



Krishnan, Kailash and Beishon, Lucy and Berge, Eivind and Christensen, Hanne and Dineen, Robert A. and Ozturk, Serefnur and Sprigg, Nikola and Wardlow, Joanna M. and Bath, Philip M.W. (2017) Relationship between race and outcome in Asian, Black and Caucasian patients with spontaneous intracerebral haemorrhage: data from the Virtual International Stroke Trials Archive (VISTA) and Efficacy of Nitric Oxide in Stroke trial (ENOS). *International Journal of Stroke* . ISSN 1747-4949 (In Press)

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Relationship between race and outcome in Asian, Black and Caucasian patients with spontaneous intracerebral haemorrhage: data from the Virtual International Stroke Trials Archive (VISTA) and Efficacy of Nitric Oxide in Stroke trial (ENOS)

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Key words: intracerebral haemorrhage, ethnicity, race, outcome, randomised controlled trial

ABBREVIATIONS

BI	Barthel Index
BP	blood pressure
EQ-5d	European quality of Life-5 Dimensions questionnaire
EQ-VAS	European quality of life-visual analogue scale
ICH	intracerebral haemorrhage
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
RCT	Randomised controlled trial

Word count

Abstract: 198

Manuscript including supplement: 5044

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ABSTRACT

Background and purpose

Although poor prognosis after intracerebral haemorrhage relates to risk factors and haematoma characteristics, there is limited evidence for the effect of race-ethnicity.

Methods

Data from 1011 patients with intracerebral haemorrhage enrolled into hyperacute trials and randomised to control were obtained from the Virtual International Stroke Trials Archive (VISTA) and Efficacy of Nitric Oxide in Stroke (ENOS) Trial. Clinical characteristics and functional outcome were compared among three racial groups – Asians, Blacks and Caucasians.

Results

The majority of patients were Caucasian (78.1%) followed by Asians (14.5%) and Blacks (5.5%). At baseline, Caucasians were older and had larger haematoma volumes; Blacks had lower Glasgow Coma Scale and higher systolic blood pressure (all $p < 0.05$). Although the primary outcome of modified Rankin scale (mRS) did not differ at 90 days ($p = 0.14$), there were significant differences in mortality ($p < 0.0001$) and quality of life (EQ-5D $p < 0.0001$; EQ-VAS $p = 0.015$). In test of multiple comparisons, Caucasians were more likely to die ($p = 0.0003$) and had worse quality of life (EQ-5D $p = 0.003$; EQ-VAS $p < 0.0001$) as compared to Asians.

Conclusion

Race-ethnicity appears to explain some of the variation in clinical characteristics and outcomes after acute intracerebral haemorrhage. Factors that explain this variation need to be identified.

INTRODUCTION

Spontaneous intracerebral haemorrhage (ICH) is a severe cause of stroke associated with significant morbidity and mortality.(1) In contrast to ischaemic stroke where incidence has declined in recent decades, the number of admissions for ICH continues to increase.(2, 3) Variations in ICH incidence and outcome occur between different race-ethnicity groups. A higher incidence of ICH is observed among black and Hispanic populations when compared with Caucasians.(4-6) The SINO-MONICA-Beijing study reported greater mortality due to ICH in China compared to other countries.(7) Death caused by stroke was reported to be higher in Asians compared to Caucasian patients in the UK and Canada.(8, 9) The causes for these observations are unclear and might be explained by increased prevalence of risk factors such as diabetes and hypertension among Asians.(10-13) Additional explanatory factors also appear to include blood pressure at presentation.(5, 14-16) However, studies assessing ICH in different race-ethnicity groups have mostly involved small centres with limited numbers of patients, and have restricted comparisons to differences between two racial populations.(5, 6, 17, 18)

In this study, we compared baseline clinical characteristics and functional outcome in three racial groups in patients with ICH. The data came from the Virtual International Stroke Trials Archive (VISTA) collaboration,(19) and the Efficacy of Nitric Oxide in Stroke (ENOS) trial.(20)

Methods

Data sources

Included patients came from the VISTA-ICH archive, which includes data from a number of completed randomised controlled trials,(19) and the acute ENOS blood pressure trial.(20, 21) Patients were those with spontaneous ICH, as diagnosed locally using routine neuroimaging, and who were treated within 6 hours of onset. We included patients allocated to the control group in ENOS, as patients assigned to intervention are not included in VISTA. Patients were excluded if: age<18, ICH attributed to trauma, planned surgical evacuation, previously dependent (mRS ≥ 2), concurrent illness with life expectancy <6 months, pregnant or breast feeding women, and those already participating in a study involving another drug or device.

Baseline data

Data at baseline were obtained for age, sex, time from ictus to treatment, medical history (previous stroke, hypertension, ischaemic heart disease, diabetes mellitus, hypercholesterolemia, atrial fibrillation, and prior antithrombotic use), level of consciousness (Glasgow Coma Scale, GCS), stroke severity (National Institutes of Health Stroke Scale, NIHSS), systolic blood pressure (SBP), and heart rate. Race (and ethnicity) was defined as Asian (Filipino, Oriental, Asian, Indian, Palestinian and Arabic), Black (black, African/American, Caribbean), Caucasian (white or Caucasian) and Others (American Indian, mixed-coloured, mixed, Hispanic, coloured, Hawaiian and Pacific Islanders).

Outcome data

Outcome at day 90 was assessed using the modified Rankin scale (mRS) and all cause mortality; where available, data on disability (Barthel Index, BI) and quality of life (Euro-QoL, EQ-5D) were also assessed.

Neuroimaging

Depending on trial protocol, CT scans were performed following treatment and then again at 72 hours. Information from CT scans was collected for haemorrhage location, lesion volume, oedema volume, presence of mass effect, subarachnoid bleeding, intraventricular haemorrhage, brain atrophy and leukoaraiosis.

Statistical analysis

The primary outcome was the mRS at day 90. Baseline characteristics and outcomes were compared by Pearson χ^2 test for categorical variables, and analysis of variance for continuous variables. The relationship between baseline haematoma volume and mRS between ethnic groups was analysed using multiple regression. Individual comparisons between ethnic groups were made using Bonferroni correction. Mortality was assessed using Kaplan-Meier curves and Cox Regression. Analyses were adjusted for age, NIHSS, ICH volume and time to treatment. Confidentiality agreements precluded identification of the individual trials in VISTA-ICH and so analyses were not adjusted for trial. Since death is present in outcome

scores such as mRS (6), HUS (0) and BI (-5), death was scored for EQ-VAS as -1. Statistical significance was set at $p \leq 0.05$. All analyses were performed using SPSS (version 21) running on an Apple Mac computer.

RESULTS

Baseline clinical and neuroimaging characteristics

A total of 1011 patients were identified: 979 recruited from VISTA-ICH,(19) and 32 from ENOS.(20) The mean age was 66.2 years, 63.2% were male, the average time to treatment was 3.7 hours, and the mean GCS was 13.8 (Table 1). The majority of patients were Caucasian (78.1%), followed by Asians (14.5%) and Blacks. Less than 2% were in the 'other group' and these were removed from further analyses. When analysed by baseline characteristics, Black patients were younger and more likely to have a previous history of hypertension and higher SBP at baseline. Caucasian patients trended to have more atrial fibrillation, and Asian patients were less likely to have a prior history of antithrombotic use. The mean ICH volume was 22.7 cm³ and most haematomas were located in the deep subcortical white matter of the brain (Table 1).

Clinical outcomes

Table 2 shows clinical and radiological outcome measures by ethnicity. The primary outcome, mRS, did not differ between race groups at either day 7 or 90 (Figure 1). Similarly, there was no difference in NIHSS during the first 7 days. Whilst the Barthel Index differed at 7 days, it was not significant at day 90 using a test of multiple comparisons. Quality of life, assessed using two measures (health utility status derived from EQ-5D, and EQ-VAS), differed between the three groups (Table 2, Figure 2); following adjustment for multiple comparisons, Caucasians had a

worse quality of life scores for both EQ-5D and EQ-VAS as compared to Asians (Table 2). Adjusted survival rates differed between race-ethnicity groups (Table 2, Figure 3), explained by a significant difference between Asians and Caucasians ($p=0.005$). There were no other significant differences for other outcomes.

Neuroimaging outcomes

ICH volume differed across the race groups on both the first follow-up scan (Table 2, Figure 4) and at 72 hours. (Table 2); in both cases, Caucasians tended to have larger haematoma (Table 2). Similarly, oedema volumes differed across the race groups on both the first follow-up scan and at day 7 with Caucasian patients have large oedema volumes than Black patients. The presence of hydrocephalus also differed and was highest in Caucasians. The presence of intraventricular haemorrhage, subarachnoid haemorrhage and midline shift did not differ between the race groups (Table 2).

When assessing the relationship between baseline haematoma volume and mRS, there was a significant difference in the slope of the regression lines between the race-ethnicity groups; blacks and Asians appeared to have a worse mRS for a given haematoma volume ($p=0.047$; Supplementary Figure 1). There were no other significant differences between any of the other comparison groups.

DISCUSSION

To our knowledge, this is the first study to examine clinical and neuroimaging features and outcomes in ICH patients across three race groups. Significant differences in age, the frequency or previous stroke and hypertension, Glasgow coma scale, blood pressure and ICH volume were present between Caucasian, Asian and black patients. Similarly, differences in neuroimaging features were present for haematoma location and volume, oedema volume, and the presence of subarachnoid haemorrhage, hydrocephalus, leukoaraiosis and cerebral atrophy. Although there was no difference in the primary outcome of mRS at day 90, significant differences in case fatality and quality of life were present. Similarly, differences in ICH and oedema volume, and the presence of hydrocephalus, were present between the race groups.

Black patients were younger and a larger proportion had a history of hypertension which could be associated with increased smoking, alcohol and drug abuse.(17, 18) It is noteworthy that BP in blacks was higher on admission and probably reflects inadequate control, poor compliance with treatment or treatment resistance.(17, 22) One study assessing race-ethnic BP differences ICH reported similar findings but the comparison groups were different.(23) Higher BP in the acute phase of ICH is common (24) and associated with neurological deterioration through haematoma expansion and re-bleeding.(24-26) The treatment implications of racial difference in BP lowering need investigation as evidence suggests that early treatment is both

safe and feasible,(20, 27) and is now recommended in guidelines.(28, 29) In contrast to a previous report of greater mortality in blacks for every stroke subtype,(30) VISTA-ENOS found reduced survival in Caucasians with ICH. This finding is difficult to explain and may relate to haemorrhage location, inherent susceptibility to ICH or quality of care or simply that race-ethnic differences persist even after controlling for such characteristics.

As would be expected, ICH survivors had a quality of life worse than that reported in the general population.(31, 32) The difference between Caucasians and Asians has been reported previously,(14, 33) and may relate to family values, cultural attitudes and care preferences.(33, 34) In one study, Asians were more likely to be living at home whilst Caucasians were less likely to be discharged home despite better functional improvement.(35) Apart from cultural and family factors, age, female sex, stroke severity, persistent neglect and socioeconomic status have also been shown to affect quality of life after stroke.(36, 37)

The strengths of the study include a relatively large sample size for a study population with detailed clinical, radiological information and multiple functional endpoints. The included patients were from neutral RCT's or control group and therefore assessment of the race-ethnic differences avoided the confounding effects of active treatment. However, there are some limitations. First, the analysis on observational data from RCT's has the disadvantage that patients were included on the basis of pre-specified selection criteria. It is possible that those with more

severe stroke with reduced level of consciousness, older patients with multiple comorbidities and pre-existing do not resuscitate orders may have been excluded. Therefore, the results may not be applicable to a population of unselected ICH patients. Second, the VISTA collaboration does not reveal the identities of the individual trials and so it is uncertain as to what inclusion criteria were used to select patients. Additionally, analyses could not be adjusted for the source trials, which is important since trials themselves are a determinant of outcome. Nevertheless, the data were subject to strict verification and so the results are externally valid. Third, ethnicity relates to culture, geography, language and it is not clear from the data if this was self-reported or defined by the investigator. Fourth, to compensate for limited numbers, distinct subpopulations were grouped into one ethnic group (for example Asians included people from China, Philippines, the Indian subcontinent, and Arabian peninsula) whilst small groups, present in the 'others' category were excluded. This may have not been appropriate as stroke risk and functional outcome vary within subpopulations living in the same country and between countries.(38, 39) Last, the analysis is limited to trials sharing information within the collaboration and therefore those studies that are not represented in VISTA would not have been included.

In conclusion, this analysis from hyperacute trials in haemorrhagic stroke found significant race differences in baseline clinical characteristics and haematoma measures. There were no difference in the primary outcome of death or dependency but differences in death rates and quality of life were apparent. Further

studies are needed to which factors explain race-ethnic differences and whether these differences become larger over time. Our results suggest that future trials should undertake measures to ensure adequate representation of all major race-ethnic groups. This might include standard definitions for race-ethnicity that reflect common features but not limited to, biological, cultural and social differences. Further research is also needed to understand where inadequacies in health care systems exist and what interventions can be made to reduce such disparities. This could include allowing more resources to developing countries or those without access to specialist stroke care teams.

ACKNOWLEDGEMENTS

VISTA-ICH Steering Committee: D. F. Hanley (Chair), K. Butcher, S. Davis, B. Gregson, K.R. Lees, P. Lyden, S. Mayer, K. Muir and T. Steiner

ENOS Steering Committee: Amarenco P, Bath PM, Berge E, Lees KR, Muir K, Pocock S, Venables G, Wardlaw JM and Whynes D

The authors thank the VISTA collaboration for sharing the relevant data and investigators and patients who participated in ENOS.

FUNDING

ENOS was funded by the Medical Research Council and sponsored by the University of Nottingham.

DISCLOSURES

VISTA is a non-profit collaboration of academics and commercial organisations. Each VISTA steering committee member has contributed to organisation of clinical trials and where industry support was involved have acknowledged this in the individual trial publications. Philip Bath is Stroke Association Professor of Stroke Medicine, Chief Investigator of ENOS, and a NIHR Senior Investigator. Joanna Wardlaw was the neuroimaging lead of ENOS. No author involved in this work has any additional interest to report.

REFERENCES

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet*. 2009;373(9675):1632-44.
2. Islam M, Anderson C, Hankey GJ, Hardie K, Carter K, Broadhurst R, et al. Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth Community Stroke Study. *Stroke*. 2008;39(3):776-82.
3. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet*. 2004;363(9425):1925-33.
4. Labovitz DL, Halim A, Boden-Albala B, Hauser WA, Sacco RL. The incidence of deep and lobar intracerebral hemorrhage in whites, blacks and hispanics. *Neurology*. 2005;65:518-22.
5. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, et al. Stroke in a biracial population: the excess burden of stroke among blacks. *Stroke*. 2004;35:426-31.
6. Bruno A, Carter S, Qualls C, Nolte KB. Incidence of spontaneous intracerebral hemorrhage among Hispanics and non-Hispanic whites in New Mexico. *Neurology*. 1996;47:405-8.
7. Chen DY, Roman GC, Wu GX, Wu ZS, Yao CH, Zhang M, et al. Stroke in China (SINO-MONICA-Beijing Study) 1984-1986. *Neuroepidemiology*. 1992;11:15-23.
8. Wild S, Mckeigue P. Cross sectional analysis of mortality by country of birth in England and Wales, 1970-92. *BMJ*. 1997;314:705-10.
9. Sheth T, Nair C, Nargundkar M, Anand S, Yusuf S. Cardiovascular and cancer mortality among Canadians of European, south Asian and Chinese origin from 1979 to 1993: an analysis of 1.2 million deaths. *CMAJ*. 1999;161(2):132-8.
10. Hsu RT, Ardron ME, Brooks W, Cherry D, Taub NA, Botha JLT. The 1996 Leicestershire community stroke & ethnicity study: differences and similarities between South Asian and white strokes. *International Journal of Epidemiology*. 1999;28:853-8.
11. Fang J, Foo SH, Jeng JS, Yip PK, Alderman MH. Clinical characteristics of stroke among Chinese in New York City. *Ethn Dis*. 2004;14(3):378-83.
12. Feigin V, Carter K, Hackett M, et al. Ethnic disparities in incidence of stroke subtypes: Auckland regional community stroke study, 2002-2003. *Lancet Neurology*. 2006;5(2):130-9.

13. Gunarathne A, Patel JV, Gammon B, Gill PS, Hughes EA, Lip GY. Ischemic stroke in South Asians: a review of the epidemiology, pathophysiology and ethnicity-related clinical features. *Stroke*. 2009;40:e415-e23.
14. Khan NA, Quan H, Hill MD, Pilote L, McAlister F, Palepu A, et al. Risk factors, quality of care and prognosis in South Asian, East Asian and White patients with stroke. *BMC Neurology*. 2013;13(74).
15. Qureshi AI, Giles WH, Croft JB. Racial differences in the incidence of intracerebral hemorrhage: effects of blood pressure and education. *Neurology*. 1999;52(8):1617-21.
16. van Asch C, Luitse M, Rinkel G, van der Tweel I, Algra A, Klijn C. Incidence, case fatality, and functional outcome of intracerebral haemorrhage overtime, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurology*. 2010;9(2):167-76.
17. Qureshi AI, Suri MA, Safdar K, Ottenlips JR, Janssen RS, Frankel MR. Intracerebral hemorrhage in blacks. Risk factors, subtypes, and outcome. *Stroke*. 1997;28(5):961-4.
18. Qureshi AI, Safdar K, Patel M, Janssen RS, Frankel MR. Stroke in young black patients. Risk factors, subtypes, and prognosis. *Stroke*. 1995;26(11):1995-8.
19. Ali M, Bath P, Brady M, David S, Diener H-C, Donnan G, et al. Development, Expansion and Use of a Stroke Clinical Trials Resource for Novel Exploratory Analyses. *International Journal of Stroke*. 2012;7:133-8.
20. Bath PMW, Woodhouse L, Scutt P, Krishnan K, Wardlaw JM, Bereczki D, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet*. 2015;385(9968):617-28.
21. ENOS Investigators. Baseline Characteristics of the 4011 patients recruited into the "efficacy of Nitric Oxide in Stroke (ENOS) trial. *International Journal of Stroke*. 2014;9(6):711-20.
22. Zahuranec DB, Wing JJ, Edwards DF, Menon RS, Fernandez SJ, Burgess RE. Poor long term blood pressure control after intracerebral hemorrhage. *Stroke*. 2012;43(10):2580-5.
23. Koch S, Elkind MS, Testai FD, Brown WM, Martini S, Sheth KN, et al. Racial-ethnic disparities in acute blood pressure after intracerebral hemorrhage. *Neurology*. 2016;87(8):786-91.
24. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke*. 1997;28(12):2370-5.

25. Fogelholm R, Avikainen S, Murros K. Prognostic value and determinants of first-day mean arterial pressure in spontaneous supratentorial intracerebral hemorrhage. *Stroke*. 1997;28:1396-400.
26. Passero S, Burgalassi L, D' Andrea P, Battistini N. Recurrence of bleeding in patients with primary intracerebral hemorrhage. *Stroke*. 1995;26:1189-92.
27. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368(25):2355-65.
28. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *International Journal of Stroke*. 2014;9(7):840-55.
29. Hemphill J, Greenberg S, Anderson C, Becker K, Bendok B, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. *Stroke*. 2015;46(7):2032-60.
30. Gillum RF. Stroke mortality in blacks. Disturbing trends. *Stroke*. 1999;30:1711-5.
31. de Haan RJ, Limburg M, Van der Muelen JHP, Jacobs HM, Aaronson NK. Quality of life after stroke: impact of stroke type and lesion location. *Stroke*. 1995;26:402-8.
32. Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. The de facto mental and addictive disorders service system. Epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. *Archives of General Psychiatry*. 1993;50:85-94.
33. Xian Y, Holloway RG, Smith EE, Schwamm L, Reeves MJ, Bhatt DL, et al. Racial/ethnic differences in process of care and outcomes among patients hospitalized with intracerebral hemorrhage. *Stroke*. 2014;45:3246-50.
34. Ottenbacher KJ, Campbell J, Kuo YF, Deutsch A, Ostir GV, Granger CV. Racial and ethnic differences in postacute rehabilitation outcomes after stroke in the United States. *Stroke*. 2008;39:1514-9.
35. McNaughton H, Feigin V, Kerse N, Barber PA, Weatherall M, Bennett D, et al. Ethnicity and functional outcome after stroke. *Stroke*. 2010;42:960-4.
36. de Haan RJ, Limburg M, Van der Meulen JHP, Jacobs HM, Aaronson NK. Quality of life after stroke. *Stroke*. 1995;26(26):402-8.
37. Christensen MC, Mayer S, Ferran JM. Quality of life after intracerebral hemorrhage: results of the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial *Stroke*. 2009;40(5):1677-82.

38. Pickle LW, Munigole M, Gilum RF. Geographic variation in stroke mortality in blacks and whites in the United States. *Stroke*. 1997;28(8):1639-47.
39. Lackland DT, Egan BM, Jones PJ. Impact of nativity and race on "Stroke Belt" mortality. *Hypertension* 1999;34(1):57-62.
40. Gray LJ, Ali M, Lyden PD, Bath PM. Interconversion of the National Institutes of Health Stroke Scale and Scandinavian Stroke Scale in acute stroke. *Journal of Stroke and Cerebrovascular Diseases*. 2009;18(6):466-8.

Table 1. Baseline characteristics of 1011 patients with intracerebral haemorrhage by ethnicity. Data are number (%) or mean (standard deviation). Comparisons by chi-square test or one-way analysis of variance.

Demographics	n	All	Caucasian	Asian	Black	Other	2p	C v A 2p	C v B 2p	A v B 2p
Number of patients (%)		1011	790 (78.1)	147 (14.5)	56 (5.5)	18 (1.8)				
<i>Clinical findings</i>										
Age (years)	1011	66.2 (12.5)	67.7 (12.1)	61.3 (12.5)	58.4 (11.3)	61.9 (11.0)	<0.001	<0.0001	<0.0001	0.13
Sex, male (%)	982	621 (63.2)	489 (63.3)	40 (65.6)	32 (57.1)	10 (71.4)	0.56	0.64	0.39	0.33
OTT (hrs)	1007	3.7 (1.2)	3.7 (1.2)	3.6 (1.4)	3.4 (1.2)	3.7 (1.2)	0.08	0.26	0.035	<0.0001
<i>Medical history</i>										
Previous stroke (%)	1011	106 (10.5)	71 (9.0)	24 (16.3)	8 (14.3)	3 (16.7)	0.017	0.011	0.23	0.83
Hypertension (%)	1011	813 (80.4)	613 (77.6)	133 (90.5)	52 (92.9)	15 (83.3)	<0.0001	<0.0001	0.006	0.78
IHD (%)	1011	105 (10.4)	92 (11.6)	10 (6.8)	3 (5.4)	0 (0)	0.07	0.11	0.19	1.00
Diabetes mellitus (%)	1011	177 (17.5)	135 (17.1)	25 (17.0)	11 (19.6)	6 (33.3)	0.89	1.00	0.59	0.68
HC (%)	997	49 (4.8)	43 (5.4)	5 (3.4)	1 (1.8)	0 (0)	0.49	0.40	0.42	1.00
Atrial fibrillation (%)	1011	68 (6.7)	62 (7.8)	4 (2.7)	2 (3.6)	0 (0)	0.047	0.022	0.43	0.67
Antithrombotic(s) (%)	162	162 (16.0)	143 (18.1)	8 (5.4)	7 (12.5)	4 (22.2)	0.005	1.00	0.77	0.87
NIHSS (/42) †	1008	13.7 (1.9)	13.7 (5.6)	13.3 (6.0)	15.1 (7.4)	13.7 (1.9)	0.12	0.37	0.08	0.07
GCS (/15)	1010	13.8 (1.8)	13.8 (1.8)	13.4 (1.9)	13.2 (2.2)	14.1 (1.7)	0.010	0.037	0.015	0.37
Systolic BP (mmHg)	1008	174.4 (29.2)	173.1 (29.3)	176.7 (26.5)	185.7 (40.0)	174.4 (29.2)	0.005	0.18	0.002	0.041
Diastolic BP (mmHg)	1007	93.2 (19.0)	91.6 (18.5)	97.1 (18.5)	106.0 (21.1)	93.8 (20.8)	<0.001	0.001	<0.0001	0.003
Heart rate (bpm)	1005	80.0 (15.1)	78.1 (15.4)	76.6 (13.8)	79.9 (14.6)	78.2 (14.1)	0.34	0.27	0.40	0.14
<i>Neuroimaging</i>										
Haematoma location (%)										
Lobar	863	134 (13.3)	122 (15.4)	5 (3.4)	7 (12.5)	0	0.001	<0.0001	0.57	0.045
Subcortical white matter	893	685 (67.8)	541 (68.5)	93 (63.3)	42 (75.0)	9 (50.0)	0.006	0.30	0.73	0.34

Thalamus	600	217 (21.5)	181 (22.9)	22 (15.0)	10 (17.9)	4 (22.2)	1.00	1.00	1.00	1.00
Brain stem/cerebellum	893	21 (2.1)	17 (2.2)	2 (1.4)	1 (1.8)	1 (5.6)	0.82	0.75	1.00	1.00
Haematoma volume (cm ³)	996	22.7 (23.1)	24.2 (24.9)	17.8 (13.1)	15.8 (14.1)	18.5 (17.3)	0.005	0.03	0.014	0.34
Oedema volume (cm ³)	874	13.9 (15.7)	14.9 (16.9)	11.1 (9.2)	9.9 (10.4)	8.1 (7.8)	0.007	0.015	0.041	0.48
Midline shift (%)	885	623 (61.6)	488 (61.8)	90 (61.2)	38 (67.9)	7 (38.9)	0.62	0.67	0.43	0.71
SAH (%)	1007	80 (7.9)	73 (9.2)	3 (2.0)	1 (1.8)	3 (16.7)	0.003	0.02	0.05	1.00
IVH (%)	876	286 (28.3)	234 (29.6)	33 (22.4)	17 (30.4)	2 (11.1)	0.22	0.14	0.75	0.26
Hydrocephalus (%)	860	619 (61.2)	517 (65.4)	64 (43.5)	29 (51.8)	9 (50.0)	<0.001	<0.0001	0.004	0.74
Leukoaraiosis (%)	619	287 (28.4)	251 (31.8)	21 (14.3)	12 (21.4)	3 (21.4)	0.28	0.29	0.18	0.66
Cerebral atrophy (%)	1007	552 (54.6)	469 (59.4)	50 (34.0)	21 (37.5)	12 (66.7)	<0.001	<0.0001	0.002	0.74

† Calculated (40) from Scandinavian Stroke Scale in ENOS

BP: blood pressure; GCS: Glasgow Coma Scale; HC: hypercholesterolemia; IHD: ischaemic heart disease; IVH: intraventricular haemorrhage; OTT: onset to treatment; SAH: subarachnoid haemorrhage

Table 2. Clinical and radiological outcomes by race groups. Data are number (%) and mean (standard deviation). Comparisons between group differences made by chi-square test or analysis of variance; multiple comparisons include Bonferroni correction.

	n	All	Caucasian	Asian	Black	Other	2p	C v A	C v B	A v B
Patients		1011	790	147	56	18		2p	2p	2p
<i>Clinical</i>										
mRS (/6)										
Day 7	538	4.1 (1.1)	4.2 (1.1)	4.2 (0.8)	3.9 (1.3)	4.6 (0.5)	0.36	1.00	0.07	0.12
Day 90	873	3.2 (1.6)	3.2 (1.6)	3.0 (1.6)	3.4 (1.7)	3.1 (1.8)	0.14	0.18	1.00	0.37
NIHSS (/42) †										
Day 1	936	13.1 (7.0)	13.1 (7.0)	12.8 (6.7)	13.2 (8.1)	12.4 (6.5)	0.89	1.00	1.00	1.00
Day 3	564	12.5 (8.0)	12.7 (8.2)	11.0 (6.3)	11.6 (8.3)	14.8 (7.0)	0.29	0.42	1.00	1.00
Day 7	534	10.8 (7.1)	10.9 (7.9)	10.2 (6.1)	10.7 (7.5)	13.1 (6.7)	0.80	1.00	1.00	1.00
Day 90	958	8.1 (9.8)	8.1 (10.1)	6.0 (5.7)	9.6 (10.4)	9.7 (10.6)	0.31	0.88	0.96	0.41
Barthel Index (/100)										
Day 7	539	28.9 (31.1)	28.6 (31.2)	30.6 (29.1)	33.9 (36.5)	14.4 (16.1)	0.010	1.00	1.00	1.00
Day 90	872	63.0 (37.4)	62.9 (37.6)	66.0 (35.7)	56.4 (39.0)	66.5 (39.1)	0.28	1.00	0.68	0.34
Day 90										
Death (%)	1011	211 (20.9)	189 (23.3)	11 (7.5)	9 (16.1)	2 (11.1)	<0.001	<0.001	0.59	0.33
EQ-5D (/1)	487	0.29 (0.37)	0.25 (0.36)	0.46 (0.40)	0.31 (0.40)	0.40 (0.39)	<0.001	<0.001	1.00	0.18
EQ-VAS (/100)	321	46.0 (33.5)	43.3 (33.6)	57.0 (30.2)	44.2 (35.2)	42.5 (60.1)	0.015	0.012	1.00	0.34
<i>Neuroimaging</i>										
ICH vol. (cm ³)										
Follow up scan	523	32.3 (32.2)	34.7 (34.4)	26.2 (23.8)	23.7 (23.6)	18.9 (24.1)	0.017	0.07	0.14	1.00

72 hours	930	27.3 (28.6)	28.7 (30.4)	23.3 (19.7)	20.1 (20.3)	21.6 (20.4)	0.019	0.13	0.09	1.00
Oedema vol. (cm ³)										
Follow up scan	428	31.8 (31.8)	34.1 (33.9)	29.1 (25.7)	19.7 (20.8)	19.7 (18.4)	0.030	0.65	0.038	0.46
72 hours	924	33.6 (30.9)	33.6 (30.9)	29.9 (22.1)	22.0 (19.6)	24.8 (23.4)	0.009	0.53	0.012	0.26
IVH (%)										
Follow up scan	399	195 (19.3)	145 (18.4)	35 (23.8)	14 (25.0)	1 (5.6)	0.98	0.90	1.00	1.00
72 hours	811	344 (34.0)	277 (35.1)	46 (31.3)	19 (33.9)	2 (11.1)	0.41	0.54	0.55	1.00
72 hours										
SAH (%)	566	97 (9.6)	87 (11.0)	7 (4.8)	2 (3.6)	1 (5.6)	0.23	0.21	0.20	0.71
Hydrocephalus (%)	791	605 (59.8)	498 (63.0)	67 (45.6)	31 (55.4)	9 (50.0)	<0.001	<0.001	0.016	0.60
Midline shift (%)	790	628 (62.1)	490 (62.0)	94 (63.9)	37 (66.1)	7 (38.9)	0.54	0.25	0.72	0.37

A: Asians; B: Blacks; C: Caucasians; EQ-5D: European Quality of Life-5 dimensions; EQ-VAS: European Quality of Life-Visual Analogue Scale; ICH: intracerebral haemorrhage; IVH: intraventricular haemorrhage; mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; SAH: subarachnoid haemorrhage

†Calculated from Scandinavian Stroke Scale in the ENOS trial (40)

Range of scores for patients in ENOS:

Barthel Index: -5 (death) to 0 (severe disability) to 100 (no disability).

Health utility status (HUS, derived from European Quality of Life-5 dimensions, EQ-5D): -0.5 (very poor quality of life, 0 (death) to 1.0 (perfect quality of life). European Quality of Life-Visual Analogue Scale (EQ-VAS): -1 (death), 0 (very poor) to 100 (excellent).

Zung Depression Scale (ZDS): 0 (normal), 100 (severe depression) to 102.5 (death)

Figure 1. Distribution of modified Rankin scores between the three race groups at day 90.

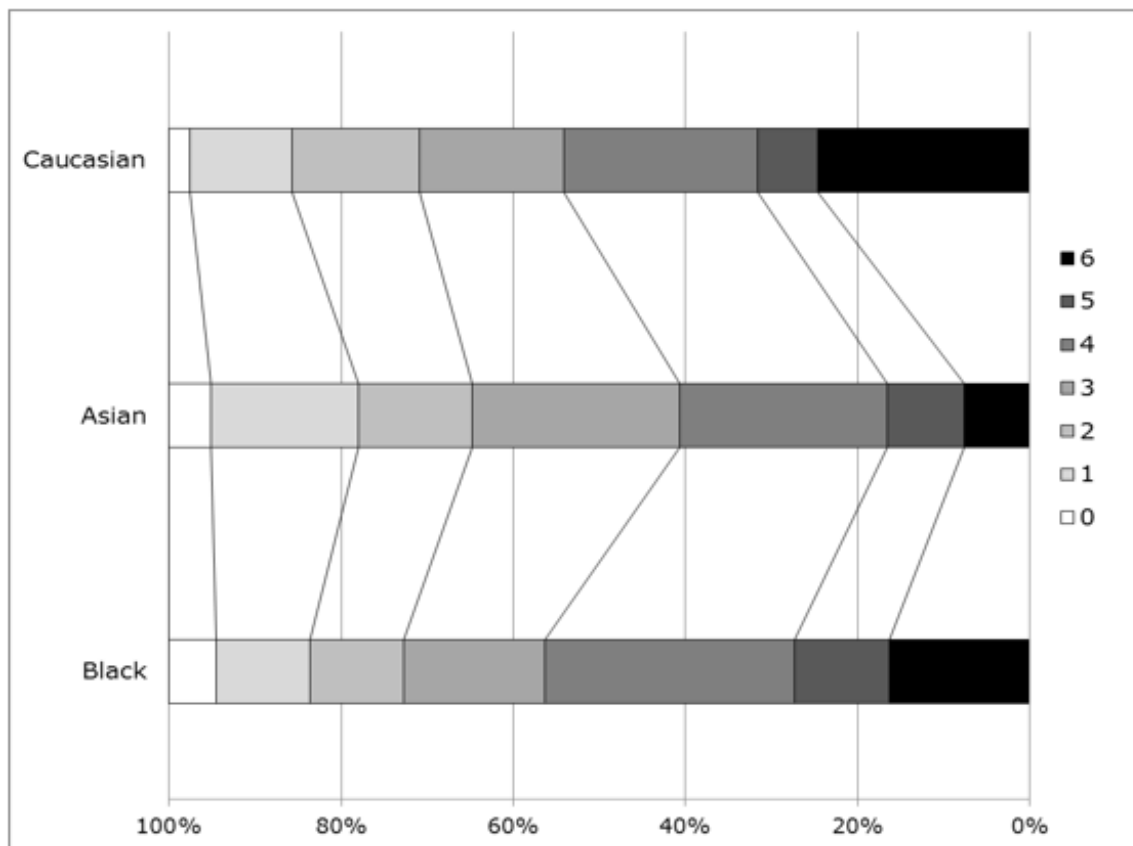


Figure 2. Box plots of Euro Quality of Life-5Dimension-3 level scores at day 90. Comparison by ANOVA $2p < 0.001$; Caucasian vs Asian $2p < 0.001$, Caucasian vs Black 1.00, Asian vs Black $2p = 0.18$.

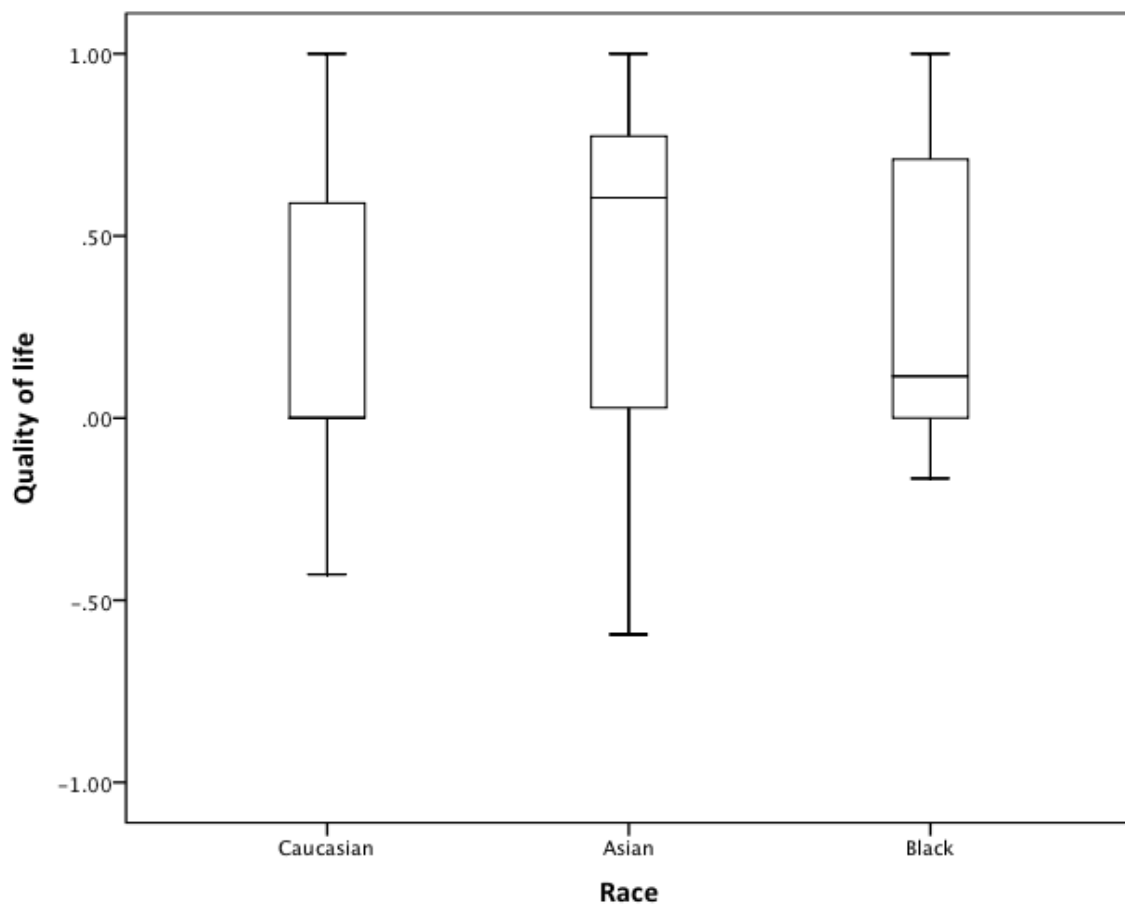
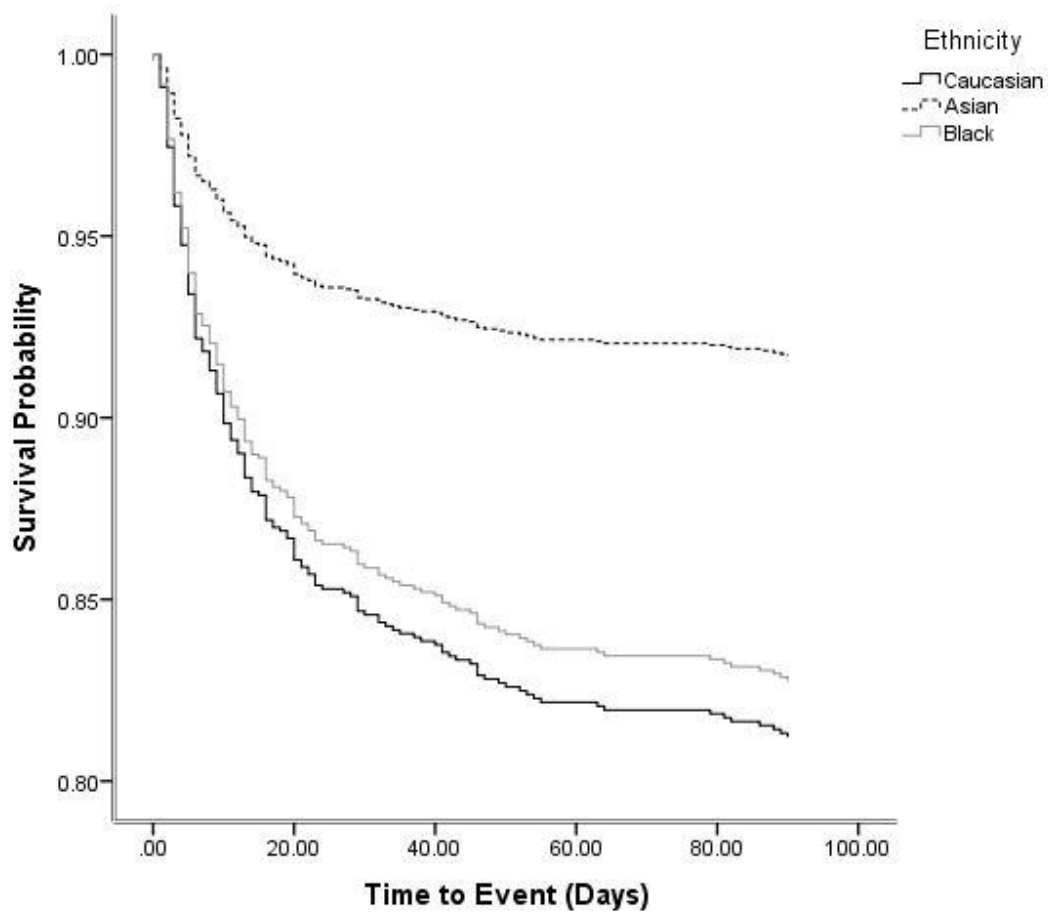
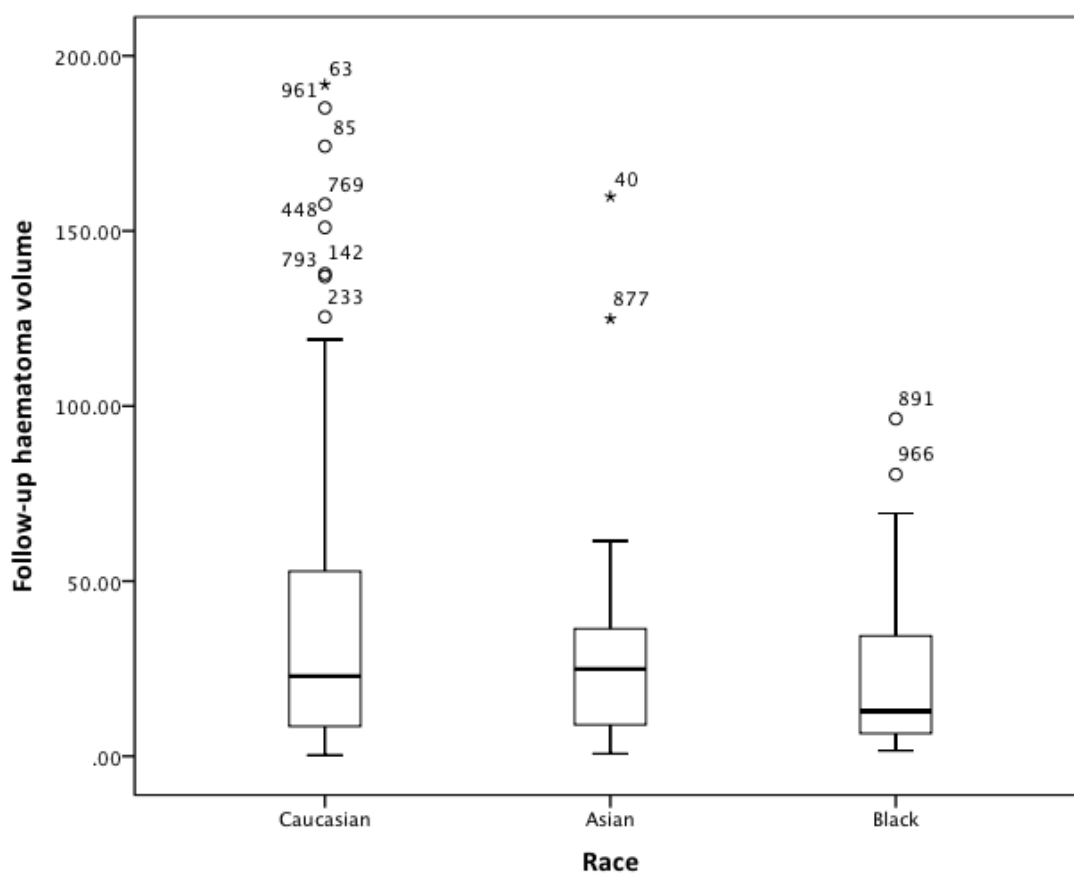


Figure 3. Cox regression with adjustment for age, baseline systolic blood pressure, stroke severity (NIHSS), haematoma volume and time to treatment: overall $p=0.021$; Asians vs Caucasians, hazard ratio 0.42 (95%



CI 0.22, 0.77); $p=0.005$.

Figure 4. Intracerebral haematoma volume on first follow-up imaging by race. Comparison by ANOVA $2p=0.017$; Caucasian vs Asian $2p=0.07$, Caucasian vs black 0.14 , Asian vs black $2p=1.0$.

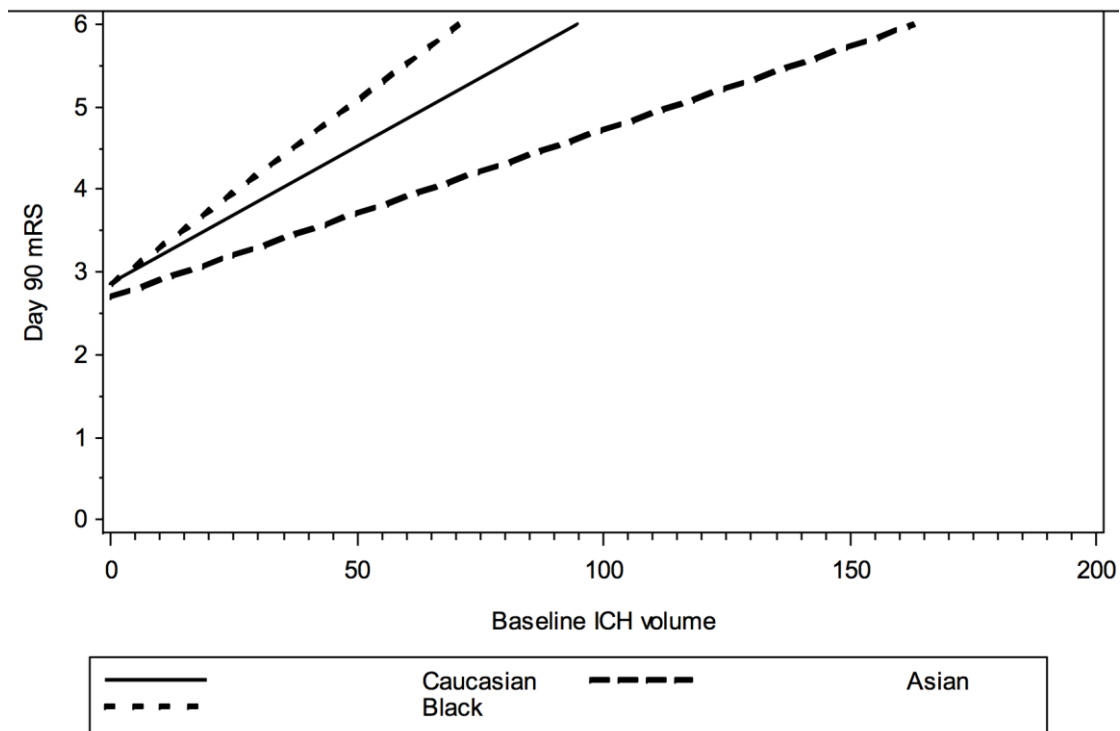


SUPPLEMENT

Relationship between race and outcome in Asian, Black and Caucasian patients with spontaneous intracerebral haemorrhage: data from the Virtual International Stroke Trials Archive (VISTA) and Efficacy of Nitric Oxide in Stroke trial (ENOS)

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Supplementary Figure 1. Relationship between haematoma volume at baseline and functional outcome, assessed as the modified Rankin Scale (mRS), at day 90 for Caucasians, Asians and Blacks. The continuous and dotted lines indicate the regression lines.



Overall comparison between the three ethnicities (using ANCOVA) showed a difference in the slopes of the regression lines between the three groups ($p < 0.0001$). Individual comparisons found significant difference in the slopes of the regression lines between Blacks vs Asians ($p = 0.047$; using Bonferroni correction).

There were no significant differences between any of the other ethnic group comparisons. Analysis was adjusted for age, baseline NIHSS, ICH volume and time to treatment.