Supplemental appendix

Effects of intensive blood pressure lowering on cerebral infarction in thrombolysed patients: insights from the ENCHANTED trial

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Inter-rater quality assessment of brain imaging analysis

Members of the brain imaging assessment group included GBZ (a radiologist) and CC, LYZ, and SO (neurologists with experience in stroke imaging). All readers rated a training set of 21 CT scans from participants of the ENCHANTED-dose arm; their reading results were compared to those of a neuroradiologist with more than 10 years of experience (i.e. used as the gold standard). Intraclass correlation coefficients (ICC) was used to assess the quality of inter-rater agreement of infarct size, with results shown in the table below.

Evaluation of agreement between readers and gold standard training set on infarct size

Rater	ICC
CC	0·925
GBZ	0·874
LYZ	0·171
SO	0·186

ICC of <0·4, 0·4-0·54, 0·55-0·69, 0·7-0·84, 0·85-1·0 are considered as 'poor', 'weak', 'moderate', 'good', and 'excellent' agreement, respectively.

CC and GBZ had excellent agreement and were considered as senior reviewers.

LYZ and SO had poor agreement and were considered as junior reviewers; they received further training.

During the formal reading process, approximately 10% of scans were re-assigned to two reviewers (one senior, one junior) for quality assessment. The results shown below indicate excellent agreement.

Evaluation of inter-rater agreement on infarct size

Raters	Number of double reviewed scans	ICC
CC and LYZ	100	0·996
GBZ and SO	98	0·893

Table S1. Distribution of patients with or without repeated braining imaging by site

Site number	Total number of patients recruited	Contribution to total number of missing brain imaging(n=719) n (%)	Contribution to brain imaging analysis(n=1477) N (%)
1655	484	310 (43·1)	174 (11·8)
692	122	98 (13·6)	24 (1·6)
666	66	63 (8·8)	3 (0·2)
1616	40	40 (5·6)	0 (0)
3728	34	34 (4·7)	0 (0)
767	39	12 (1·7)	27 (1·8)
3727	23	12 (1·7)	11 (0·7)
1644	95	11 (1·5)	84 (5·7)
601	57	11 (1·5)	46 (3·1)
3738	10	10 (1·4)	0 (0)
3192	25	8 (1·1)	17 (1·1)
3725	13	8 (1·1)	5 (0·3)
687	62	7 (1·0)	55 (3·7)
1656	22	7 (1·0)	15 (1·0)
55	8	7 (1·0)	1 (0·1)
1653	173	6 (0·8)	167 (11·3)
3159	70	6 (0·8)	64 (4·3)
823	25	6 (0·8)	19 (1·3)
3154	50	5 (0·7)	45 (3·0)
526	21	4 (0·6)	17 (1·2)
3194	6	4 (0·6)	2 (0·1)
3714	30	3 (0·4)	27 (1·8)
1652	29	3 (0·4)	26 (1·8)
917	22	3 (0·4)	19 (1·3)
3150	16	3 (0·4)	13 (0·9)
3740	3	3 (0·4)	0 (0)
509	37	2 (0·3)	35 (2·4)
772	9	2 (0·3)	7 (0·5)
3039	8	2 (0·3)	6 (0·4)
3193	5	2 (0·3)	3 (0·2)
658	3	2 (0·3)	1 (0·1)
796	3	2 (0·3)	1 (0·1)
3753	3	2 (0·3)	1 (0·1)
3042	2	2 (0·3)	0 (0)
3724	2	2 (0·3)	0 (0)
1673	87	1 (0·1)	86 (5·8)
3732	36	1 (0·1)	35 (2·4)
538	30	1 (0·1)	29 (2·0)
277	24	1 (0·1)	23 (1·6)
3742	14	1 (0·1)	13 (0·9)
3755	10	1 (0·1)	9 (0·6)
261	7	1 (0·1)	6 (0·4)
745	6	1 (0·1)	5 (0·3)
3130	6	1 (0·1)	5 (0·3)
28	5	1 (0·1)	4 (0·3)
533	5	1 (0·1)	4 (0·3)
775	4	1 (0·1)	3 (0·2)
1613	4	1 (0·1)	3 (0·2)
3126	4	1 (0·1)	3 (0·2)

Site number	Total number of patients recruited	Contribution to total number of missing brain imaging(n=719) n (%)	Contribution to brain imaging analysis(n=1477) N (%)
3748	3	1 (0·1)	2 (0·1)
3185	1	1 (0·1)	0 (0)
3749	1	1 (0·1)	0 (0)
238	4	0 (0)	4 (0·3)
260	20	0 (0)	20 (1·4)
278	6	0 (0)	6 (0·4)
282	4	0 (0)	4 (0·3)
285	13	0 (0)	13 (0·9)
286	7	0 (0)	7 (0·5)
287	3	0 (0)	3 (0·2)
289	32	0 (0)	32 (2·2)
499	1	0 (0)	1 (0·1)
517	4	0 (0)	4 (0·3)
690	2	0 (0)	2 (0·1)
780	4	0 (0)	4 (0·3)
828	1	0 (0)	1 (0·1)
912	2	0 (0)	2 (0·1)
915	1	0 (0)	1 (0·1)
1649	8	0 (0)	8 (0·5)
1669	30	0 (0)	30 (2·0)
1672	1	0 (0)	1 (0·1)
2132	5	0 (0)	5 (0·3)
2344	12	0 (0)	12 (0·8)
2381	20	0 (0)	20 (1·4)
3115	9	0 (0)	9 (0·6)
3116	3	0 (0)	3 (0·2)
3121	24	0 (0)	24 (1·6)
3128	7	0 (0)	7 (0·5)
3129	1	0 (0)	1 (0·1)
3136	2	0 (0)	2 (0·1)
3158	2	0 (0)	2 (0·1)
3166	13	0 (0)	13 (0·9)
3177	2	0 (0)	2 (0·1)
3184	1	0 (0)	1 (0·1)
3215	2	0 (0)	2 (0·1)
3227	10	0 (0)	10 (0·7)
3229	5	0 (0)	5 (0·3)
3234	15	0 (0)	15 (1·0)
3236	2	0 (0)	2 (0·1)
3266	2	0 (0)	2 (0·1)
3630	5	0 (0)	5 (0·3)
3634	1	0 (0)	1 (0·1)
3643	20	0 (0)	20 (1·4)
3654	3	0 (0)	3 (0·2)
3674	1	0 (0)	1 (0·1)
3739	3	0 (0)	3 (0·2)
3741	7	0 (0)	7 (0·5)
3743	1	0 (0)	1 (0·1)
3747	4	0 (0)	4 (0·3)
3750	1	0 (0)	1 (0·1)
3751	2	0 (0)	2 (0·1)

Site	Total number of	Contribution to total number of missing brain imaging(n=719)	Contribution to brain imaging analysis(n=1477)
number	patients recruited	n (%)	N (%)
3756	1	0 (0)	1 (0·1)
3757	3	0 (0)	3 (0·2)

Table S2. Characteristics of patients included and excluded in follow-up brain imaging analysis

Variable	Included N=1477 (67·3%)	Excluded N=719 (32·7%)	p value
Time from stroke onset to randomisation, h	3·3 (2·5-4·0)	3·5 (2·7-4·3)	<0·0001
Alteplase dosage, mg	0·9 (0·6-0·9)	0·9 (0·7-0·9)	0·003
Male	892/1477 (60%)	469/717 (65%)	0·03
Age, y	67·7 (12·1)	65·2 (12·2)	<0·0001
Asian ethnicity	955/1477 (65%)	663/719 (93%)	<0·0001
Systolic BP, mm Hg	165·8 (9·3)	164·1 (8·8)	<0·0001
Diastolic BP, mm Hg	90·8 (11·6)	91·2 (11·0)	0·48
Heart rate, beats per minute	79·4 (14·8)	79·2 (14·9)	0·81
NIHSS score*	8 (5-13)	7 (4-110)	<0·001
Severe (≥14)	323/1477 (22%)	114/719 (16%)	<0·001
GCS score†	15 (14-15)	15 (14-15)	0·09
Hypertension	1065/1476 (72%)	503/716 (70%)	0·35
Currently treated hypertension	756/1476 (51%)	256/716 (36%)	<0·0001
Coronary artery disease	215/1476 (15%)	94/716 (13%)	0·36
Other heart disease	78/1476 (5%)	16/716 (2%)	<0·001
Atrial fibrillation	234/1474 (16%)	78/716 (11%)	<0·01
Diabetes mellitus	336/1476 (23%)	160/716 (22%)	0·83
Hypercholesterolaemia	214/1476 (15%)	35/716 (5%)	<0·0001
Current smoker	319/1474 (22%)	125/716 (178%)	0·02
Pre-stroke independent (mRS score 0)	1219/1475 (83%)	658/716 (92%)	<0·0001
Anticoagulant use	21/1476 (1%)	8/716 (1%)	0·56
Aspirin or other antiplatelet agent	300/1476 (20%)	86/386 (12%)	<0·0001
Statin/other lipid lowering agent	281/1476 (19%)	57/716 (8%)	<0·0001
Final diagnosis not stroke	22/1460 (2%)	11/700 (2%)	0·91
Presumed stroke pathology‡			<0·0001
Extracranial atheroma	122/1438 (9%)	27/689 (4%)	
Intracranial atheroma	415/1438 (29%)	388/689 (56%)	
Small vessel disease	433/1438 (30%)	190/689 (28%)	
Cardioembolic	241/1438 (17%)	48/689 (7%)	
Dissection	6/1438 (0%)	1/689 (0%)	
Other/uncertain aetiology	221/1438 (15%)	35/689 (5%)	
SBP parameters, mm Hg			
Highest over 24 h	176·4 (14)	172·7 (13)	<0·0001
Lowest over 24 h	118·0 (13)	119·5 (13)	<0·01
Mean over 1-24 h	144 (13)	141 (11)	<0·0001
Variability 1-24 h	12·4 (6)	10·9 (6)	<0·0001
Magnitude reduction in 1 h	22·1 (16)	22·2 (15)	0·94

Data are n (%), mean (SD), or median (IQR).

CT denotes computed tomography, GCS Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale.

*Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficit.

†Scores range from 15 (normal) to 3 (deep coma).

‡Diagnosis according to the clinician's interpretation of clinical features and results of investigations at the time of separation from hospital.

P value are from t-test for mean (SD), Wilcoxon Rank Sum test for median (IQR) and Chi-square test for n (%).

Table S3. Characteristics of patients included and excluded in analysis of CT scans at 24-26 h

Characteristics	Included N=635 (28·9%)	Excluded N=1561 (71·1%)	P value
Time from stroke onset to randomisation, h	3·3 (2·5-4·0)	3·4 (2·6-4·1)	0·02
Alteplase dosage, mg	0·9 (0·6-0·9)	0·9 (0·6-0·9)	<0·0001
Female	262/635 (41%)	573/1561 (37%)	0·05
Age, years	68·9 (11·9)	66·1 (12·3)	<0·0001
Asian ethnicity	341/635 (54%)	1277/1559 (82%)	<0·0001
Systolic BP, mm Hg	166·1 (9·1)	164·9 (9·2)	0·01
Diastolic BP, mm Hg	89·9 (11·6)	91·3 (11·4)	<0·01
Heart rate, beats per minute	79·1 (14·7)	79·4 (14·8)	0·78
NIHSS score*	7 (4-12)	8 (5-12)	0·04
Severe (≥14)	129/635 (20%)	308/1561 (20%)	0·76
GCS score†	15 (14-15)	15 (14-15)	0·13
Hypertension	458/634 (72%)	1110/1558 (71%)	0·64
Currently treated hypertension	344/634 (54%)	668/1558 (42·9%)	<0·0001
Coronary artery disease	89/634 (14%)	220/1558 (14·1%)	0·96
Other heart disease	33/634 (5%)	61/1558 (3·9%)	0·18
Atrial fibrillation	107/633 (17%)	205/1557 (13·2%)	0·02
Diabetes mellitus	144/634 (23%)	352/1558 (22·6%)	0·95
Hypercholesterolaemia	111/634 (18%)	138/1558 (8·9%)	<0·0001
Current smoker	45/632 (23%)	299/1558 (19·2%)	0·05
Pre-stroke independent (mRS 0)	515/634 (81%)	1362/1557 (87·5%)	<0·001
Anticoagulants	12/634 (2%)	17/1558 (1·1%)	0·14
Aspirin or other antiplatelet	144/634 (23%)	242/1558 (16%)	<0·0001
Statin/other lipid lowering agent	134/634 (21%)	204/1558 (13%)	<0·0001
Presumed stroke‡	622/630 (99%)	1505/1530 (98%)	0·53
Presumed stroke pathology‡			<0·0001
Extracranial atheroma	62/622 (10%)	87/1505 (6%)	
Intracranial atheroma	130/622 (21%)	673/1505 (45%)	
Small vessel disease	192/622 (31%)	431/1505 (29%)	
Cardioembolic	107/622 (17%)	182/1505 (12%)	
Dissection	2/622 (0%)	5/1505 (0%)	
Uncertain aetiology	129/622 (21%)	127/1505 (8%)	
SBP parameters, mm Hg			
Highest over 24 h	161·2 (15·7)	156·9 (15·7)	<0·0001
Lowest over 24 h	130·4 (14·2)	128·6 (13·5)	<0·01
Mean over 1-24 h	145·1 (12·3)	142·1 (12·1)	<0·0001
Variability 1-24 h	12·6 (6·6)	11·6 (6·2)	0·0003
Magnitude reduction in 1 h	20·6 (16·1)	22·7 (15·5)	<0·01

Data are n (%), mean (SD), or median (IQR).

CT denotes computed tomography, GCS Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale.

*Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficit.

†Scores range from 15 (normal) to 3 (deep coma).

‡Diagnosis according to the clinician's interpretation of clinical features and results of investigations at the time of separation from hospital.

P value are from t-test for mean (SD), Wilcoxon Rank Sum test for median (IQR) and Chi-square test for n (%).

Table S4. Characteristics of patients in follow-up brain imaging analysis (N=1477), according to CT scans undertaken at 24 to 36 h versus any brain imaging at another time

Characteristics	Included N=635 (43·0%)	Excluded N=842 (57·0%)	p value
Time from stroke onset to randomisation, h	3·3 (2·5-4·0)	3·3 (2·5-4·0)	0·64
Alteplase dosage, mg	0·9 (0·6-0·9)	0·9 (0·6-0·9)	<0·01
Female	262/635 (41-%)	323/842 (38-%)	0·26
Age, years	68·9 (11·9)	66·8 (12·3)	<0·01
Asian Ethnicity	341/635 (54%)	614/842 (73%)	<0·0001
Systolic BP, mm Hg	166·1 (9·1)	165·7 (9·5)	0·41
Diastolic BP, mm Hg	89·9 (11·6)	91·5 (11·6)	0·01
Heart rate, beats per minute	79·1 (14·7)	79·5 (14·8)	0·60
NIHSS score*	7 (4-12)	8 (5-13)	<0·0001
Severe (≥14)	129/635 (20%)	194/842 (23%)	0·21
GCS score†	15 (14-15)	15 (14-15)	0·40
Hypertension	458/634 (72%)	607/842 (72%)	0·95
Currently treated hypertension	344/634 (54%)	412/842 (49%)	0·04
Coronary artery disease	89/634 (14·0%)	126/842 (15·0%)	0·62
Other heart disease	33/634 (5·2%)	45/842 (5·3%)	0·91
Atrial fibrillation	107/633 (16·9%)	127/841 (15·1%)	0·35
Diabetes mellitus	144/634 (22·7%)	192/842 (22·8%)	0·97
Hypercholesterolaemia	111/634 (17·5%)	103/842 (12·2%)	<0·01
Current smoker	145/632 (22·9%)	174/842 (20·7%)	0·29
Pre-stroke independent (mRS 0)	515/634 (81·2%)	704/841 (83·7%)	0·21
Anticoagulants	12/634 (1·9%)	9/842 (1·1%)	0·19
Aspirin or other antiplatelet	144/634 (23%)	156/842 (19%)	0·05
Statin/other lipid lowering agent	134/634 (21%)	147/842 (18%)	0·07
Non-stroke	8/630 (1%)	14/830 (2%)	0·52
Presumed stroke‡	622/630 (99%)	816/830 (98%)	0·52
Presumed stroke pathology‡			<0·0001
Extracranial atheroma	62/622 (10%)	60/816 (7%)	
Intracranial atheroma	130/622 (21%)	285/816 (35%)	
Small vessel disease	192/622 (31%)	241/816 (30%)	
Cardioembolic	107/622 (17%)	134/816 (16%)	
Dissection	2/622 (0%)	4/816 (1%)	
Other/uncertain aetiology	129/622 (21%)	92/816 (11%)	
SBP parameters, mm Hg			
Highest over 24 h	161·2 (15·7)	158·2 (16·3)	<0·001
Lowest over 24 h	130·4 (14·2)	128·6 (14·0)	0·02
Mean over 1-24 h	145·1 (12·3)	142·7 (12·7)	<0·001
Variability 1-24 h	12·6 (6·6)	12·2 (6·1)	0·16
Magnitude reduction in 1 h	20·6 (16·1)	23·2 (16·3)	<0·01
Brain imaging features			
Old vascular lesions	265/574 (46%)	59/160 (37%)	0·04
Brain atrophy	405/621 (65%)	101/177 (57%)	0·05
Periventricular white matter changes	297/620 (48%)	134/159 (84%)	<0·0001

Data are n (%), mean (SD), or median (IQR).

CT denotes computed tomography, GCS Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale.

*Scores on the NIHSS range from 0 to 42, with higher scores indicating greater neurological deficit·

†Scores range from 15 (normal) to 3 (deep coma).

‡Diagnosis according to the clinician's interpretation of clinical features and results of investigations at the time of separation from hospital.

P value are from t-test for mean (SD), Wilcoxon Rank Sum test for median (IQR) and Chi-square test for n (%).

Table S5. Baseline characteristics of patients with follow-up MRI at 24 to 36 h, by treatment

Characteristics	Intensive group N=94	Guideline group N=99	p value
Time from stroke onset to randomisation, h	3·4 (2·7-4·0)	3·3 (2·6-4·0)	0·29
Alteplase dosage, mg	0·9 (0·6-0·9)	0·9 (0·6-0·9)	0·64
Male	62/94 (66%)	57/99 (58%)	0·23
Age, y	65·4 (9·4)	64·0 (11·2)	0·35
Asian Ethnicity	84/94 (89%)	90/99 (91%)	0·72
Systolic BP, mmHg	165·4 (8·7)	163·9 (8·8)	0·25
Diastolic BP, mmHg	92·6 (12·8)	91·9 (10·6)	0·67
Heart rate beats per minute	77·6 (12·4)	79·9 (13·1)	0·21
NIHSS*	7 (4-10)	8 (4-12)	0·40
Severe (≥14)	17/94 (18%)	19/99 (19%)	0·84
GCS†	15 (14-15)	15 (14-15)	0·93
Severe (3-8)	5/94 (5%)	6/99 (6%)	0·82
Hypertension	71/94 (76%)	56/99 (57%)	<0·01
Currently treated hypertension	44/94 (47%)	31/99 (31%)	0·03
Coronary artery disease	14/94 (15%)	5/99 (5%)	0·02
Other heart disease	1/94 (1%)	2/99 (2%)	0·59
Atrial fibrillation	10/94 (11%)	9/99 (9%)	0·72
Diabetes mellitus	26/94 (28%)	21/99 (21%)	0·30
Hypercholesterolaemia	5/94 (5%)	4/99 (4%)	0·67
Current smoker	19/94 (20%)	17/99 (17%)	0·59
Pre-stroke independent (mRS 0)	85/94 (90%)	92/99 (93%)	0·53
Anticoagulants	-	1/99 (1%)	0·33
Aspirin or other antiplatelet	11/94 (12%)	11/99 (11%	0·90
Statin/other lipid lowering agent	12/94 (13%)	13/99 (13%)	0·94
Presumed stroke	94/94 (100%)	98/99 (99%)	0·33
Stroke pathology‡			0·42
Extracranial atheroma	5/94 (5%)	8/98 (8%)	
Intracranial atheroma	39/94 (42%)	42/98 (43%)	
Small vessel disease	36/94 (38%)	35/98 (36%)	
Cardioembolic	7/94 (7%)	10/98 (10%	
Dissection	0/94(0%)	0/98(0%)	
Other/uncertain aetiology	7/94(7%)	3/98 (3%)	
Brain imaging features			
Old vascular lesions	49/84 (58%)	57/89 (64%)	0·44
Brain atrophy	50/94 (53%)	57/95 (60%)	0·35
Periventricular white matter changes	73/88 (83%)	67/81 (83%)	0·97
Time from stroke onset to follow-up scan, h	29·5 (2·9)	29·0 (3%)	0·08

Data are n/N (%), mean (SD), or median (IQR).

CT denotes computed tomography, GCS Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale.

*Scores range from 0 to 42, with higher scores indicating more severe neurological deficit.

†Scores range from 15 (normal) to 3 (deep coma).

‡Diagnosis according to the clinician's interpretation of clinical features and results of investigations at the time of separation from hospital.

Table S6. Baseline characteristics of patients with CT/MRI at 24 to 36 h, by treatment

Variable	Intensive group N=388	Guideline group N=425	p value
Time from stroke onset to randomisation, h	3·3 (2·5-4·0)	3·3 (2·6-4·0)	0·89
Alteplase dosage, mg	0·9 (0·6-0·9)	0·9 (0·6-0·9)	0·63
Male	234/388 (60%)	248/425 (58%)	0·57
Age, y	68·0 (11·8)	67·9 (11·7)	0·94
Asian ethnicity	244/388 (63%)	259/425 (61%)	0·57
Systolic BP, mmHg	165·7 (9·1)	165·9 (9·0)	0·77
Diastolic BP, mmHg	91·5 (11·8)	89·6 (11·5)	0·02
Heart rate, beats per minute	79·1 (14·4)	79·0 (14·3)	0·93
NIHSS*	7 (4-12)	7 (4-12)	0·68
Severe (≥14)	80/388 (21%)	81/425 (19%)	0·58
GCS†	15 (14-15)	15 (14-15)	0·82
Hypertension	279/387 (72%)	294/425 (69%)	0·36
Currently treated hypertension	202/387 (52%)	210/425 (49%)	0·43
Coronary artery disease	47/387 (12%)	61/425 (14%)	0·35
Other heart disease	10/387 (3%)	26/425 (6·1)	0·01
Atrial fibrillation	55/387 (14%)	69/424 (16%)	0·42
Diabetes mellitus	85/387 (22%)	103/425 (24%)	0·44
Hypercholesterolaemia	54/387 (14%)	65/425 (15%)	0·59
Current smoker	85/386 (22%)	92/424 (22%)	0·91
Pre-stroke independent (mRS 0)	319/387 (82%)	358/425 (84%)	0·49
Antihypertensive agents	36/387 (9%)	40/424 (9%)	0·95
Anticoagulant use	6/387 (2%)	7/425 (2%)	0·91
Aspirin or other antiplatelet	72/387 (19%)	94/425 (22%)	0·22
Statin/other lipid lowering agent	69/387 (18%)	90/425 (21%)	0·23
Presumed stroke	383/386 (99%)	416/422 (99%)	0·38
Stroke pathology‡			0·39
Extracranial atheroma	34/383 (9%)	39/416 (9%)	
Intracranial atheroma	98/383 (26%)	110/416 (26%)	
Small vessel disease	134/383 (35%)	122/416 (29%)	
Cardioembolic	52/383 (14%)	70/416 (17%)	
Dissection	2/383 (1%)	-	
Other/uncertain aetiology	63/383 (16%)	75/416 (18%)	
Brain imaging features			
Old vascular lesions	192/349 (55%)	219/386 (57%)	0·64
Brain atrophy	240/385 (62%)	266/414 (64%)	0·57
Periventricular white matter changes	208/378 (55%)	223/402 (56%)	0·90

Data are n/N (%), mean (SD), or median (IQR).

CT denotes computed tomography, GCS Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale.

*Scores range from 0 to 42, with higher scores indicating more severe neurological deficit.

†Scores range from 15 (normal) to 3 (deep coma).

‡Diagnosis according to the clinician's interpretation of clinical features and results of investigations at the time of separation from hospital.

Table S7.Baseline characteristics of patients with any follow-up brain imaging, by treatment

Characteristics	Intensive group N=725	Guideline group N=752	p value
Time from stroke onset to randomisation, h	3·3 (2·5-4·0)	3·2 (2·6-4·0)	0·95
Alteplase dosage, mg	0·8 (0·1)	0·8 (0·1)	0·11
Male	441/725 (61%)	451/752 (60%)	0·74
Age, y	67·5 (12·4)	67·9 (11·9)	0·46
Asian ethnicity	465/725 (64%)	490/752 (65%)	0·68
Systolic BP, mm Hg	165·9 (9·5)	165·7 (9·2)	0·63
Diastolic BP, mm Hg	91·3 (11·7)	90·3 (11·5)	0·09
Heart rate, beats per minute	79·7 (14·5)	79·1 (15·0)	0·43
NIHSS*	8 (5-13)	8 (5-13)	0·11
Severe (≥14)	164/725 (23%)	159/752 (21%)	0·49
GCS†	15 (14-15)	15 (14-15)	0·76
Hypertension	531/724 (73%)	534/752 (71%)	0·32
Currently treated hypertension	381/724 (53%)	375/752 (50%)	0·29
Coronary artery disease	108/724 (15%)	107/752 (14%)	0·71
Other heart disease	35/724 (5%)	43/752 (6%)	0·45
Atrial fibrillation	105/724 (15%)	129/750 (17%)	0·17
Diabetes mellitus	151/724 (21%)	185/752 (25%)	0·07
Hypercholesterolaemia	103/724 (14%)	111/752 (15%)	0·77
Current smoker	158/723 (22%)	161/751 (21%)	0·85
Pre-stroke independent (mRS 0)	599/724 (83%)	620/751 (83%)	0·93
Antihypertensive agents	68/724 (9%)	70/749 (9%)	0·98
Anticoagulants	10/724 (1%)	11/752 (2%)	0·89
Aspirin or other antiplatelet	139/724 (19%)	161/752 (21%)	0·29
Statin/other lipid lowering agent	132/724 (18%)	149/752 (20%)	0·44
Non-stroke	10/717 (1%)	12/743 (2%)	0·73
Presumed stroke	707/717 (99%)	731/743 (98%)	0·73
Stroke pathology‡			0·42
Extracranial atheroma	58/707 (8%)	64/731 (9%)	
Intracranial atheroma	193/707 (27%)	222/731 (30%)	
Small vessel disease	234/707 (33%)	199/731 (27%)	
Cardioembolic	115/707 (16%)	126/731 (17%)	
Dissection	3/707 (0%)	3/731 (0%)	
Other/uncertain aetiology	104/707 (15%)	117/731 (16%)	
Brain imaging features			
Old vascular lesions	358/651 (55%)	385/691 (56%)	0·79
Brain atrophy	447/709 (63%)	447/733 (61%)	0·42
Periventricular white matter changes	372/691 (54%)	395/712 (56%)	0·54

Data are n/N (%), mean (SD), or median (IQR).

CT denotes computed tomography, GCS Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale.

*Scores range from 0 to 42, with higher scores indicating more severe neurological deficit.

†Scores range from 15 (normal) to 3 (deep coma).

‡Diagnosis according to the clinician's interpretation of clinical features and results of investigations at the time of separation from hospital.

Table S8. Relationship of intensive BP lowering treatment and secondary outcomes, by type of follow-up brain imaging

	Treatment group*		Unadjusted		Adjusted†	
	Intensive	Guideline	OR (95% CI)	p value	OR (95% CI)	P value
Any intracranial haemorrhage						
CT at 24-36 h	39/300 (13%)	54/335 (16%)	0·77 (0·49-1·20)	0·25	0·74 (0·46-1·19)	0·21
MR at 24-36 h	12/94(13%)	13/99 (13%)	0·97 (0·42-2·25)	0·94	0·84 (0·33-2·17)	0·72
CT/MR at 24-36 h	51/388 (13%)	65/425 (15%)	0·83 (0·56-1·24)	0·36	0·79 (0·52-1·20)	0·27
Any scan during follow-up	102/725 (14%)	135/752 (18%)	0·74 (0·56-0·99)	0·04	0·76 (0·57-1·01)	0·06
Parenchymal haematoma§						
CT at 24-36 h	14/300 (5%)	22/335 (7%)	0·66 (0·35-1·32)	0·25	0·76 (0·38-1·54)	0·45
MR at 24-36 h	7/94(7%)	6/99 (6%)	1·25 (0·40-3·88)	0·70	0·95 (0·26-3·49)	0·94
CT/MR at 24-36 h	22/388 (6%)	30/425 (7%)	0·79 (0·45-1·39)	0·41	0·82 (0·45-1·49)	0·51
Any scan during follow-up	45/725 (6%)	63/752 (8%)	0·73 (0·49-0·12)	0·12	0·76 (0·50-1·14)	0·18
Death or disability (mRS 2-6)						
CT at 24-36 h	148/296 (50%)	165/331 (50%)	1·01 (0·74-1·38)	0·97	1·00 (0·71-1·39)	0·98
MR at 24-36 h	39/94 (42%)	43/99 (43%)	0·96 (0·54-1·721)	0·90	0·86 (0·45-1·65)	0·65
CT/MR at 24-36 h	185/384 (48%)	207/421 (49%)	0·96 (0·72-1·26)	0·76	0·95 (0·71-1·28)	0·74
Any scan during follow-up	372/720 (52%)	392/747 (63%)	0·97 (0·79-1·19)	0·75	1·00 (0·81-1·24)	0·97

BP denotes blood pressure, CT computed tomography, MR magnetic resonance, mRS modified Rankin scale, OR odds ratio

*Data are n/N (%).

†Adjusted variables including pre-specified covariates (age, sex, ethnicity, pre-morbid function [mRS scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent or warfarin], and history of stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomised alteplase dose) and further covariates that <0·1 from the baseline characteristics (diastolic BP, other heart disease for CT at 24-36 hr, medical history of hypertension for MRI at 24-36 hr, diastolic BP and other heart disease for CT/MR at 24-36 hr, diastolic BP at admission for any follow-up scan). §Parenchymal haematoma type of haemorrhage according to Heidelberg classification.

Table S9. Location cerebral infarction by blood pressure treatment, according to scan type

	Treatment group		P value
	Intensive	Guideline	
CT at 24-36 h	/300	/335	
Supratentorial	49 (16%)	65 (19%)	0·31*
Infratentorial	3 (1%)	6 (2%)	0·40*
Brain-stem	3 (1%)	2 (1%)	0·57*
Cerebellum	2 (1%)	5 (2%)	0·32*
MRI at 24-36 h	/94	/99	
Supratentorial	47 (50%)	48 (49%)	0·80*
Infratentorial	11 (12%)	6 (6%)	0·17*
Brain-stem	9 (10%)	6 (6%)	0·36*
Cerebellum	2 (2%)	0 (0%)	0·24*
CT/MRI at 24-36 h	/388	/425	
Supratentorial	93 (24%)	110 (26%)	0·51*
Infratentorial	12 (3%)	12 (3%)	0·66*
Brain-stem	10 (3%)	7 (2%)	0·35*
Cerebellum	4 (1%)	5 (1%)	1·00*
Any scan during follow-up	/420	/478	
Supratentorial	184 (44%)	206 (43%)	0·78*
Infratentorial	26 (6%)	27 (6%)	0·51*
Brain-stem	21 (5%)	15 (3%)	0·16*
Cerebellum	9 (2%)	15 (3%)	0·36*

Data are N (%)

BP denotes blood pressure, CT computed tomography, MRI magnetic resonance imaging

*Chi-square test p value

Table S10. Type and volume of intracerebral haemorrhage by blood pressure treatment, and according to type of brain imaging

	Treatment group		p value
	Intensive	Guideline	
CT at 24-36 h			
Type	/39	/54	
HI1	15 (39%)	15 (28%)	0·28*
HI2	9 (23%)	16 (30%)	0·48*
PH1	6 (15%)	7 (13%)	0·74*
PH2	8 (21%)	16 (30%)	0·32*
Volume, mL	/15	/29	
Median	4·8 (1·3-13·7)	5·8 (2·5-19·5)	0·63†
MRI at 24-36 h			
Type	/12	/13	
HI1	4 (33%)	2 (20%)	0·57*
HI2	2 (17%)	3 (23%)	0·69*
PH1	6 (50%)	4 (31%)	0·65*
PH2	2 (17%)	2 (15%)	0·93*
Volume,	/4	/5	
Median	13·4 (5·5-59·0)	12·3 (9·3-27·6)	1·00†
CT/MR at 24-36 h			
Type	/51	/65	
HI1	19 (37%)	16 (26%)	0·20*
HI2	11 (22%)	18 (28%)	0·45*
PH1	12 (24%)	11 (17%)	0·38*
PH2	10 (20%)	18 (28%)	0·31*
Volume, mL	/19	/34	
Median	7·0 (2·0-20·0)	8·0 (2·5-20·0)	0·90†
Any scan during follow-up		/135	
Type	/102	/135	
HI1	31 (30%)	38 (28%)	0·71*
HI2	23 (23%)	31 (22%)	0·94*
PH1	25 (25%)	60 (22%)	0·68*
PH2	20 (20%)	33 (24%)	0·38*
Volume, mL	/42	/64	
Median	12·3 (2·2-25·4)	10·2 (2·3-25·9)	0·84†

BP denotes blood pressure, CT computed tomography, MR magnetic resonance, HI haemorrhagic infarction, PH parenchymal haematoma, SD standard deviation

*Chi-square test p value

†Wilcoxon rank p value

Any variable with frequency <10, Fisher exact test was reported.

Table S11. Results of primary analysis and interaction of cerebral infarction and any intracranial haemorrhage

	Intensive versus guideline-based BP lowering		p for interaction
Death or disability (mRS 2-6)	Adjusted OR (95 CI)	p value	Infarct size (ml) and intracranial haemorrhage
CT at 24-36 h	1·06 (0·72-1·56)	0·76	<0·0001
MRI at 24-36 h	0·75 (0·35-1·64)	0·47	0·02
CT/MRI at 24-36 h	0·97 (0·69-1·37)	0·87	<0·0001

BP denotes blood pressure, CI confidence interval, CT computed tomography, ICH intracranial haemorrhage, MRI magnetic resonance imaging, mRS modified Rankin scale, OR odds ratio

P for interaction between BP treatment and infarct size was 0·9686, 0·1433, and 0·4750, for CT at 24-36 h, MR at 24-36 h, and CT/MR at 24-36 h, respectively.

P for interaction between BP treatment and intracranial haemorrhage was 0·6642, 0·3310, and 0·8940 for CT at 24-36 hrs, MR at 24-36 h, and CT/MR at 24-36 hrs, respectively.

* CT at 24-36 h: Multivariable logistic regression model adjusted age, sex, ethnicity, pre-morbid function [mRS scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent or warfarin], and history of stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomised alteplase dose, diastolic BP, other heart disease, infarct volume at follow up, any intracranial haemorrhage and interaction between infarct volume and any intracranial haemorrhage

* MR at 24-36 h: Multivariable logistic regression model adjusted age, sex, ethnicity, pre-morbid function [mRS scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent or warfarin], and history of stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomised alteplase dose, medical history of hypertension, infarct volume at follow up, any intracranial haemorrhage and interaction between infarct volume and any intracranial haemorrhage

* CT/MR at 24-36 h: Multivariable logistic regression model adjusted age, sex, ethnicity, pre-morbid function [mRS scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent or warfarin], and history of stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomised alteplase dose, diastolic BP and other heart disease, infarct volume at follow up, any intracranial haemorrhage and interaction between infarct volume and any intracranial haemorrhage

Table S12. Blood pressure parameters and outcome in patients with any follow up scan

Variable	Complete cases data with any follow-up scan (N=1463)
Early SBP control parameters, mm Hg	/1463
Attained SBP*	144 (12·5)
SBP variability†	12 (6·3)
Magnitude of SBP reduction in the first h‡	22 (16·3)
Magnitude of SBP reduction in the 24 h§	36 (15·9)
BP management	
Standard BP management	744/1463 (51%)
Early intensive BP management	719/1463 (49%)
Outcomes	
Infarct size, mL	1·4 (0·0-16·9)
Location	/893
Supratentorial	388 (43%)
Infratentorial	53 (6%)
Brain-stem	24 (3%)
Cerebellum	36 (4%)
Any intracranial haemorrhage	236/1463 (16%)
Type	/236
HI1	69 (29%)
HI2	54 (23%)
PH1	55 (23%)
PH2	53 (23%)
Volume, mL	10·3 (2·2-23·0)
Functional outcome at 90-days	/1455
Ordinal shift of full range of scores	
0	354 (24%)
1	343 (24%)
2	220 (15%)
3	174 (12%)
4	150 (10%)
5	79 (5%)
6	135 (9%)
2-6 (death or disability)	758 (52%)
3-6 (death or major disability)	538 (37%)

Data are numbers/denominator, mean (SD), or median (IQI). BP indicates blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; IQI, interquartile interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SBP systolic blood pressure.

*Mean SBP in 1–24 h.

†SD of SBP in 1–24 h.

‡SBP at randomisation minus minimum SBP within the first h.

§SBP at randomisation minus minimum SBP within the first 24 h.

Table S13. Associations of early systolic blood pressure control parameters and infarct size in any follow up scan

BP parameter	Unadjusted		Model 1		Model 2		Model 3	
	Log Δmean (95 CI)*	p value	Log Δmean (95 CI)*	p value	Log Δmean (95 CI)*	p value	Log Δmean (95 CI)*	p value
Attained SBP	0·27 (0·11-0·43)	0·001	0·23 (0·09-0·37)	0·002	0·20 (0·03-0·38)	0·02	0·15 (0·01-0·30)	0·03
Variability of SBP	0·001 (-0·31-0·31)	1·00	-0·04 (-0·33-0·25)	0·80	-0·03 (-0·37-0·31)	0·86	-0·04 (-0·33-0·25)	0·78
Magnitude of SBP	-0·03 (-0·15-0·09)	0·63	-0·06 (-0·17-0·05)	0·28	-0·01 (-0·14-0·12)	0·88	-0·01 (-0·11-0·10)	0·90

CI denotes confidence interval, SBP systolic blood pressure, SD standard deviation

*Estimates of mean difference is reported for infarct size using log-linear regression model by an average every 10 mm Hg increases in the SBP measures

Model 1 (N=1325): age, sex, ethnicity, clinical severity (National Institute of Health Stroke Scale [NIHSS] score), time to randomised BP lowering, history of hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, previous stroke, pre-morbid modified Rankin scale (mRS), antithrombotic medication, trial arm, dose of rtPA, final pathological diagnosis of stroke, imaging modality (CT vs· MRI) and time to second scan (<24 and =24 hours)

Model 2 (N=729) further adjust baseline volume of cerebral ischaemia (on the diagnostic CT) with reduced observations

Model 3 (N=1463): multiple imputation adjusted covariates mentioned in both Model 1 and 2

Figure S1. Patient flow for MRI at 24-36 hours

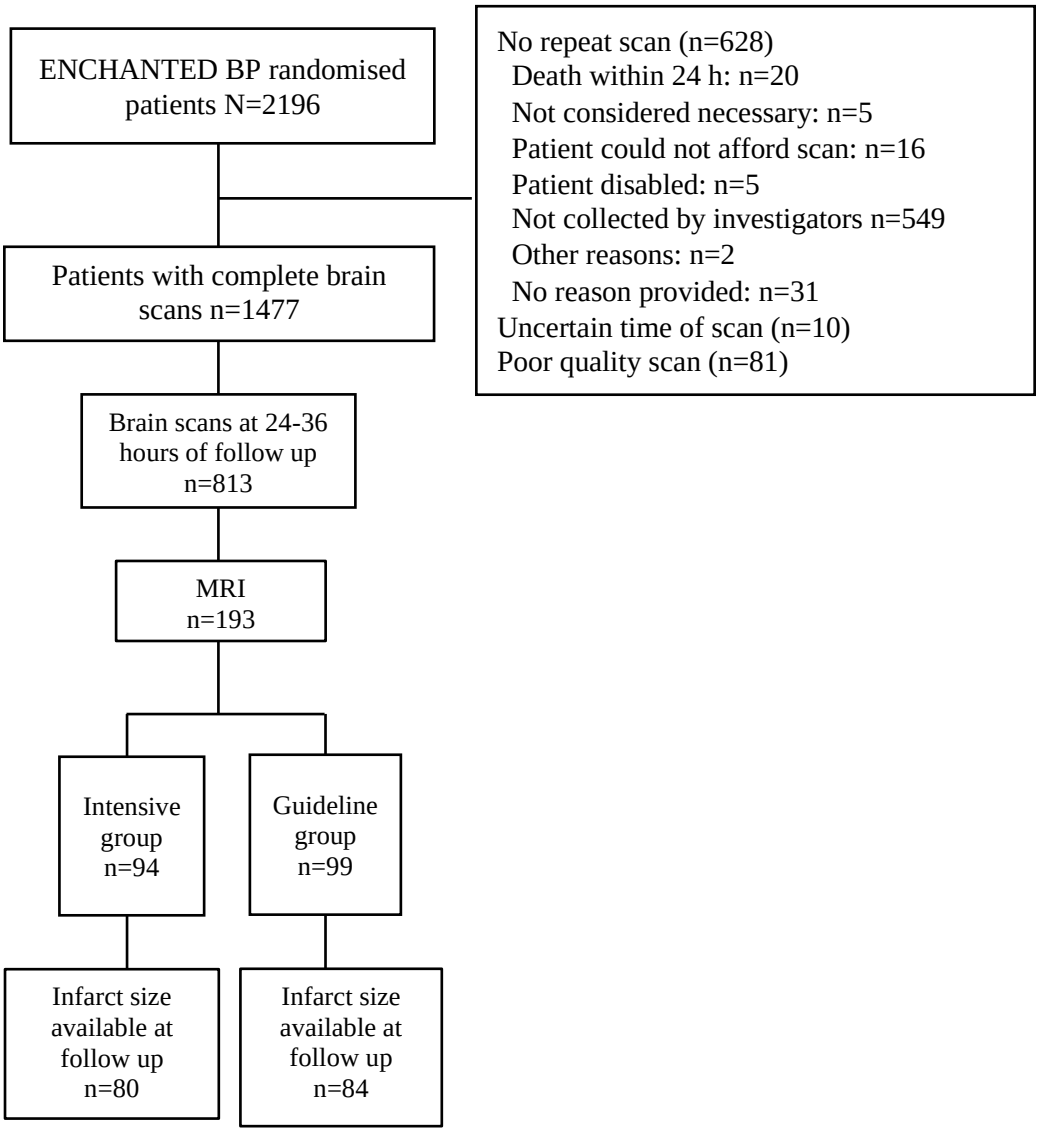


Figure S2. Patient flow for CT/MRI at 24-36 h

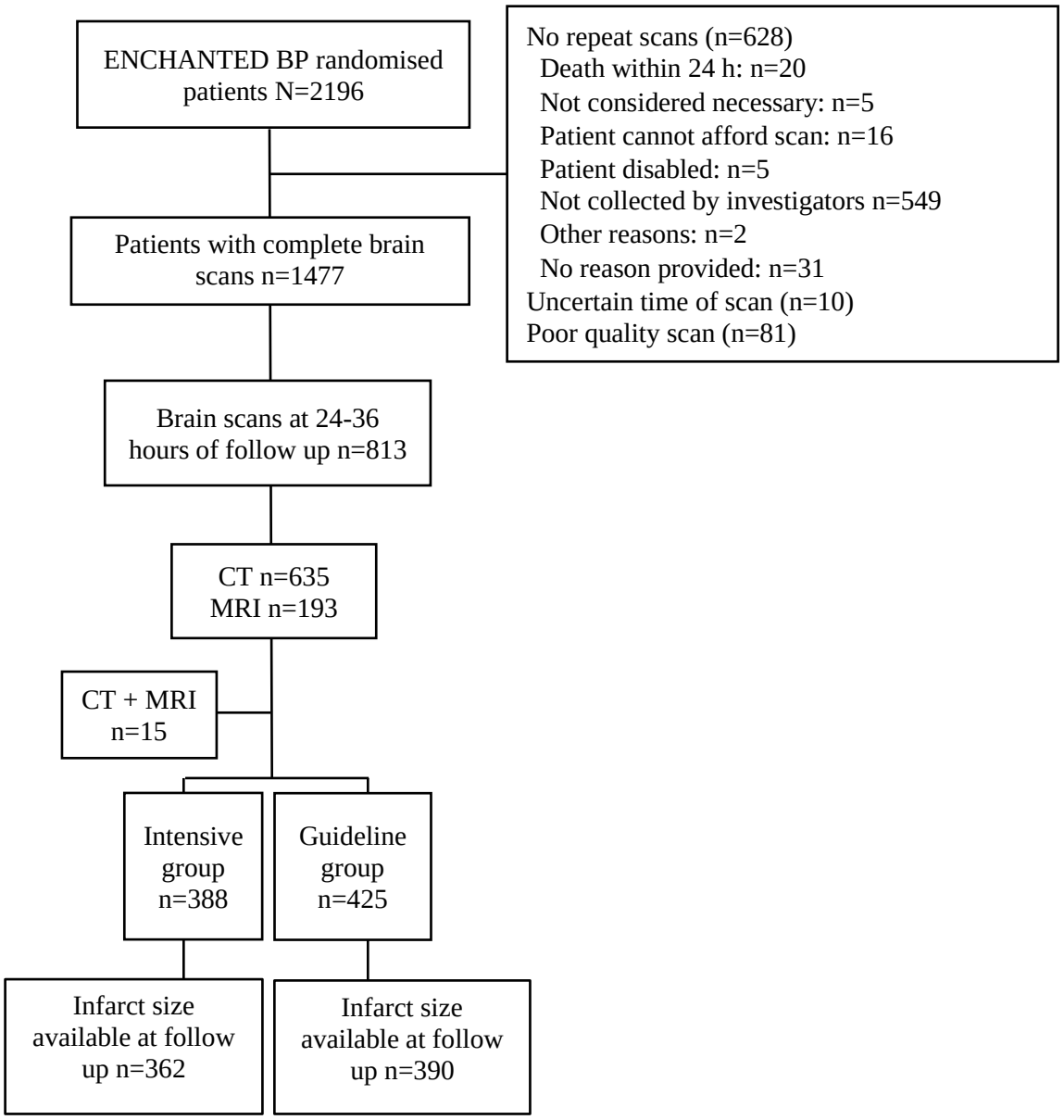


Figure S3. Patient flow for any scan during follow-up

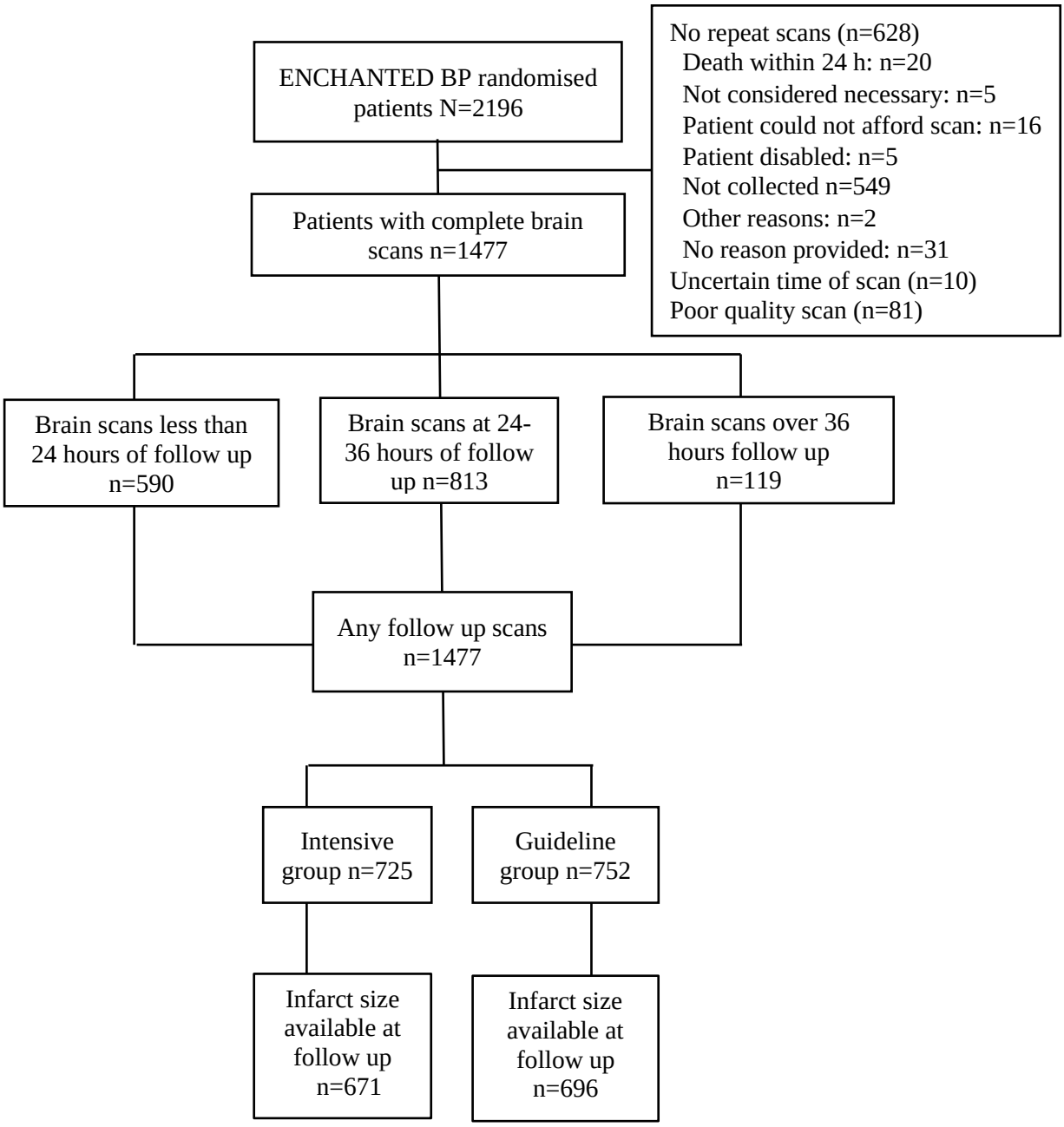
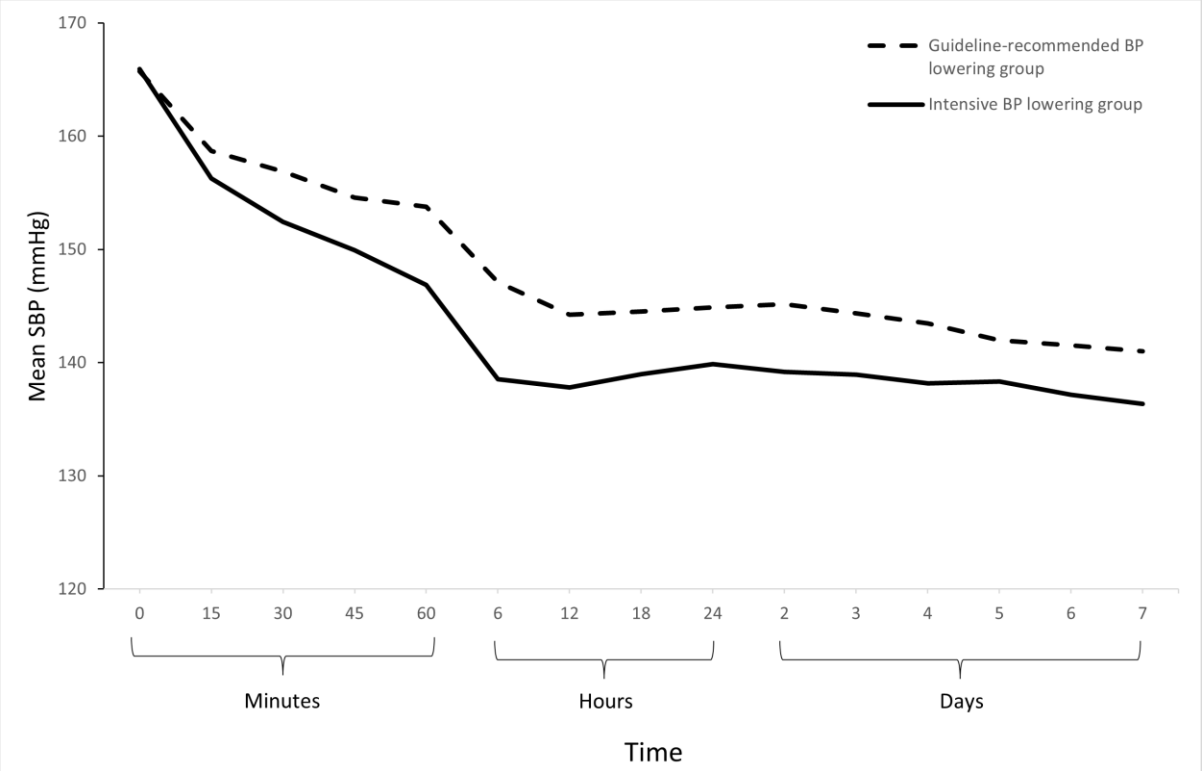


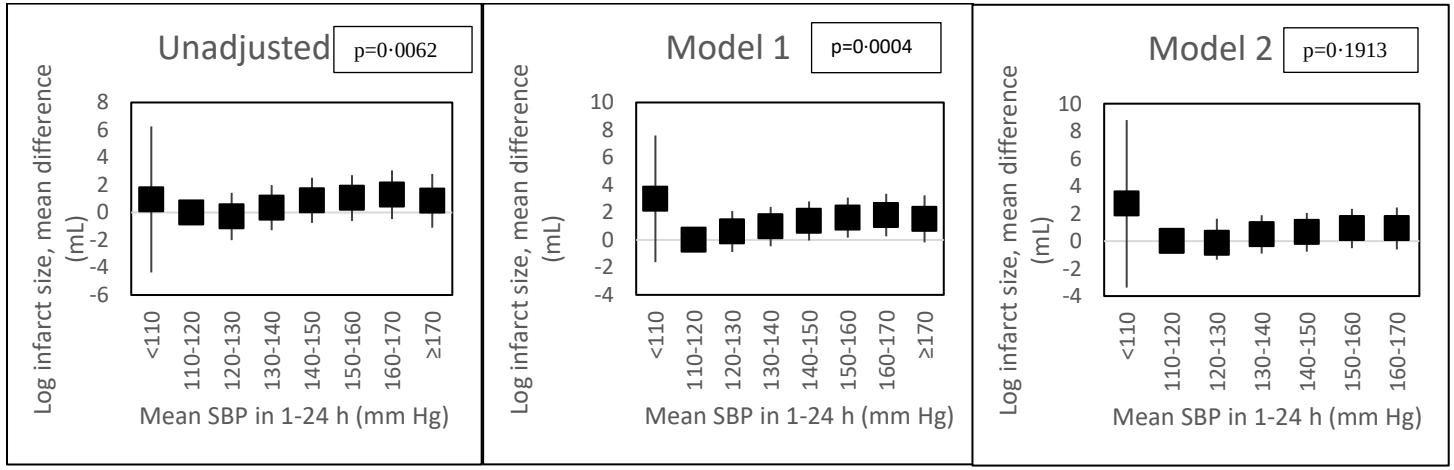
Figure S4. Mean systolic and diastolic blood pressure from randomisation to Day 7 for any follow-up scan



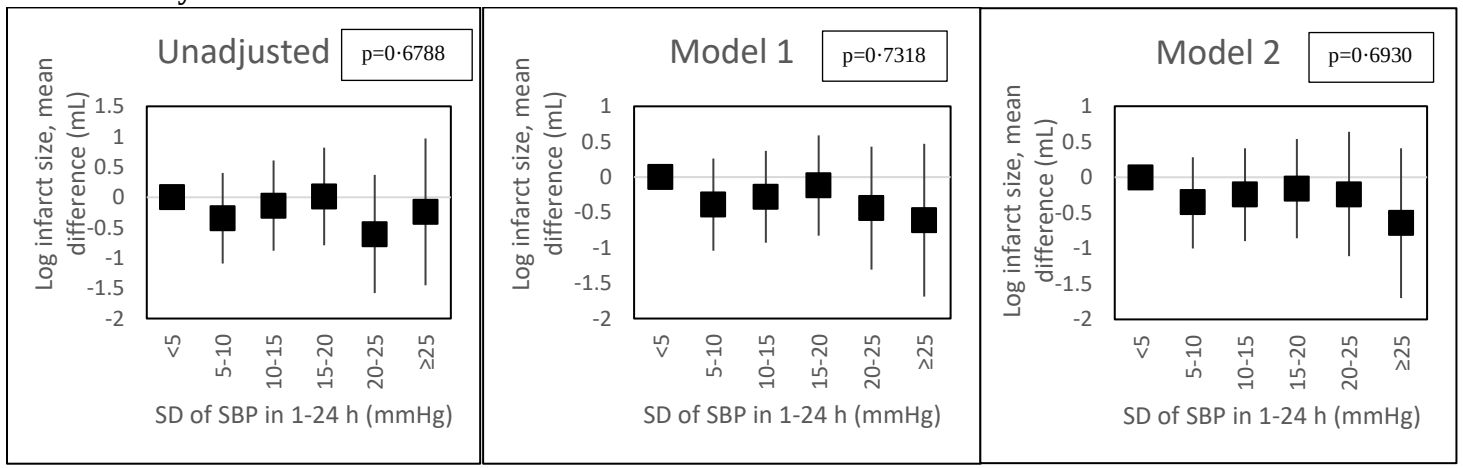
Blood pressure values are shown for intensive and guideline-recommended blood pressure lowering groups based on recordings at 15-min intervals for the first hour after randomisation (time 0), hourly from h 1 to 6, 6-h until 24 h, and twice daily until Day 7.

Figure S5. Associations of categorical early systolic blood pressure measures and infarct size in any follow up scan

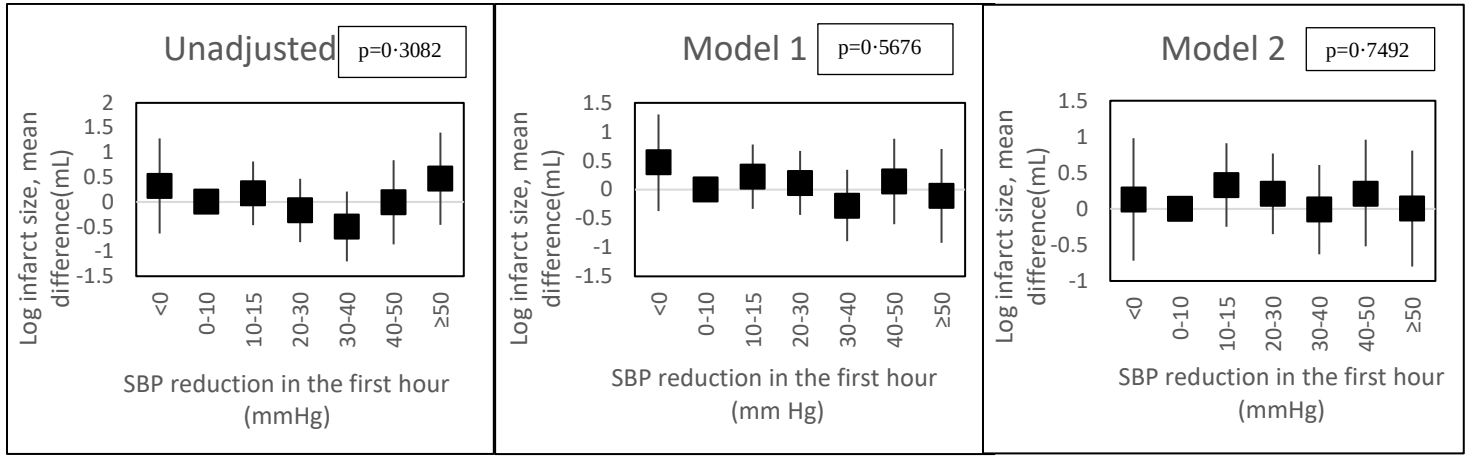
A. Attained SBP



B. Variability of SBP



C. Magnitude of reduction of SBP



SBP denotes systolic blood pressure, SD standard deviation

*Estimates of mean difference is reported for infarct size using log-linear regression model by an average every 10 mm Hg increases in the SBP measures

Model 1 (N=1325): age, sex, ethnicity, clinical severity (National Institutes of Health Stroke Scale [NIHSS] score), time to randomised BP lowering, history of hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, previous stroke, pre-morbid mRS, antithrombotic medication, trial arm, dose of intravenous alteplase, final pathological diagnosis of stroke, imaging modality (CT versus MRI) and time to selected scan (<24 and =24 h)

Model 2 (N=1463): multiple imputation adjusted covariates mentioned in both Model 1.