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ONLINE SUPPLEMENT

Predicting presence of macrovascular causes in non-traumatic intracerebral haemorrhage; the DIAGRAM prediction score

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Supplementary Methods. Assessment of small vessel disease on admission non-contrast CT

All non-contrast CTs (NCCT) were rated independently by two experienced neuroradiologist for presence of small vessel disease (SVD). Disagreements were resolved by a third observer. Characteristics of interest were:

- Presence of white matter lesions (WML), and if so: WML location (periventricular, subcortical or both) and severity (<1 cm, >1 cm, or confluent);
- Presence of a hypodensity elsewhere on NCCT, and if so: location.

Signs of small vessel disease on NCCT was defined as presence of white matter lesions, or an ischemic lesion in basal ganglia, thalamus or posterior fossa.

Table I: Causes of intracerebral haemorrhages in the development cohortel

	No (%) of patients			
Causes	(n=298)			
Macrovascular:				
Arteriovenous malformation	34 (11)			
Dural arteriovenous malformation	13 (4)			
Cavernoma	10 (3)			
Cerebral venous sinus thrombosis	4 (1)			
Aneurysm	7 (2)			
Developmental venous anomaly*	1 (0.3)			
Subtotal	69 (23)			
Other:				
Probable cerebral amyloid angiopathy	18 (6)			
Hypertensive vasculopathy†	36 (12)			
Neoplasm	3 (1)			
Cocaine use	1 (0.3)			
Haemorrhagic infarction	2 (0.7)			
Unknown‡	169 (57)			
Subtotal	229 (77)			

^{*}Partially thrombosed large developmental venous anomaly without evidence of adjacent cavernoma.

[†]Intracerebral haemorrhage in basal ganglia, thalamus, or posterior fossa in presence of hypertension.

[‡]In 30 of these patients, lobar haemorrhage in the presence of hypertension was observed.

Table II: Regression equations of multivariable models

Regression equation model based on patient characteristics and NCCT

-2.1828-0.0408*AGE+2.1224*no SVD+1.6923*Lobar+2.5472*Posterior fossa

Regression equation model based on patient characteristics, NCCT and CTA

-3.4045-0.0281*AGE+2.1585*no SVD+1.2038*Lobar+2.0049*Posterior fossa+2.4201*CTA

No SVD no signs of small vessel disease, CTA positive or inconclusive CTA

Table III: Calculation of the DIAGRAM and DIAGRAM+ prediction scores

	DIAGRAM score	DIAGRAM + score		
	Points	Points		
Age ≤50	1	1		
Absence of small vessel disease	2	2		
ICH location				
Deep	0	0		
Lobar	2	1		
Posterior fossa	3	2		
Positive CTA	-	3		

NCCT non contrast CT, ICH intracerebral haemorrhage

An individual DIAGRAM or DIAGRAM+ score is the sum of the points assigned to each of the predictors. The maximum score is 6 for the model based on patient characteristics and NCCT (DIAGRAM score), and 8 for the model based on additional CTA (DIAGRAM + score).

Table IV: Overview of prediction models for macrovascular causes and external validation studies

Model development

Model	Prospective/ retrospective	Patient selection	N	Mean age	MVC (%)	Reference standard	C-statistic
SICH score ^{e2}	R	Patients who underwent CTA within 24h	623	65	15	CTA	0.86 (0.83- 0.89)
Simple ICH score ^{e3}	R	Patients who underwent DSA	160	41	51	DSA	0.65 (0.56- 0.73)
DIAGRAM score	Р	Patients < 70 y, excl of patients >45 y with HT and deep ICH or post fossa ICH	298	53	23	1y FU	0.83 (0.78- 0.88)* 0.91 (0.88- 0.94)‡

R retrospective, P prospective, y year, FU follow-up, MVC macrovascular cause, HT hypertension * model based on patient characteristics and non contrast CT, ‡ model based on patient characteristics, non contrast CT and CTA.

Model validation

Model	Prospective/ retrospective	Patient selection	N	Mean age	MVC (%)	Reference standard	C-statistic
SICH score ^{e2}	P (temporal)	Patients who underwent CTA	222	67	13	СТА	0.87 (0.82- 0.91)
SICH score ^{e4}	R (external)	Patients who underwent DSA or neurosurgical evacuation	341	57	18	DSA or neurosurgical inspection	0.82 (0.78- 0.86)
SICH score ^{e5}	R (external)	Patients who underwent CTA, MRA, DSA or pathological examination	204	?	24	CTA, MRA, DSA, neurosurgical or pathological inspection	0.73 (0.65- 0.80)
Simple ICH scoree3	Р	Patients who underwent CTA, MRA or DSA.	106	57	32	CTA, MRA or DSA	0.67 (0.55- 0.79)
DIAGRAM score	R prospective MVC	Patients who underwent CTA and DSA	173	49	45	DSA	0.66 (0.58- 0.74)* 0.88 (0.83- 0.94)‡

R retrospective, P prospective, MVC macrovascular cause, * model based on patient characteristics and non contrast CT, ‡ model based on patient characteristics, non contrast CT and CTA, ^{2,3,4,5} references, please see page 14 of supplementary file.

Included patients (n=298) CTA assessment not possible (n=7): Further assessment CTA failed (n=1) (7 MRA, 4 DSA) CTA of insufficient quality (n=6) (n=7 negative) CTA results (n=291) CTA positive (n=59) CTA negative (n=220) CTA inconclusive (n=12) DSA assessment positive (n=1) (AVM) Treatment, no MRA assessment No further tests DSA assessment (n=3): MRA MRA assessment further tests (n=34): (n=14): Negative (n=1) (n=203)assessment (n=5): Negative (n=13) Refusal (n=10) AVM (n=1) (n=11)Aneurysm (n=2) Aneurysm (n=1) Deceased (n=4) DAVF (n=1) AVM(n=2)AVM (n=9) CVST(n=1)Cavernoma (n=5) CVST (n=3)DAVF (n=2) DVA (n=1) MRA positive (n=5) MRA negative MRA inconclusive MRA positive MRA negative MRA inconclusive Carvernoma (n=3) (n=193)(n=5)(n=1)(n=4)(n=6)No DSA No DSA No DSA No DSA DSA assessment (n=1)(n=3) (n=101)* (n=4)(n=44): DSA assessment Negative (n=23) DSA unsuitable negative (n=2) DSA assessment DSA assessment Aneurysm (n=4) → for assessment DSA assessment (n=3): (n=3): AVM (n=10) (n=3)negative (n=1) DSA assessment Negative (n=1) Negative (n=2) No DSA DAVF (n=7) (n=1)(n=3)Positive (n=2) Positive (n=1) AVM(n=1)(2 AVM) (AVM) MRA magnetic resonance angiography DSA assessment Repeated MRI CTA computed tomography angiography positive (n=1) (n=89): DSA digital subtraction angiography (cavernoma) Negative (n=79) AVM arteriovenous malformation Positive (n=10) CVST cerebral venous sinus thrombosis (7 AVM, 3 DAVF) DAVF dural arteriovenous fistula *An underlying carvernoma was identified DVA developmental venous anomaly by repeated MRI 10 months after the ictus MRI magnetic resonance imaging

Figure I: Flowchart of angiographic examinations in DIAGRAMe1

Figure II: CT scan of a patient with (A) and without (B) white matter hypodensities indicative of small vessel disease

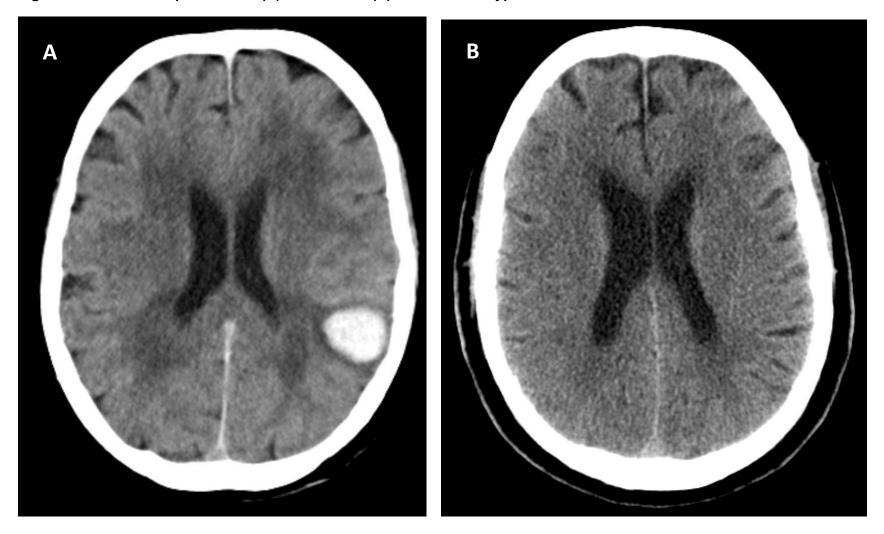
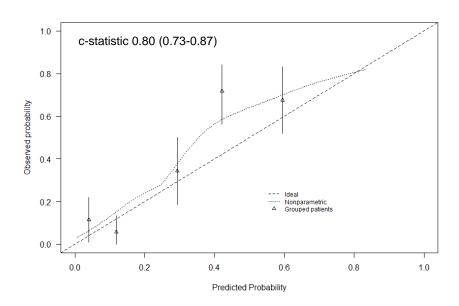


Figure III: Calibration plots and c-statistics of DIAGRAM models excluding DIAGRAM patients who did not undergo DSA according to the study protocol. Model based on patient characteristics and NCCT (A), model based on patient characteristics, NCCT and CTA (B)

A.



В.

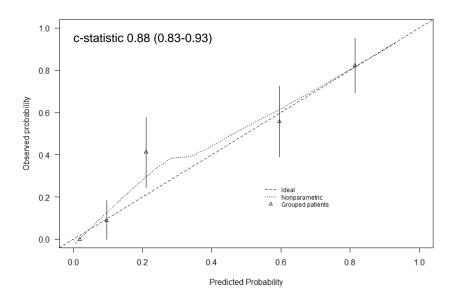
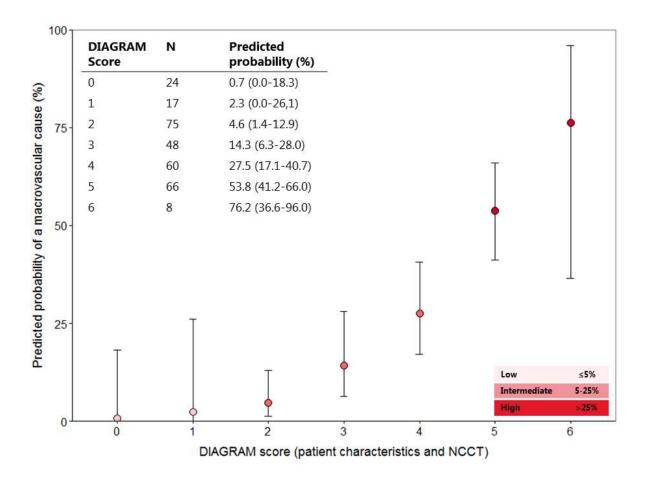


Figure IV: Predicted one year probability of an underlying macrovascular cause based on the DIAGRAM prediction scores. Model based on patient characteristics and NCCT (A), model based on patient characteristics, NCCT and CTA (B)

A.



В.

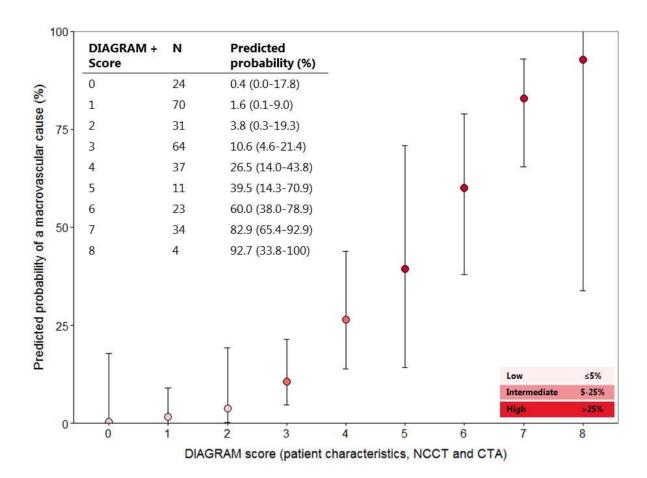
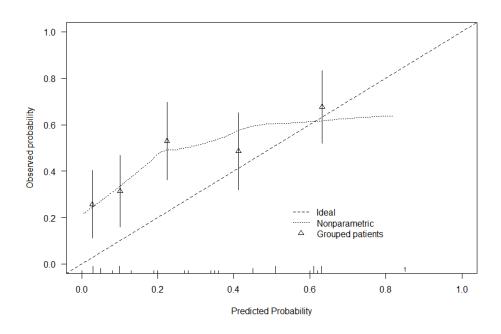
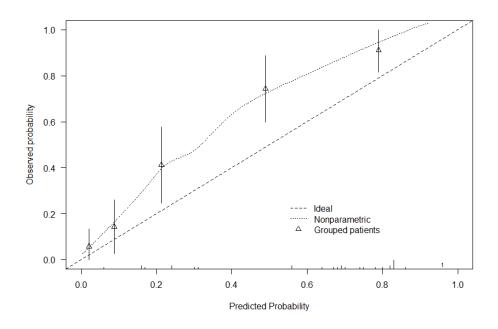


Figure V: Calibration plots of DIAGRAM models in validation cohort before recalibration. Model based on patient characteristics and NCCT (A), model based on patient characteristics, NCCT and CTA (B)

A.



В.



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