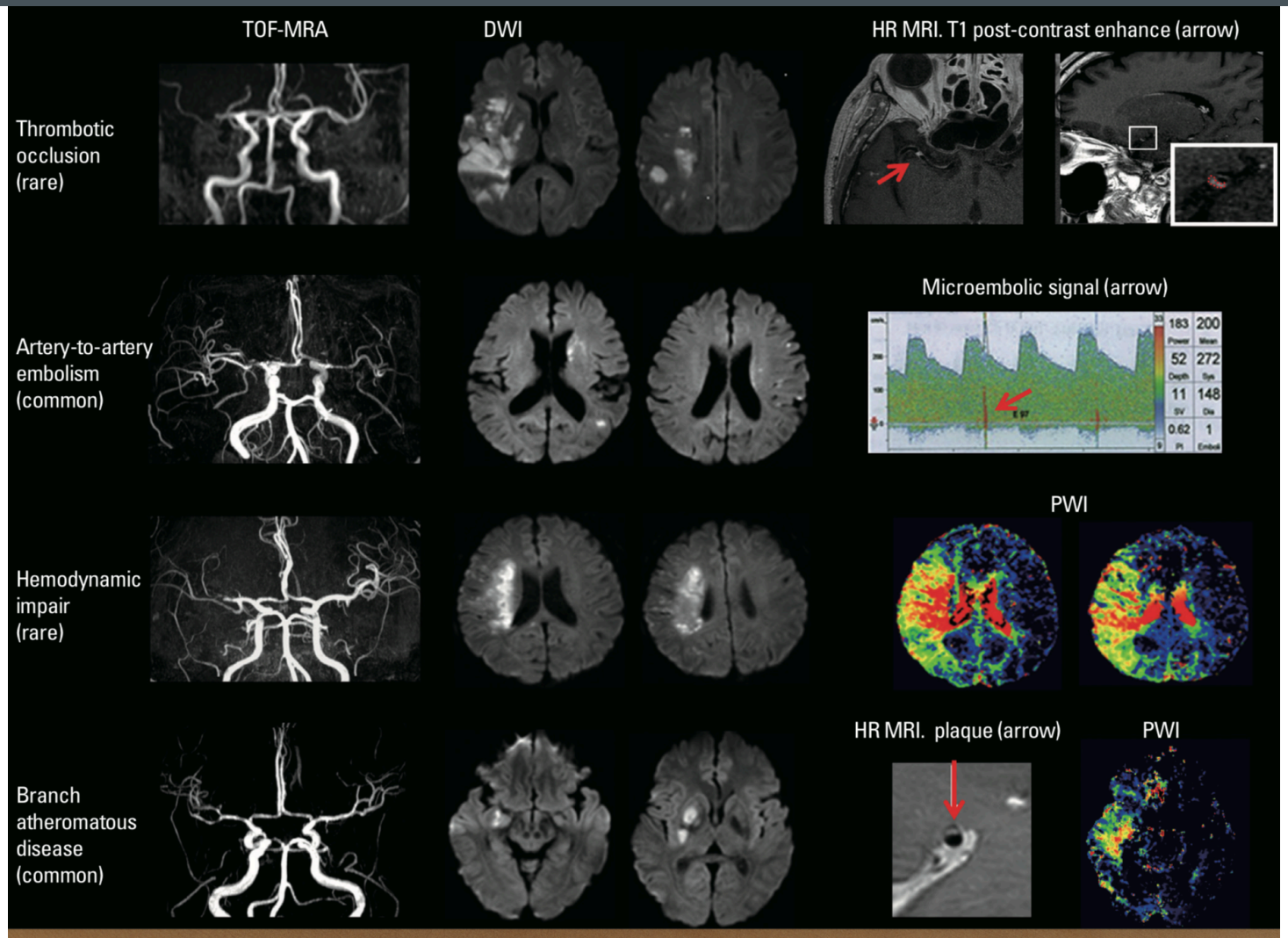
TRATTAMENTO INTENSIVO CON STATINE DOPO ICTUS ISCHEMICO ACUTO DOVUTO AD ATEROSCLEROSI INTRACRANICA

BACKGROUND

- Intracranial atherosclerotic disease (ICAD) is a major cause of ischaemic stroke worldwide and is more prevalent in Asians and Blacks

- ICAD is associated with a high risk of recurrent stroke

MECHANISMS OF STROKE IN PATIENTS WITH ICAD



Journal of Stroke 2014;16(1):27-35

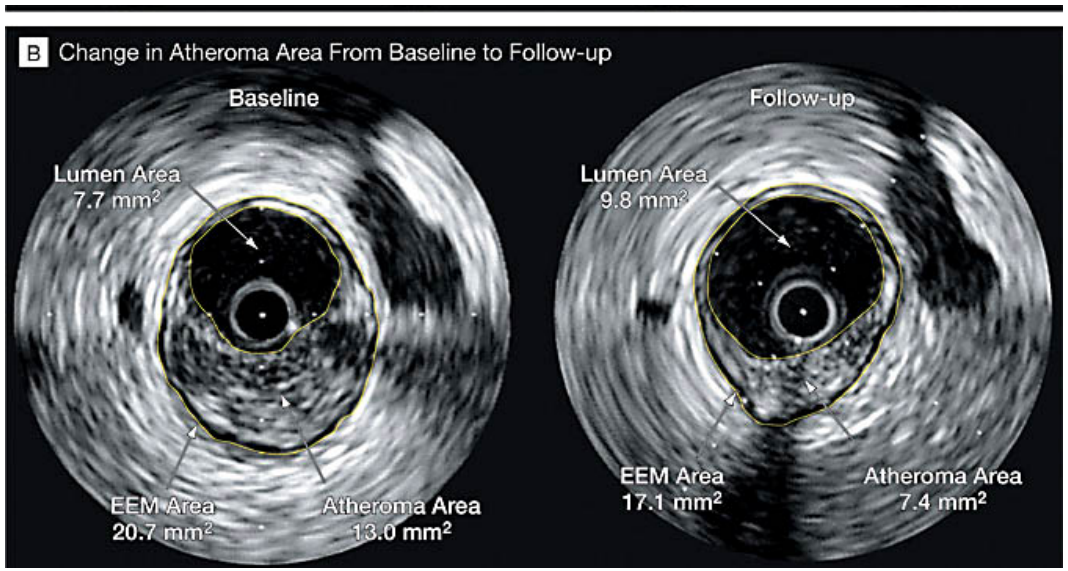
BACKGROUND

- Therapeutic strategies for symptomatic intracranial stenosis

1. Antithrombotics	✗	limited effects on the stabilisation of vulnerable atherosclerotic plaques
2. Percutaneous transluminal angioplasty and stenting	✗	high risk of peri-procedural stroke
3. Aggressive medical management of risk factors	✓	**recommended**

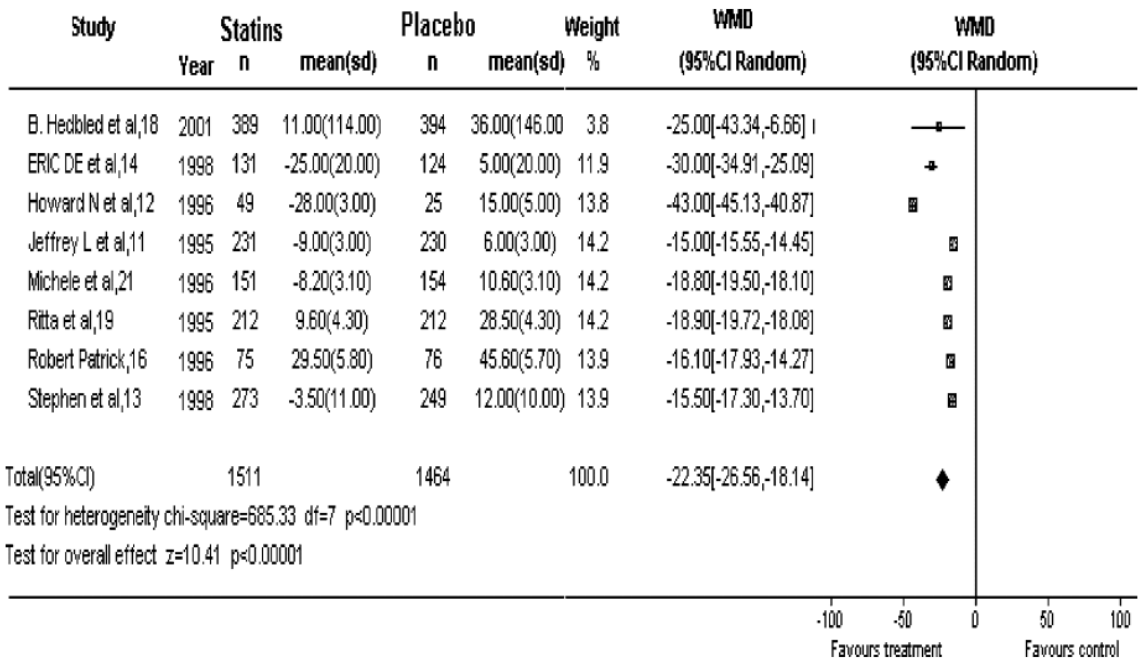
BACKGROUND

Effect of Intensive Compared With Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis



JAMA. 2004;291(9):1071-1080

Effects of statins therapy on the rate of carotid atherosclerosis progression in RCT (between statins and placebo group)



Atherosclerosis 2004;177:433–42.

RESEARCH PAPER

Intensive Statin Treatment in Acute Ischaemic Stroke Patients with Intracranial Atherosclerosis: a High-Resolution Magnetic Resonance Imaging study (STAMINA-MRI Study)

Jong-Won Chung,[1] Jihoon Cha,[2] Mi Ji Lee,[1] In-Wu Yu,[1] Moo-Seok Park,[3] Woo-Keun Seo,[1] Sung Tae Kim,[4] Oh Young Bang[1]

Chung J, et al. J of Neurology, Neurosurgery & Psychiatry Online First: 01 August 2019.

METHODS

- Single-arm, prospective, observational study
- Inclusion criteria:
  - statin-naive patients
  - acute ischaemic stroke caused by symptomatic intracranial atherosclerosis (proximal portion of the middle cerebral artery, basilar artery or intracranial portion of the internal carotid artery)
- Exclusion criteria:
  - extracranial artery stenosis above 50%
  - stroke attributable to cardioembolic origin
  - severe hepatic or renal dysfunction
- Patients received high-dose statins (atorvastatin 40–80mg and rosuvastatin 20mg)

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ENDPOINTS

- **Primary outcome:** change in vascular characteristics after statin treatment measured on HR-MRI as
  - stenosis degree
  - remodelling index
  - wall area index
  - enhancement volume of atherosclerotic plaque

- **Secondary endpoints**
  - changes in serum biomarkers: liver function, fasting glucose, lipid profiles, lipoprotein(a), apolipoprotein A1-B
  - clinical outcomes: modified Rankin scale (mRS) score at 3months and recurrent stroke, transient ischaemic attack or all-cause death at 6 months

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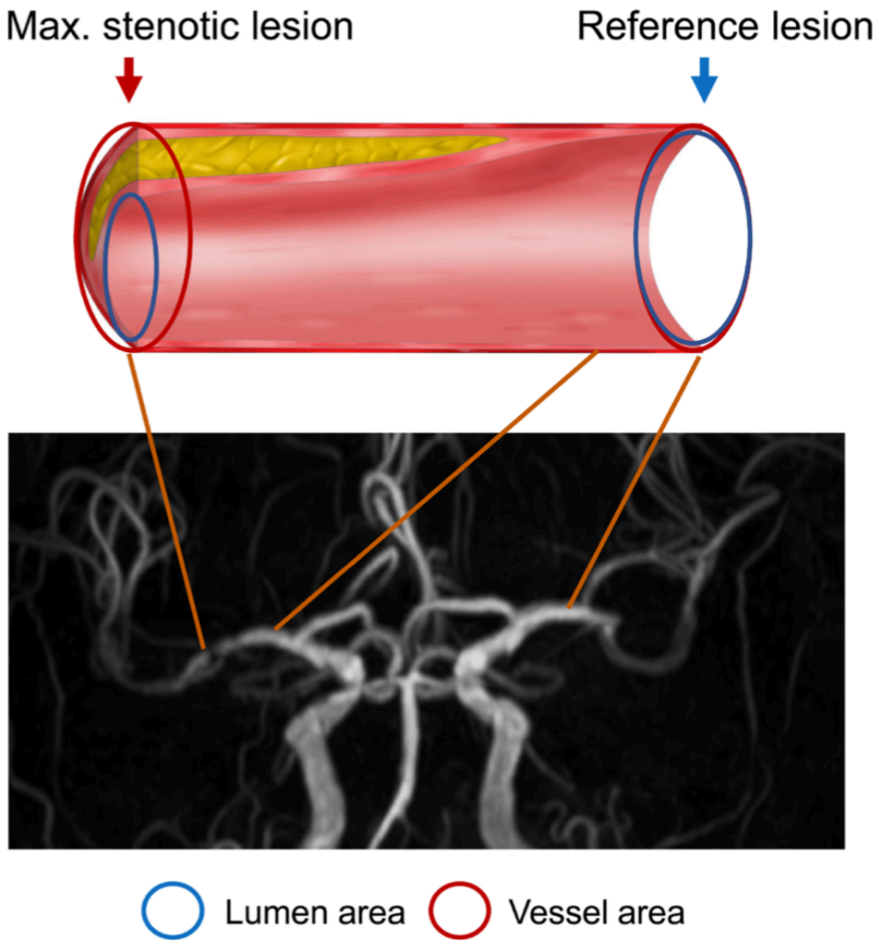
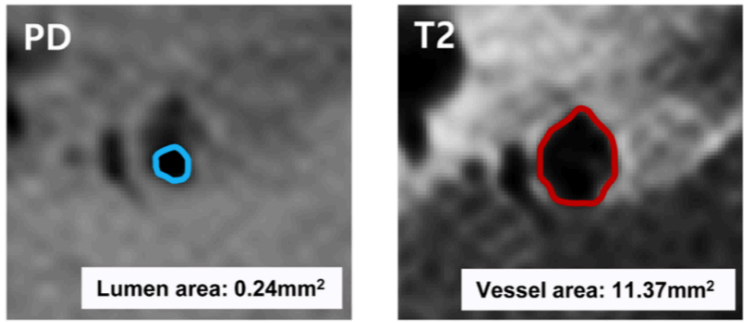
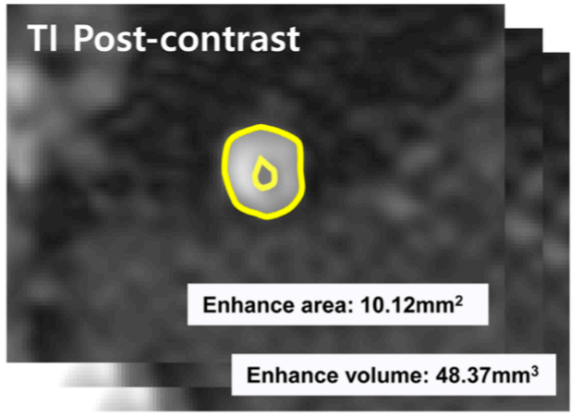
HR-MRI MEASUREMENTS







Max. stenotic lesion HR-MRI measurements

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BASELINE CHARACTERISTICS

Table 1 Baseline characteristic of study participants

	N=77
Age (yr), mean±SD	62.6±13.7
Male sex, n (%)	47 (61.0)
Body mass index (kg/m^2)	24.3±4.5
Stroke risk factors, n (%)	
Hypertension	49 (63.6)
Diabetes	30 (39.0)
Previous ischaemic stroke	10 (39.0)
Coronary artery disease	15 (19.5)
Current smoking	21 (27.3)
Time parameters, median (IQR)	
Onset to initial HR-MRI	4(2–6)
Initial to follow-up HR-MRI	179(163–189)
Vascular territory of infarction	
Middle cerebral artery	64 (83.1)
Basilar artery	13 (16.9)
Initial NIHSS score, median (IQR)	3(1–5)
Infarct pattern	
Deep only pattern	29 (37.7)
Small cortical only pattern	32 (41.6)
Large cortical/cortical-deep patterns	16 (20.8)
Infarct volume (mL)	7.3±11.15
Statin type	
Atorvastatin 40 mg	10 (13.0)
Atorvastatin 80 mg	8 (10.4)
Rosuvastatin 20 mg	59 (76.6)
Antiplatelet drug	
Mono	2 (2.6)
Dual	75 (97.4)

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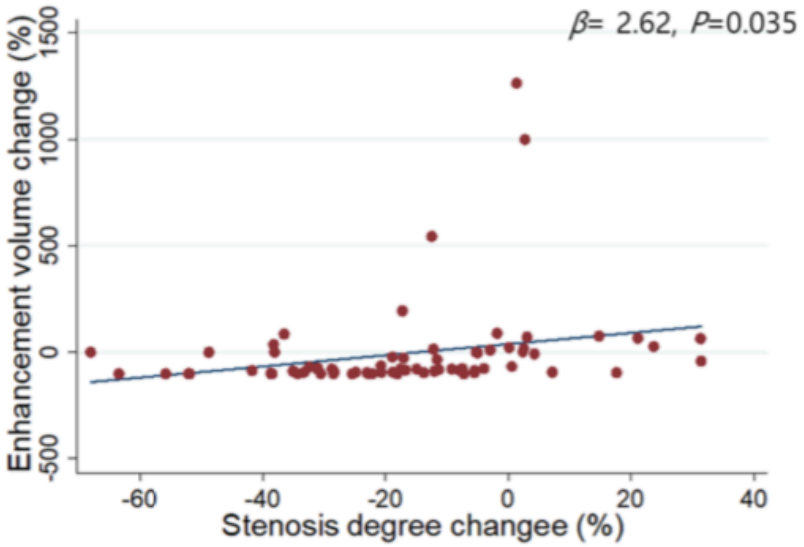
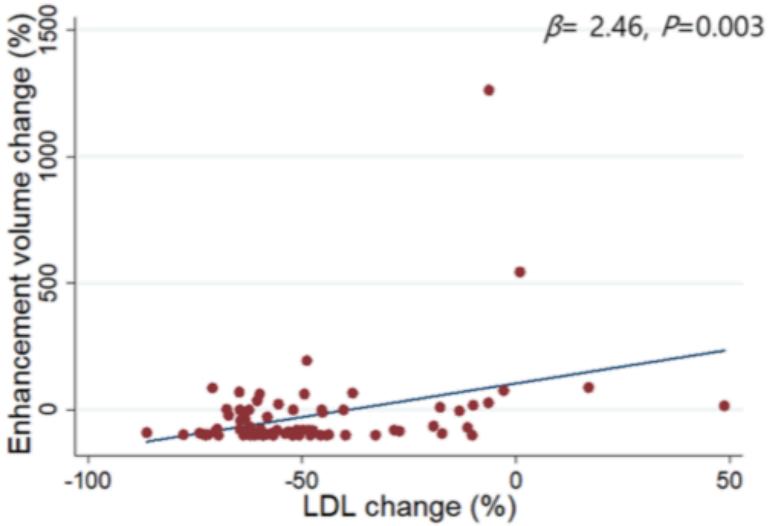
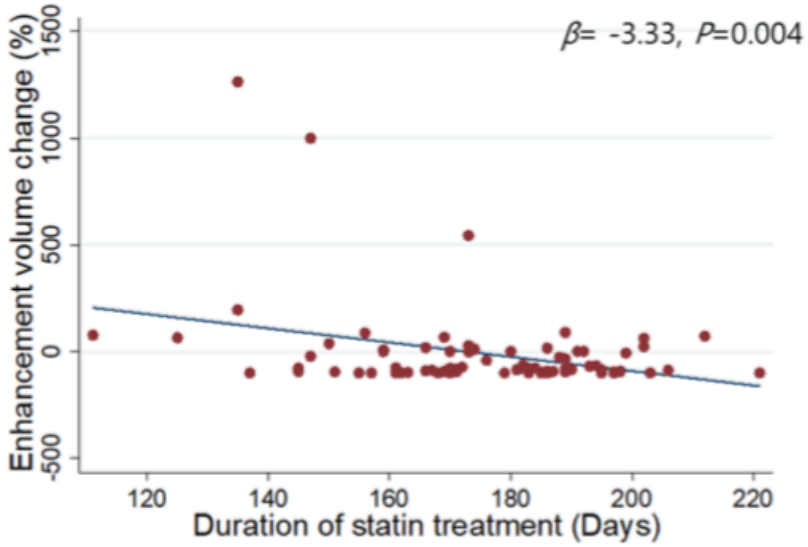
CHANGES IN LDL-C AND DURATION OF STATIN TREATMENT IN STENOSIS DEGREE AND ENHANCEMENT VOLUME CHANGES







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LABORATORY AND HR-MRI CHANGES

Table 2 Laboratory and HR-MRI changes

	Initial	Follow-up	P value
Laboratory			
Aspartate transaminase (IU/L)	26.51±14.02	23.54±7.13	0.118
Alanine aminotransferase (IU/L)	25.63±17.49	24.34±13.04	0.619
Alkaline phosphatase (IU/L)	68.03±16.35	67.52±18.89	0.899
Creatine kinase (IU/L)	100±71.75	116.23±88.72	0.475
Fasting glucose (mg/dL)	121.23±53.57	117.29±38.46	0.612
hsCRP (mg/dL)	0.27±0.61	0.22±0.62	0.625
D-dimer (μg/mL)	0.68±1.60	0.46±0.44	0.040
Total cholesterol (mg/dL)	193.39±43.63	123.20±24.53	<0.001
Triglyceride (mg/dL)	159.00±90.37	121.85±53.28	0.003
HDL cholesterol (mg/dL)	48.82±15.19	49.35±13.77	0.822
LDL cholesterol (mg/dL)	125.81±35.69	60.95±19.28	<0.001
Non-HDL cholesterol (mg/dL)	144.5±40.8	73.7±21.0	<0.001
Lipoprotein(a)	20.81±19.75	21.16±22.05	0.921
Apolipoprotein A1	132.6±35.47	140.18±20.63	0.240
Apolipoprotein B	106.06±26.58	63.73±16.73	<0.001
HR-MRI			
Vascular morphology			
Stenosis degree (%)	76.47±20.23	64.05±1.29	<0.001
Remodelling index	1.09±0.35	1.03±0.30	0.195
Wall area index	7.50±4.28	5.86±4.04	0.016
Vascular activation			
Enhancement in symptomatic vessel, n (%)	73 (94.8)	58 (75.3)	0.001
Enhancement pattern, n (%)			0.280
Concentric	10 (13.7)	7 (12.1)	
Eccentric	63 (86.3)	51 (87.9)	
Enhancement volume (mm^3)	32.07±39.15	17.06±4.53	0.013

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REGRESSION ANALYSES FOR CHANGES IN THE ENHANCEMENT VOLUME ON SERIAL HR-MRI

	Univariate analysis			Multivariable analysis		
	Coefficient	SE	P value	Coefficient	SE	P value
Mean age (yr)	–2.3	1.74	0.211			
Male sex, n (%)	–58.91	48.95	0.233			
Body mass index (kg/m^2)	–7.18	5.34	0.183	–7.78	4.13	0.064
Hypertension	63.66	49.56	0.203			
Diabetes	–2.13	49.4	0.966			
Coronary artery disease	–49.85	60.58	0.413			
Current smoking	8.91	54.1	0.87			
LDL-C change (%)	2.67	0.81	0.002	2.24	0.78	0.005
Duration of statin treatment (days)	–3.33	1.12	0.004	–2.38	0.92	0.012
Vascular territory of infarction						
Basilar artery (reference)	1					
Middle cerebral artery	58.93	63.98	0.360			
Initial stenosis degree	1.1	1.24	0.376			
Initial remodelling index	16.68	69.52	0.811			
Initial wall area index	–6.71	5.62	0.236			
Initial enhancement volume	–0.61	0.62	0.325			

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BASELINE CHARACTERISTICS OF STUDY SUBJECTS BY HIGH-DOSE STATIN RESPONSE MEASURED BY PLAQUE ENHANCEMENT VOLUME

	Good responder (N=50)	Non-responder and poor responder (N=27)	P value
Age (years)	63.6±13.4	60.9±14.4	0.411
Male sex, n (%)	35 (70.0)	12 (44.4)	0.028
Body mass index (kg/m^2)	24.2±3.7	24.5±5.7	0.814
Stroke risk factors, n (%)			
Hypertension	31 (62.0)	18 (66.7)	0.685
Diabetes	21 (42.0)	9 (33.3)	0.457
Previous ischaemic stroke	6 (12.0)	4 (14.8)	0.726
Coronary artery disease	10 (20.0)	5 (18.5)	0.876
Current smoking	16 (32.0)	5 (18.5)	0.205
Time parameters, median (IQR)			
Onset to initial HR-MRI	4(2–6)	3(2–6)	0.394
Onset to follow-up HR-MRI	183(168–189)	173(150–189)	0.034
Vascular territory of infarction			0.32
Middle cerebral artery	40 (80.0)	24 (88.9)	
Basilar artery	10 (20.0)	3 (11.1)	
Initial NIHSS score, median (IQR)	3(2–5)	4(3–6)	0.785

	Good responder (N=50)	Non-responder and poor responder (N=27)	P value
Infarct pattern			0.847
Deep only pattern	20 (40.0)	9 (33.3)	
Small cortical only pattern	20 (40.0)	12 (44.4)	
Large cortical/cortical-deep patterns	10 (20.0)	6 (22.2)	
Infarct volume (ml)	7.4±11.8	7.1±10.1	0.913
Statin type			0.576
Atorvastatin 40 mg	6 (12.0)	4 (14.8)	
Atorvastatin 80 mg	4 (8.0)	4 (14.8)	
Rosuvastatin 20 mg	40 (80.0)	19 (70.4)	
LDL-C change (mg/dL)	−74.8±34.1	−47.3±38.2	0.002
hsCRP change (mg/dL)	0.04±0.91	−0.27±0.89	0.195
Non-HDL change (mg/dL)	−81.3±36.3	−52±45.1	0.003
Lipoprotein(a), initial	22.23±20.3	18.2±18.8	0.422
Lipoprotein(a) change	0.75±14.65	−0.11±4.5	0.791
Achieved LDL target (2017 AACE)*	37 (74.0)	19 (70.4)	0.733
Achieved LDL target (2018 AHA)†	38 (76.0)	12 (44.4)	0.006

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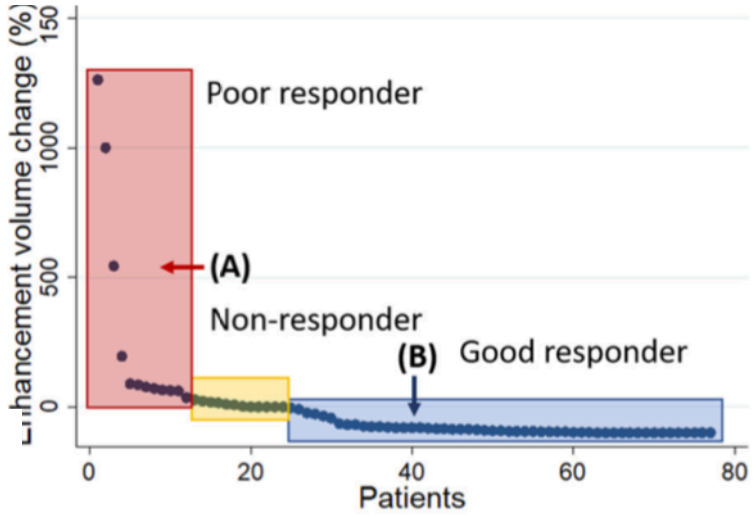
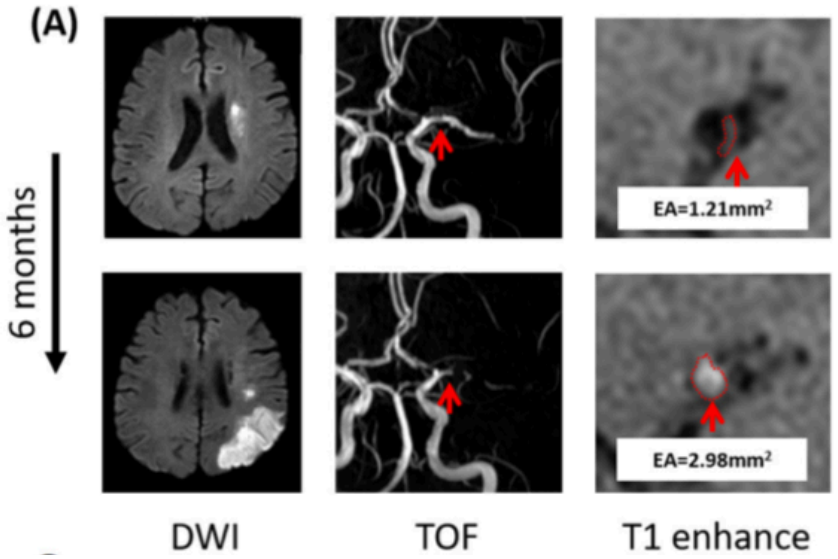
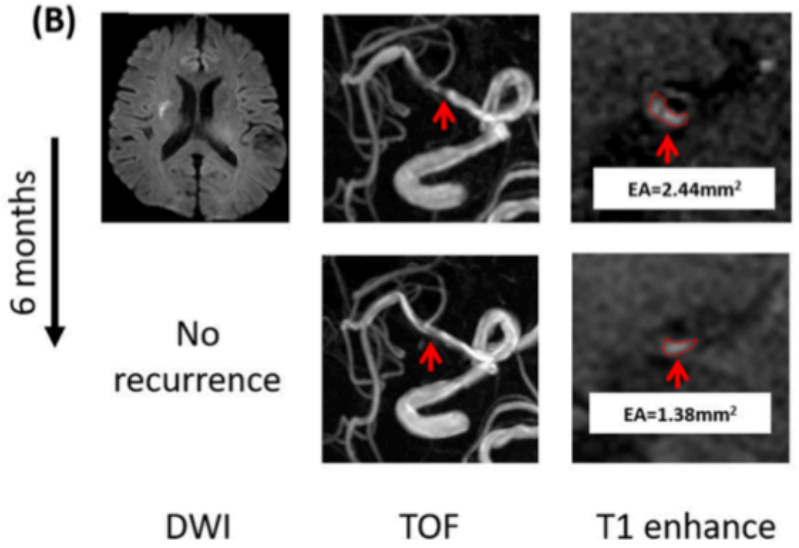
EXAMPLES OF POOR AND GOOD RESPONDERS



Poor responder



Good responder



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STUDY LIMITATIONS

- Single-centre study with small number of patients comprising only the Korean population
- Significant variability in the time interval between initial and follow-up HR-MRIs and in statin treatment duration
- Single-arm study with all the patients treated with high-dose statin
- Antiplatelet, antihypertensive and hypoglycaemic drug can interfere with progression of atherosclerotic plaque
- Simple size not sufficient to detect differential effect in anterior and posterior circulation vessels
- Only two-dimensional images were acquired for image analyses in this study
- Factors associated with non- or poor response not determined →ongoing STAMINA-MRI genetic substudy

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CONCLUSIONS

- High-dose statin treatment effectively stabilises symptomatic intracranial atherosclerotic plaques
- 35% of patients with ICAD are statin non-responders/poor responders
- Further studies are needed to determine laboratory and genetic factors associated with poor statin response and alternative therapeutic options, such as PCSK9 inhibitors or combination with ezetimibe for these patients

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