (40)
History of Stroke or TIA(%)	101 (33)	121 (39)	81 (26)	118 (38)	92 (30)	141 (46)
Coronary Artery disease(%)	119 (39)	183 (60)	106 (34)	90 (29)	84 (27)	80 (26)
High cholesterol(%)	62 (20)	33 (11)	68 (22)	95 (31)	64 (21)	43 (14)
Atrial fibrillation(%)	46 (15)	143 (46)	14 (4)	11 (4)	4 (1)	22 (7)
Excessive ETOH(%)	15 (5)	11 (4)	17 (6)	17 (6)	16 (5)	15 (5)
NIHSS, median (IQR)	3 (2,7)	6 (1,10)	3 (1,7)	3 (1,8)	3 (2,4)	2 (1,5)
Presented within 3 h(%)	88 (29)	34 (41)	16 (18)	15 (27)	24 (32)	23 (27)
Systolic BP (SD)	161 (30)	152 (32)	160 (30)	164 (28)	168 (28)	158 (28)
Diastolic BP (SD)	84 (18)	84 (19)	85 (19)	82 (15)	87 (16)	83 (15)
Mean arterial pressure (SD)	110 (19)	107 (21)	110 (20)	109 (17)	114 (17)	108 (17)
Diagnostic Testing(%)						
Any neuroimaging	305 (99)	304 (99)	305 (99)	308 (100)	304 (99)	304 (99)
Magnetic resonance imaging	129 (42)	77 (25)	135 (44)	187 (61)	152 (49)	115 (37)
Transthoracic echocardiogram	149 (48)	172 (56)	146 (47)	176 (57)	132 (43)	129 (42)
Transesophageal echocardiogram	9 (3)	4 (1)	14 (4)	0 (0)	24 (8)	4 (1)
Electrocardiogram	268 (87)	282 (92)	268 (87)	275 (89)	268 (87)	251 (81)
Conventional angiography	16 (5)	4 (1)	7 (2)	49 (16)	10 (3)	21 (7)
Carotid duplex sonography	197 (64)	165 (54)	196 (64)	214 (70)	224 (73)	193 (63)

Means or medians reported with standard deviation or inter-quartile range as appropriate in parentheses. NLUE, Nonlacunar stroke of either possible cardioembolic or possible large-artery aetiology; TIA, transient ischaemic attack; ETOH, Alcohol consumption; MA, Mexican American.

Sensitivity analysis

The results from the sensitivity analysis yielded similar relationships between stroke subtype and SBP. Specifically, a 10 mmHg decrease in SBP was associated with a 14% increased odds of the cardioembolic combined with the NLUE subtype versus the other two stroke subtypes combined (95% CI: 5–24%). A 5 year increase in age was associated with a 14% increased odds of cardioembolic combined with the NLUE subtype versus other subtypes combined (95% CI: 4.5–27%). Finally, the odds of cardioembolic combined with the NLUE versus other stroke types combined were 1.87 times higher amongst those with a history of CAD versus those without (95% CI: 1.13–3.10).

Table 2 Odds of stroke subtype for a 10 unit decrease in SBP – unadjusted model

Stroke subtype	OR	95% CI
Cardioembolism	1.20	1.08–1.34
NLUE[a]	1.10	0.99–1.22
Large artery	1.04	0.93–1.17
Small vessel	1.00	Referent

[a]NLUE, nonlacunar stroke of either possible cardioembolic or possible large-artery aetiology.

Table 3 Odds of stroke subtype – adjusted model

	Stoke subtype	OR	95% CI
SBP (10 mmHg) ($P = 0.01$)	Cardioembolic	1.20	1.07–1.35
	NLUE	1.12	1.11–1.25
	Large artery	1.04	1.03–1.18
	Small vessel	1.00	Referent
Age (5 year) ($P < 0.01$)	Cardioembolic	1.26	1.07–1.48
	NLUE	1.01	0.88–1.16
	Large artery	0.93	0.80–1.09
	Small vessel	1.00	Referent
CAD ($P < 0.01$)	Cardioembolic	3.12	1.56–6.24
	NLUE	1.33	0.67–2.64
	Large artery	1.15	0.52–2.54
	Small vessel	1.00	Referent

SBP, systolic blood pressure; CAD, coronary artery disease; NLUE, nonlacunar stroke of either possible cardioembolic or possible large-artery aetiology; Referent, small vessel.

Discussion

We found that lower presenting SBP was associated with cardioembolic ischaemic stroke subtype. If future work confirms this association, clinicians could consider a more thorough evaluation for cardiac sources of emboli in individuals who present with a lower blood pressure. Such a strategy may help maximize the number of patients who are initiated on appropriate secondary prevention strategies to reduce the

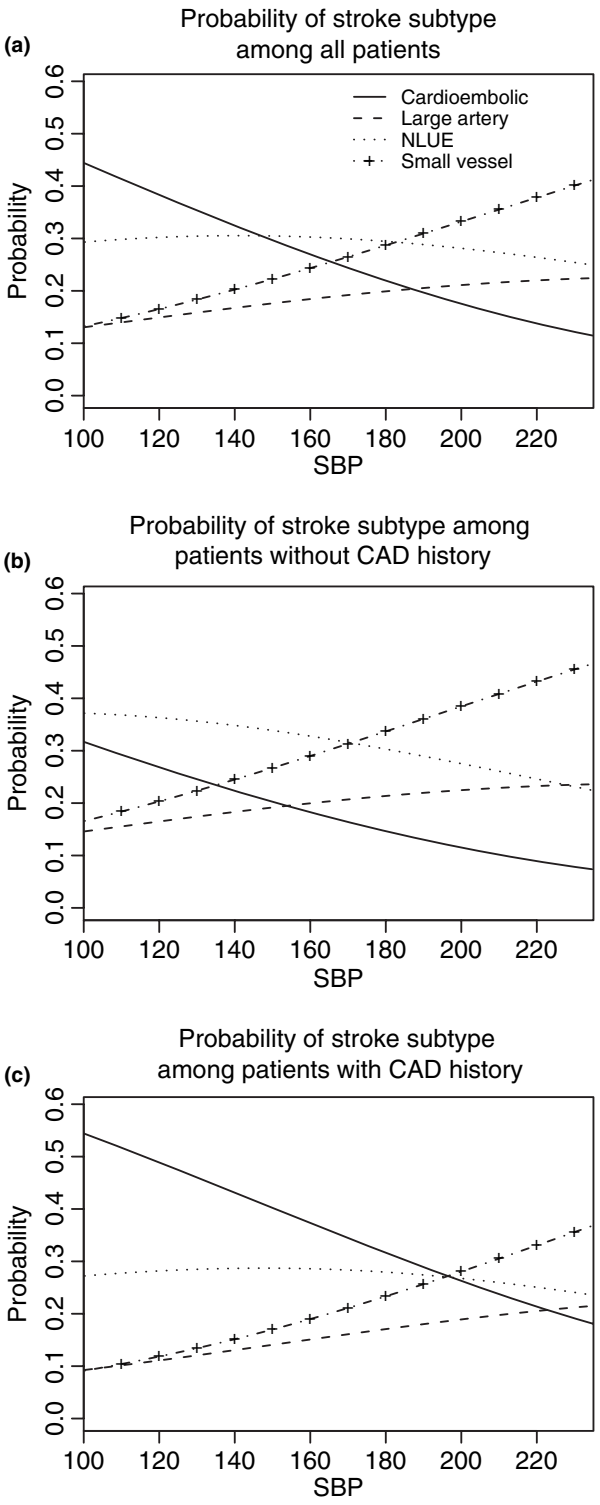

Fig. 1 Probability of stroke subtype. The probability of stroke subtype based on presenting blood pressure for unadjusted (a) and adjusted (b) and (c) models. NLUE, nonlacunar stroke of unknown aetiology, i.e. nonlacunar stroke of either possible cardioembolic or possible large artery aetiology.

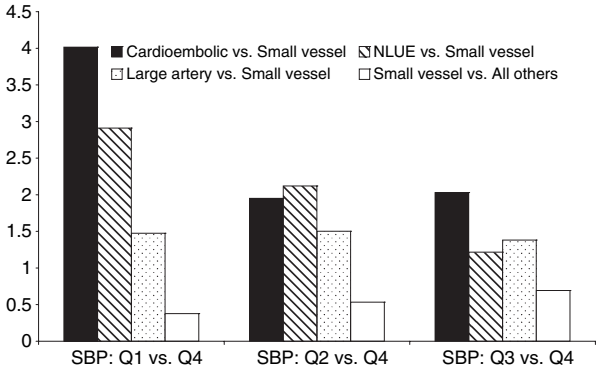

Fig. 2 Adjusted odds ratios of stroke subtype versus small vessel occlusion by quartiles of systolic blood pressure. Systolic blood pressure quartiles: Q1, 90–139 mmHg; Q2,140–159 mmHg; Q3, 160–181 mmHg; Q4, 182–260 mmHg. For all odds ratios, Q4 was the referent. NLUE, nonlacunar stroke of unknown aetiology i.e. nonlacunar stroke of either possible cardioembolic or possible large artery aetiology.

burden of recurrent stroke. Current guidelines recommend anticoagulation to prevent recurrence in most cases of cardioembolic stroke, though acute anticoagulation is not recommended [14, 15]. Additional data would be needed, including cost considerations, before widespread changes in practice could be recommended.

Prior studies examining the relationship between blood pressure during acute hospitalization and stroke subtype have demonstrated similar trends, with small vessel occlusion having higher, and cardioembolic stroke having lower, SBP throughout the hospitalization [3, 6, 7, 16]. Our findings are congruent with the findings of these studies, and importantly expand this observation to a community setting without an academic medical centre. In addition, the current report provides estimates of risk of cardioembolic stroke given initial, presenting blood pressure rather than trends throughout acute hospitalization. This may allow for a higher suspicion of cardioembolic stroke at the time of presentation. The mechanism underlying the association of presenting blood pressure and ischaemic stroke subtype is uncertain. Possible factors include prior hypertension and pre-existing cardiac disease along with the treatment for these conditions, as well as size and cerebral location of the stroke. Further evaluation of these mechanisms is warranted.

The distribution of stroke subtype in this community is similar to the overall distribution of stroke subtype reported in the TOAST trial, a meta-analysis of population-based stroke incidence studies, and a population-based stroke study from Germany [8, 17, 18]. A recent population-based study published from France did show a higher incidence of large artery atherosclerosis as the aetiological subtype (35.8%); however, the investigators reported a proportion of cardioembolic stroke similar to that of the current study and other studies [19]**.** About 20% of the patients in the current investigation had an 'undetermined' classification. Prior studies using the TOAST classification system have characterized about one-third to one-half of subjects as 'undetermined aetiology' [8, 17, 20]. This 'undetermined' group was different in our sample from the determined group, notably their strokes were minimally less severe, and they more frequently had a history of prior stroke or TIA. The likely explanation for our study having a smaller 'undetermined' group is the inclusion of the NLUE category which allowed for the classification of patients in whom insufficient information existed to distinguish between large artery and cardioembolic aetiology. In the current report, the point estimate of the OR for the association between NLUE and presenting SBP was intermediate between the definite cardioembolic and the large artery groups. This is consistent with the presumed mix of both (cardioembolic and large artery) subtypes in the NLUE subtype.

This investigation has several important limitations. First, a significant portion of patients were classified as either NLUE or 'undetermined'. It is likely that these groups contained missed cases of cardioembolic stroke. Perhaps less diagnostic testing was performed in patients with minor stroke, which would diminish the ability to assign a classification, and tend to increase the likelihood that patients with minor stroke would be classified as either NLUE or 'undetermined'. Another limitation is that the time interval between stroke onset and blood pressure measurement was not collected in the BASIC study; blood pressure has been previously shown to decrease after stroke onset [21, 22]. In addition, the

primary aims of BASIC did not include this sub-study and the findings should be used for hypothesis generation rather than direct application to widespread clinical practice. It is possible that clinicians were more thorough in examining for cardiac sources of emboli in patients with low SBP. In addition, the BASIC study did not collect information on history of congestive heart failure. This and other cardiac parameters not included in our analysis may be helpful in predicting cardioembolic subtype in patients presenting with ischaemic stroke. Despite these limitations, this study was conceived without prior examination of the data, and the BASIC study abstractors were blinded to this study question, as were the study neurologists who assigned the subtypes.

In summary, this work demonstrates that lower presenting SBP, along with increasing age and history of CAD are associated with classification into cardioembolic aetiology of ischaemic stroke in a representative bi-ethnic community. Further prospective exploration and confirmation of this relationship is needed, including further study of possible mechanisms for this observed association.

Author contributions

LBM is the primary investigator for the BASIC project. LBM and WJM conceptualized and designed this study, assisted by BNS, MAS, DLB and LDL. LBM and KU performed the assignment of subtypes. LBM, FPB, KU and JEM performed validation of cerebrovascular events. BNS was the statistician and designed and performed the statistical analysis of the database. LBM, WJM, BNS, MAS, DLB and LDL interpreted the data. WJM and LBM drafted and edited the manuscript, assisted by BNS, MAS, DLB, LDL, KU, DBZ, JJM, FPB and JEM. All authors have seen and approved the final version of this manuscript.

Conflict of interest statement

The authors have no relevant financial interests related to the material in the manuscript.

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