뇌졸중 임상시험에서의 영상 평가

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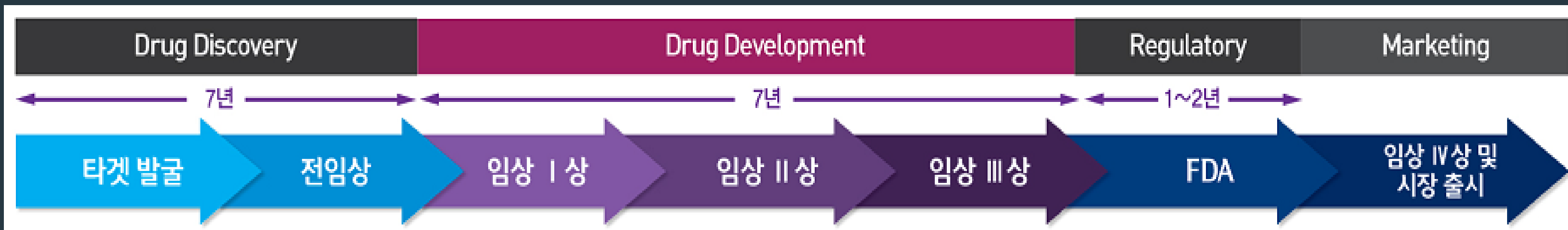
Overview

- Clinical trial imaging in Acute ischemic stroke: Review
- Experience as Imaging CRO and IIRC
- IIRC: Outcomes and Central reading
- Guidelines

신약개발



임상 수요에 맞는 타겟 발굴	약물에 반응성이 좋은 환자군 선별	인허가 규정에 맞는 개발전략
메커니즘 기반 개발 전략	Proof of Concept 검증	
빠른 의사결정 (Go/No-Go)	효율적 독성 예측 시스템	규제기관과의 적극적 정보 공유와 교류
전임상시험의 예측력 제고	새로운 임상시험 방법론	

Biomarkers (Imaging, -Omics)

Advanced Clinical Trial

Animal Model | **Toxicology**

NICHE MARKET

Clinical trial imaging in Acute ischemic stroke

1. European Cooperative Acute Stroke Study (ECASS, JAMA 1995), The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS, NEJM 1995): 급성 뇌경색 환자에서의 IV alteplase의 약물 유효성 평가를 위한 Randomized multicenter clinical trial로서 noncontrast CT를 약물 적용 환자군 선정과 alteplase의 주요한 합병증인 뇌출혈의 검출 및 분류를 위하여 이용함. Primary·Secondary outcome은 임상지표였으며 noncontrast CT는 Safety parameters로서 사용됨.
2. The European Atrial Fibrillation Trial Study Group (NEJM 1995): Nonrheumatic atrial fibrillation환자에서 뇌졸중의 리스크를 줄이기 위한 항응고제의 약물 유효성 평가를 위한 Randomized multicenter clinical trial로서 항응고제의 주요한 합병증인 뇌출혈의 검출 및 분류를 위하여 이용함. Primary·Secondary outcome은 임상지표였으며 Safety parameters로서 noncontrast CT를 이용함.
3. Low-molecular-weight Heparin for the treatment of acute ischemic stroke (NEJM 1995): 뇌졸중 환자에서 low-molecular-weight Heparin의 유효성 평가를 위한 연구로서 Primary outcome은 임상지표를 사용하였고 Secondary outcome으로서 low-molecular-weight Heparin의 합병증 (예: 뇌경색 후 뇌출혈)을 밝히고자 하였으며 noncontrast CT를 이용하여 뇌경색 후 뇌출혈을 객관적으로 평가하고자 하였고 Independent image review system을 도입하였음.
4. The Multicenter Acute Stroke Trial-Europe Study Group (MAST-E, NEJM 1996): 중대뇌동맥의 중등도 이상의 뇌졸중 환자에서 IV streptokinase의 유효성 평가를 위한 연구로서 Primary·Secondary outcome은 임상지표였으며 noncontrast CT를 Safety parameters와 환자 배제 기준으로서 사용함. Independent image review system을 도입하여 noncontrast CT상 뇌경색과 뇌출혈을 평가하였음.

Clinical trial imaging in Acute ischemic stroke

5. ECASS II (Lancet 1998): 급성 뇌졸중 환자에서 IV alteplase의 6시간까지의 연장 사용에 관한 유용성 평가를 위한 연구로서 noncontrast CT를 약물 적용 환자군 선정과 alteplase의 주요한 합병증인 뇌출혈의 검출 및 분류를 위하여 이용함. Primary·Secondary outcome은 임상지표였으며 **noncontrast CT는 Safety parameters로서** 사용됨. **Noncontrast CT가 환자 선정의 전면에 나온 연구이며** 뇌경색, 뇌출혈의 **검출 뿐 아니라 뇌경색의 부피를 정량적으로 분석**하였음.
6. Phenylpropanolamine and the Risk of Hemorrhagic stroke (NEJM 2000): Phenylpropanolamine (식욕 억제 및 감기 치료제)의 hemorrhagic stroke 발생에 미치는 영향을 평가한 연구로서 subarachnoid hemorrhage와 intracerebral hemorrhage 검출에 noncontrast CT를 이용하였음.
7. Pravastatin therapy and the Risk of Stroke (NEJM 2000): Prevastatin의 stroke risk 감소에 대한 유효성 평가를 위한 연구로서 **CT, MR, Angiography를 Ischemic stroke, Hemorrhagic stroke의 진단과 분류에 이용**하였음.
8. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS, Stroke 2005): 급성 뇌졸중 환자에서 Desmoteplase의 9시간까지의 연장 사용에 대한 유효성 평가를 위한 연구로서 **DWI, TOF-MRA, FLAIR, PWI**의 MR 영상 검사가 **환자 선정 및 outcome에서 주요한 역할**을 수행함. **Primary outcome**으로서 **PWI**의 **정량적 감소**와 **MRA**의 **재개통 소견**을 사용하였고 유효성 평가의 **다른 outcome**으로서 **DWI의 뇌경색 범위의 변화**를 이용하였음. DWI은 뇌경색의 진단 및 부피 측정을 위해 사용되었고 **FLAIR는 만성적 허혈성 병변 검출에 사용**하였음.

Clinical trial imaging in Acute ischemic stroke

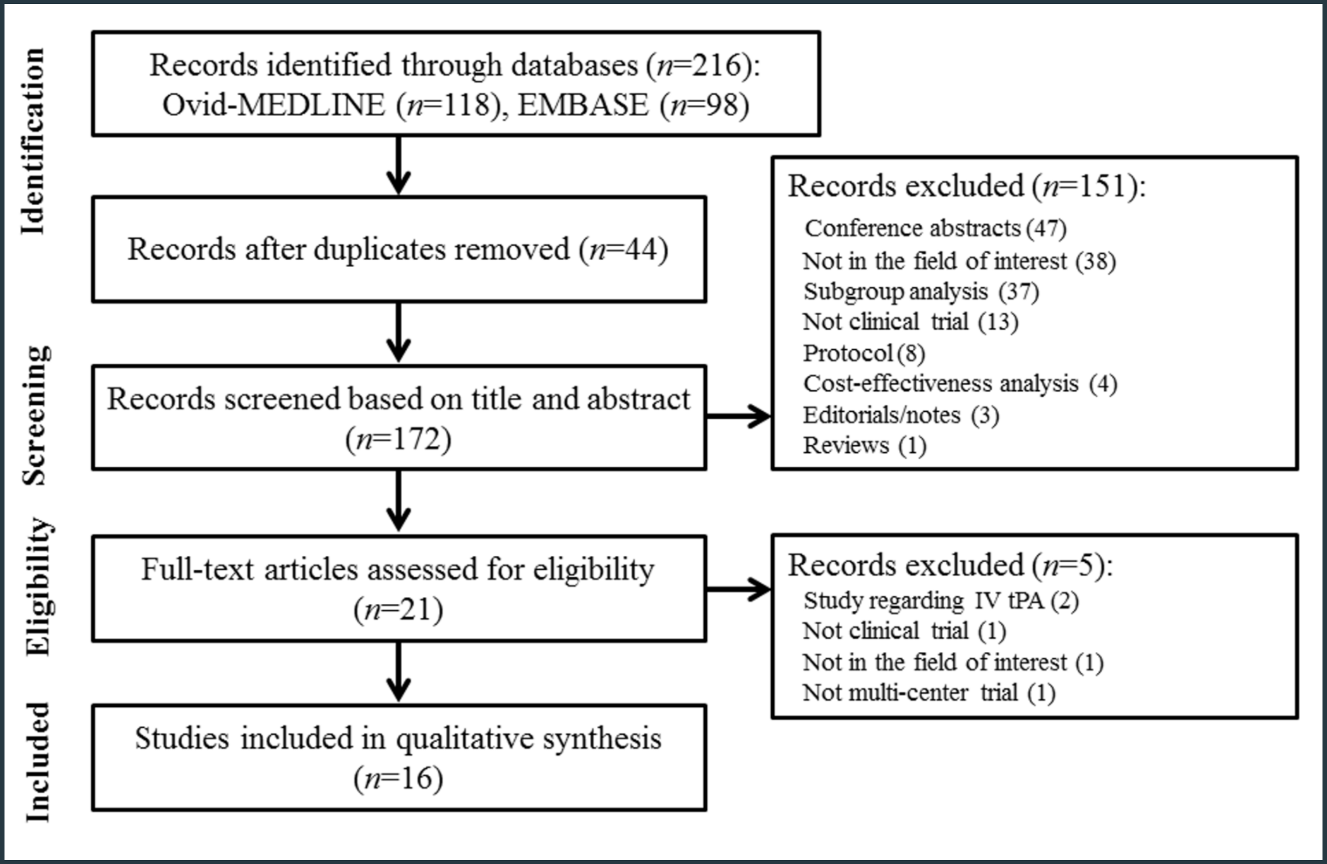
9. Recombinant Activated Factor VII for Acute Intracerebral hemorrhage (NEJM 2005): 급성 뇌출혈 환자에서의 Recombinant Activated Factor VII의 유효성 평가를 위한 연구로서 **Noncontrast CT상 뇌출혈 부피의 변화를 Primary outcome으로 사용**하였음. Digital CT **정보를** imaging core lab**으로 전송**하여 Neuroradiologist에 의한 Independent image review system을 이용하여 Primary outcome을 분석하였음.
10. The Dose Escalation of Desmoteplase in Acute Stroke (DEDAS, Stroke 2006): 급성 뇌졸중 환자에서 Desmoteplase의 9시간 연장 사용에 대한 유효성 평가를 위한 연구로서 **MRI를 Primary efficacy endpoint로 사용**하였고 **Safety endpoint로서 noncontrast CT**를 이용하였음. **DWI**을 이용한 **정성적·정량적 뇌경색 부피 분석**, **MRA**를 이용한 **혈관의 재개통 분석**, **관류 MR**을 이용한 **정량적 관류 분석**, **Noncontrast CT**를 이용한 **뇌출혈 발생률**을 연구의 주요 결과로서 보고하였음. Imaging core lab**과** Independent image review system을 통한 정성적·정량적 분석을 시행하였음.
11. The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE, Ann Neurol 2006): 급성 뇌졸중 환자에서 **MRI profile과 임상지표를 직접적으로 비교**하는 연구로서 **DWI, DSC PWI, FLAIR, GRE, MRA, T1-weighted imaging**을 이용하여 정성적·**정량적 분석을** 시행하였음.
12. The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET, Lancet 2008): Alteplase의 6시간 연장 사용의 유효성 평가를 위한 연구로서 임상지표를 우선하여 영상바이오마커 지표가 Primary endpoint로서 사용되었음. **Primary endpoint**로서 **DWI (baseline)** 과 **T2-weighted imaging** (=FLAIR, 90 days after)사이의 뇌경색 부피 변화를 사용하였음. **정량적 영상 분석 소프트웨어를** 이용하여 뇌경색 부피 변화를 측정하였음. PWI, MRA를 이용하여 관류 변화와 재개통 여부를 판정하였음.

Clinical trial imaging in Acute ischemic stroke

13. The Factor Seven for Acute Hemorrhagic Stroke (FAST, NEJM 2008): 급성 뇌출혈 환자에서 Recombinant activated factor VII의 유효성 평가를 위한 연구로서 **Primary endpoint**로서 **Noncontrast CT**를 이용한 뇌출혈 부피 변화를 이용하였음. **정량적 영상 분석 소프트웨어**를 이용하여 뇌출혈 부피 변화 결과를 산출하였음.
14. DIAS II (Lancet Neurol 2009): 급성 뇌졸중 환자에서 Desmoteplase의 9시간 연장 사용에 대한 유효성 평가를 위한 연구로서 **환자 선정과 Secondary outcome**을 위하여 **CT와 MR을 사용**하였음. 환자 선정을 위해 **DWI과 PWI을 이용한 회생가능한 반음영의 정량적 분석을** 시행하였고 **Secondary outcome**을 위하여 **DWI과 noncontrast CT를 이용한 뇌경색 부피 분석**을 하였음. 치료에 의한 혈관의 재개통여부를 위해 MR 혹은 CT angiography를 이용하였으며 Safety outcome으로서 Noncontrast상의 뇌출혈 발생을 사용하였음. Imaging core lab과 함께 정량적 영상분석이 이용되었음.
15. A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke (NEJM 2012): 급성 뇌졸중 환자에서 IV Tenecteplase의 유효성 평가를 위한 연구로서 **환자 선정을 위해 CT angiography**를 이용하여 혈관의 폐색 정도와 여부를 평가하였고 **CT perfusion**을 이용하여 뇌경색 병변 범위와 관류상태를 평가하였음. Primary outcome으로서 **관류 영상**을 통한 관류 상태 변화를 측정하였고 **Secondary outcome**으로서 **뇌경색 부피 변화와 혈관 재개통 분석**을 하였으며 **Secondary imaging safety outcome**으로서 **뇌출혈 양 변화를 영상 검사를 통하여 분석**하였음. MR 검사로서는 **GRE, FLAIR, DWI, PWI, MRA**가 사용되었음. Imaging core lab과 Independent image review system을 통한 정성적·정량적 분석을 시행하였으며 정량적 영상 분석을 위해서 Commercial software를 사용하였음.

Clinical trial imaging in Acute ischemic stroke

- 2012 ~ 2018
- Randomized, Multi-center clinical trials in endovascular treatment for acute cerebral ischemic stroke



Author	Publication year	Trial nickname	No. of patients (n)	No. of centers	Purpose	[a]Inclusion time (hours)	Eligibility	
							Inclusion	Inclusion: Neuroimaging
Nogueira RG, et al. (5)	2018	DAWN	206	26	Efficacy of EVT	6-24	1) Ineligible or failed respond to IVT, 2) NIHSSs 10-42	1) Mismatch between clinical and infarct volume on CT or MR, 2) Occlusion of intracranial ICA or M1 on CTA or MRA
Albers GW, et al. (6)	2018	DEFUSE 3	182	38	Efficacy of EVT	6-16	NIHSSs ≥ 6	[b]1) Mismatch between infarct volume and penumbra on CT or MR, 2) Occlusion of ICA and M1 on CTA or MRA
Muir KW, et al. (12)	2017	PISTE	65	10	Efficacy of EVT	6	NIHSSs ≥ 6	Occlusion of intracranial ICA, M1, or single M2 on CTA or MRA
Lapergue B, et al. (13)	2017	ASTER	381	8	Comparison of Aspiration and Stent retrieval	6		Occlusion of intracranial ICA, M1, or M2 on CTA or MRA
Mocco J, et al. (14)	2016	THERAPY	108	36	Efficacy of EVT		NIHSSs ≥ 8	1) Occlusion of intracranial ICA and MCA on CTA and Thrombus > 8 mm on CT
Bracard S, et al. (15)	2016	THRACE	414	26	Efficacy of EVT	5	NIHSSs 10-25	Occlusion of intracranial ICA, M1, or upper 1/3 BA on CTA or MRA
Saver JL, et al. (7)	2015	SWIFT PRIME	196	39	Efficacy of EVT	6	NIHSSs 8-29	Occlusion of intracranial ICA and M1 on CTA or MRA (TICI 0-1)
Jovin TG, et al. (8)	2015	REVASCAT	206	4	Efficacy of EVT	8	1) Ineligible or failed respond to IVT, 2) NIHSSs ≥ 6	Occlusion of intracranial ICA or M1 on CTA, MRA, or DSA (TICI 0-1)
Goyal M, et al. (9)	2015	ESCAPE	316	22	Efficacy of EVT	12	NIHSSs > 5	1) Infarct core (small: ASPECTS 6-10) on NECT, 2) Occlusion of carotid T/L and M1/Immediate M2 on CTA, [c]3) Moderate-to-good collaterals (filling of 50 % or more of MCA) on CTA, 3) Groin puncture ≤ 60 min after NECT and CT-to-recanalization time ≤ 90 min
Campbell BC, et al. (10)	2015	EXTEND-IA	70	14	Efficacy of EVT	6		1) Occlusion of ICA, M1, or M2 on CTA or MRA, 2) Infarct core volume (< 70 ml on CTP-CBF or DWI), [b]3) Mismatch between infarct core and penumbra on CT or MR
Berkhemer OA, et al. (11)	2015	MR CLEAN	500	16	Efficacy of EVT	6	NIHSSs ≥ 2	Occlusion of intracranial ICA, M1-2, A1-2 on CTA, MRA, DSA, or TCD
Kidwell CS, et al. (16)	2013	MR RESCUE	127	22	Efficacy of EVT and penumbral imaging	8	1) Ineligible or failed respond to IVT, 2) NIHSSs 6-29	1) Occlusion of ICA, M1-2 on CTA or MRA, 2) Multimodal CT or MR (MR RESCUE protocol)
Ciccone A, et al. (17)	2013	SYNTHESIS	362	24	Efficacy of EVT	6		
Broderick JP, et al. (18)	2013	IMS III	656	58	Efficacy of EVT	5	NIHSSs ≥ 10 or 8-9 with occlusion of ICA or M1 or BA	Occlusion of ICA or M1 or BA on CTA in NIHSSs 8-9
Saver JL, et al. (19)	2012	SWIFT	113	18	Efficacy and Safety of Solitaire	8	1) Ineligible or failed respond to IVT, 2) NIHSSs 8-30,	Occlusion of M1, M2, ICA, BA, or VA on DSA (TIMI 0-1)
Nogueira RG, et al. (20)	2012	TREVO 2	178	27	Efficacy and Safety of Trevo	8	1) Ineligible or failed respond to IVT, 2) NIHSSs 8-29	Occlusion of M1, M2, ICA, BA, or VA on DSA

Clinical trial imaging in Acute ischemic stroke

Trial nickname	Eligibility	Outcomes				Conclusion
	Exclusion: Neuroimaging	Primary	Secondary	Safety	Imaging	
DAWN	1) Intracranial hemorrhage, 2) Significant mass effect and midline shift, 3) Intracranial tumor on CT or MR, 4) Steno-occlusion or Tortuosity of cervical ICA on CTA or MRA	[d] mRS	Clinical indexes, Infarct core volume, Recanalization, Reperfusion,	1) Death (90 days), 2) SICH (24 hours), 3) NIHSSs increase, 4) SAE	Included in Second outcomes	Positive
DEFUSE 3	1) ASPECTs < 6 on NECT, 2) Significant mass effect and midline shift on 3) Intracranial tumor on CT or MR, 4) ICA dissection of cervical ICA, 5) ≥ 1 vascular territory infarct on CTA or MRA	[d] mRS	Clinical index	1) Death (90 days), 2) SICH (36 hours), 3) SAE	1) Infarct core volume, 2) Recanalization 3) Reperfusion	Positive
PISTE	1) Intracranial hemorrhage, 2) Infarct (> 1/3 MCA hypodensity), 3) Occlusion of extracranial ICA or BA	[d] mRS	Clinical indexes, Recanalization	1) Death (90 days), 2) ICH (24 hours), 3) Procedural complication	[f] Reperfusion	Negative
ASTER	Occlusion of Cervical carotid artery	Revascularization	Clinical indexes, Revascularization, Time to successful revascularization	1) Procedural complication, 2) Intracranial hemorrhage (24 hours)	Included in Primary and Secondary outcomes	No difference
THERAPY	1) Significant mass effect with midline shift, 2) Infarct (acute ischemic change) > 1/3 of MCA territory, 3) intracranial hemorrhage, 4) Intracranial tumor, 5) Ipsilateral extracranial steno-occlusion, 6) Preexsting arterial injury	[d] mRS	Clinical indexes, Infarct core volume	1) SAE, 2) SICH (24 hours), 3) Death (90 days)	Included in Second outcomes	Negative
THRACE	1) Steno-occlusion of ipsilateral cervical carotid artery, 2) Intracranial hemorrhage, 3) Intracranial tumor, 4) Mass effect with midline shift on CT or MR	[d] mRS	Clinical indexes	1) Death (90 days), 2) Hemorrhage (24 hours), 3) Procedural complication	None	Positive
SWIFT PRIME	1) ASPECTs < 6 on NECT or DWI, [b]2) > 1/3 MCA territory or > 100 cc in other vascular territory (hypodensity on CT or hyperintensity on MR), 3) Intracranial hemorrhage, 4) Mass effect, 5) Intracranial tumor on CT or MR, 6) Occlusion of BA or PCA, 7) Occlusion or Dissection of cervical ICA on CTA or MRA	[d] mRS	Clinical indexes, Revascularization, Reperfusion	1) SAE, 2) SICH (27 hours)	Included in Second outcomes and [g]Infarct core volume	Positive
REVASCAT	1) Intracranial hemorrhage, 2) Significant mass effect and midline shift, 3) Intracranial tumor, 4) Steno-occlusion of cervical ICA on CTA, MRA or DSA, 5) Infarct volume (ASPECTs < 7 on CT; ASPECTs < 6 on DWI)	[d] mRS	Clinical indexes, Infarct core volume, Revascularization, Recanalization	1) Death (90 days), 2) SICH (90 days), 3) Procedural complication, 4) SAE	Included in Second outcomes	Positive
ESCAPE	1) Infarct core (moderate to large: ASPECTs 0-5) on NCCT, 2) Infarct core on CTA or CTP (moderate to large: no or minimal collaterals in a region greater than 50 % of MCA territory compared to contralateral side on CTA, low CBV and very low CBF ASPECT < 6 [≥8 cm coverage] or low CBV and very low CBF > 1/3 MCA territory[<8 cm coverage] on CTP), 3) Suspected intracranial dissection, 4) Chronic intracranial occlusion	[d] mRS	Clinical indexes, Reperfusion, Recanalization	1) Death, 2) SICH, 3) Malignant infarct, 4) Procedural complication	Included in Second outcomes	Positive
EXTEND-IA	1) Infarct volume (hypodensity > 1/3 MCA territory) on NECT, 2) Intracranial hemorrhage on CT or MR, 3) Difficulty or inability to access to cerebral arteries (proximal stenosis, dissection)	Reperfusion, NIHSSs (3 days)	Clinical indexes, [f] Infarct core volume, Recanalization	1) Death, 2) SICH, 3) Parenchymal hematoma	Included in Primary and Secondary outcomes	Positive
MR CLEAN	Intracranial hemorrhage on CT or MR	[d] mRS	Clinical indexes, Infarct core volume, Reperfusion, Recanalization	1) Neurologic deterioration, 2) SICH, 3) Procedural complication, 4) SAE (death)	Included in Second outcomes	Positive

Clinical trial imaging in Acute ischemic stroke

Trial nickname	Eligibility	Outcomes				Conclusion
	Exclusion: Neuroimaging	Primary	Secondary	Safety	Imaging	
MR RESCUE	1) Intracranial hemorrhage, 2) cervical carotid steno-occlusion on CTA or MRA	[d] mRS	Clinical indexes, Infarct core volume, Reperfusion, Revascularization	1) Death (90 days), 2) ICH (7 days), 3) SAE	Included in Second outcomes	Negative
SYNTHESIS	1) Intracranial hemorrhage, 2) Intracranial tumor except small meningioma, 3) Acute infarct (may be > 4.5 hours after onset)	[d] mRS	Clinical indexes	1) Hemorrhage, 2) Infarct, 3) death , 4) NIHSSs $\geq$ 4 increase, 5) Extracerebral events at 7 days	None	Negative
IMS III	1) Infarct (> 1/3 of MCA territory), 2) Intracranial hemorrhage, 3) Significant mass effect with midline shift, 4) Intraparenchymal tumor, 5) Baseline CTA without evidence of an arterial occlusion	[d] mRS	Clinical indexes, Infarct core volume, Reperfusion, Recanalization	1) Death, 2) Hemorrhage, 3) Major complication d/t nonintracerebral bleeding, 4) Recurrent stroke, 5) Device or procedural complication	Included in Second outcomes	Negative
SWIFT	1) Infarct volume (> 1/3 MCA territory or > 100 cc of volume, 2) Intracranial hemorrhage, 3) Intracranial tumor or mass effect on CT or MR, 4) Complete cervical carotid occlusion, carotid dissection on DSA	Recanalization	Clinical indexes, Time to Successful recanalization	1) SICH, 2) Death 3) SAE	Included in Primary outcomes	Positive
TREVO 2	1) Infarct volume (> 1/3 MCA territory or > 100 cc of volume), 2) Intracranial hemorrhage, 3) Significant mass effect with midline shift, 4) Intracranial tumor on CT or MR, 5) Cervical carotid steno-occlusion including excessive tortuosity	Reperfusion	Clinical indexes, Time to Successful reperfusion, Asymptomatic SICH	1) Death, 2) SICH, 3) SAE, 4) Device or procedural complication	Included in Primary outcomes	Positive

Infarct core volume and hemorrhagic transformation in the outcomes

Trial nickname	Infarct core volume				Hemorrhagic transformation
	Baseline	24 hours	5-7 days or discharge	Definition	Classification
DAWN	DWI, CTP	DWI, NECT		RAPID (with semi-automated algorithm using manual lesion outlining; CTP -CBF, < 30 % of contralateral normal tissue; DWI, based ADC) Manually outlining hypodense lesion (NECT)	ECASS
DEFUSE 3	DWI, CTP	MR (DWI), CT		RAPID	ECASS
PISTE					ECASS (PH1, 2), SITS-MOST
ASTER					ECASS
THERAPY	CT	CT		ASPECTs	ECASS
THRACE					ECASS
SWIFT PRIME	DWI, CTP	[a]DWI/FLAIR/MRP, NECT/CTP		RAPID (DWI[ADC], < 620 X 10^6 mm^2; CTP-CBF, > 70 % reduced region)	ECASS
REVASCAT	DWI, NECT	DWI, NECT		Quantomo	ECASS, SITS-MOST
ESCAPE					
EXTEND-IA	CTP	DWI, NECT		RAPID (CTP-CBF, automated ischemic core volume < 30 % of normal tissue), DWI or NECT (manually outlined)	SITS-MOST
MR CLEAN	NECT, CTP		NECT	Semi-automated algorithm for CT hypodensity	ECASS
MR RESCUE	DWI (MRP), CT		FLAIR, CT	Study-specific predictive model on baseline, Hyperintensity (FLAIR), Hypodensity (CT)	ECASS
SYNTHESIS					Study specific definitions
IMS III	CT	CT		ASPECTs, digital measurement	ECASS
SWIFT					ECASS
TREVO 2					ECASS, SITS-MOST

Revascularization, Reperfusion, Recanalization

Trial nickname	Revascularization			Reperfusion			Recanalization		
	Imaging	Time interval	Definition	Imaging	Time interval	Definition	Imaging	Time interval	Definition
DAWN				DSA	Post-procedure	mTICI (2b-3)	CTA or MRA	24 hours	No, Partial, or Complete
DEFUSE 3				1) CTP or MRP, 2) DSA	1) 24 hours, 2) Post-procedure	1) Reduction (>90%) in perfusion lesion volume with Tmax > 6s, 2) mTICI (2b-3)	CTA or MRA	24 hours	Complete or not
PISTE				DSA	Post-procedure	mTICI (2b-3)	CTA or MRA	24 hours	IST-3 CTA score
ASTER	DSA	Post-procedure	mTICI (2b-3)						
THERAPY									
THRACE									
SWIFT PRIME	DSA	Post-procedure	mTICI (2b-3)	CTP or MRP	27 hours	Reduction (≥90%) in perfusion lesion volume			
REVASCAT	DSA	Post-procedure	mTICI (2b-3)				CTA or MRA	24 hours	Patent or Occluded
ESCAPE				DSA	Post-procedure	TICI (2b-3)	CTA	2-8 hours	mAOL (2-3)
EXTEND-IA				CTP or MRP	24 hours	RAPID (Reduction [%] in perfusion lesion volume with T max > 6 s)	CTA or MRA,	24 hours	TIMI (2-3)
MR CLEAN				DSA	Post-procedure	mTICI (2b-3)	CTA or MRA	24 hours	mAOL (2-3)
MR RESCUE	CTA or MRA	7 days	TICI (2a-3)	CTP or MRP	7 days	Reduction (≥90%) in perfusion lesion volume with Tmax > 6s			
SYNTHESIS									
IMS III				DSA	Post-procedure	TICI (2-3)	CTA > MRA	24 hours	Partial or Complete recanalization
SWIFT							DSA	Post-procedure	TIMI (2-3)
TREVO 2				DSA	Post-procedure	TICI (2-3)			

IIRC, Imaging core lab, Standardization

Trial nickname	Independent image review and core laboratory	Reviewers	Standardization	[a]CT: MR
DAWN	Used		Same imaging modality is encouraged to be used during follow-up.	131: 75 (63.6: 36.4 %)
DEFUSE 3	Used		The baseline and follow-up imaging should be performed with DEFUSE 3 protocol, which is installed at all study sites.	133:49 (73.1: 26.9 %)
PISTE	Used	3 Neuroradiologists		
ASTER	Used	2 + 1		
THERAPY	Used	1 Neuroradiologist	Nonenhanced thin-section ($\leq$ 2.5 mm) CT	
THRACE	Used	4 Neuroradiologists for CT and MR, 3 Interventional neuroradiologists for DSA		
SWIFT PRIME	Used	2+1	Sponsor will collaborate with participating centers to evaluate and optimize the quality of imaging and image transfer.	189: 15 (92.6: 7.4 %)
REVASCAT	Used			
ESCAPE	Used		NECT and CTA protocols were presented.	13: 54 (19.4: 80.6 % at 24 hours)
EXTEND-IA	Used	Neuroradiologist/Stroke neurologist	The imaging protocols will follow current international consensus guidelines. Standard CT and MR protocols were presented.	
MR CLEAN	Used	Two neuroradiologists		24: 94 (20 : 80 %)
MR RESCUE	Used		MR RESCUE protocols were presented.	
SYNTHESIS	Used			
IMS III	Used	3 CT experts (including one neuroradiologist was mandatory)		
SWIFT	Used	2 neurointerventionalists	It is preferred that whether CT or MR is taken at baseline, the same imaging modality should be obtained at follow-up.	
TREVO 2	Used			

Imaging CRO

Imaging support for multicenter clinical trials

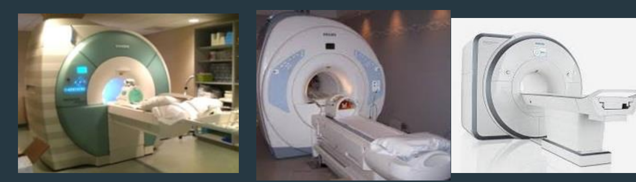
- Imaging protocol / charter
- Global standards

Quantitative Imaging Biomarkers Alliance RSNA

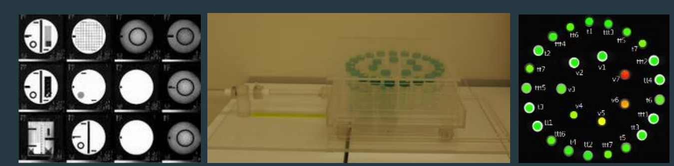
Guidance for Industry
Standards for Clinical Trial Imaging Endpoints

- Site training
- Site monitoring

- Imaging acquisition



- QA/QC
- Data management



- Post-processing
- Image analysis
- Central reading

High Quality Imaging Service

Central Imaging Core Lab in clinical trials

Independent image review committee (IIRC)

0. Consultant or Design (Imaging CRO)

1. Protocol setting: Imaging protocol standard

2. Standardization

3. Site training: Imaging acquistion & transfer

4. Site monitoring: QC/QA

5. Image analysis considering endpoints (Imaging core lab > IRC)

6. Central reading (IIRC)

Independent image review committee (IIRC)

1. Reader 1 – Independent reader
2. Reader 2 – Independent reader
3. Moderator – Independent reader or Adjudicator
4. Outside Reader 3 – Consult or Evaluation

1. Image review committe (IRC)
2. Data & Safety monitoring board (DSMB)

Anticoagulation

1. 에독사반(edoxaban)은 factor Xa를 선택적으로 저해하는 약물로서, 심방세동을 가진 환자에서 뇌경색 위험을 낮추는 데 있어 와파린과 비슷한 정도의 효능을 가지면서도, 출혈의 위험은 유의하게 낮은 새로운 경구용 항응고제(Novel oral anticoagulants, NOAC)이다. 에독사반은 factor Xa 저해 기능을 가지는 다른 NOAC들과 비교해서도 출혈 위험이 적은 것으로 알려져 있다.
2. 비판독성 심방세동에 의한 급성 허혈성 뇌졸중 환자에서 조기 에독사반 투여의 효과 및 안전성 평가를 위한 무작위배정, 평행대조, 다기관 예비 임상시험 (Early adminstration of edoxaban after acute ischemic stroke in patients with non-valvular atrial fibrillation: a randomized, multi-center, parallel-group trial (PILOT)
3. 가설: 비판막성 심방세동을 가진 급성 뇌경색 환자에서 에독사반의 조기 투여가 고식적 항응고제 투여에 비해 뇌경색의 이른 재발을 줄일 수 있다.
4. Phase II

Anticoagulation

5. 다기관 뇌졸중 치료제 임상시험: 국내 3개 기관

6. 68 Participants

7. Primary endpoint: DWI (Recurred infarct 10-14 days after the onset)

8. Secondary endpoints

   1) Imaging indexes: GRE (Hemorrhagic transformation), TOF-MRA (Recanalization)

   2) Clinical indexes: NIHSS deterioration, mRS

9. Safety endpoints

   1) Symptomatic ICH

   2) Hemorrhage

10. Imaging CRO/Imaging core lab/IIRC

Outcomes

1. New infarct or recurred infarct

   1) Definition: New separate restricted lesions on follow-up diffusion-weighted imaging (DWI) outside the region of the acutely symptomatic lesion and which is not detected on initial DWI.

   2) Classification: Local recurrent infarcts are defined as new lesions within the territory of the initial perfusion deficit based on angiography and/or perfusion-weighted imaging. Distant recurrent infarcts are defined as new lesions outside the territory of the initial perfusion deficit based on angiography and/or perfusion-weighted imaging.The initial perfusion is assessed primarily on angiography followed by perfusion-weighted imaging.

Outcomes

1. New infarct or recurred infarct

2) Primary outcome → eCRF (Anatomic and Vascular territory)

3) DWI → Standardization (Phantom), Presence or absence, local or distant, numbers

4) Measurement → Semi automated analysis in-house software

Outcomes

2. Hemorrhagic transformation
   1) Definition and classification → ECASS
   2) Secondary outcome
   3) CT and MR → Discrepancy
   4) MR: Standardization (SWI vs GRE) → Same imaging modality between initial and F/U
   5) Measurement → Semi automated analysis in-house software

Outcomes

3. Infarct core

   1) Definition or Criteria: b1000 after ADC correction

   2) Secondary outcome

   3) MR (DWI), ASPECT (X)

   4) Measurement: DWI, Δ Infarc core volume

   5) Semi automated analysis in-house software

Outcomes

4. Steno-occlusion

   1) Definition: Recanalization

   2) Secondary outcomes

   3) MRA > CTA

   4) Scoring: mAOL (MR RESCUE, ESCAPE)

Neuroprotective agent

1. Prospective, Randomized, Double-blinded, Phase IIa
2. 80 participants
3. Primary endpoint: CT
4. Secondary endpoint: SAE, mRS, sICH, NIHSS, Barthel index, Death rate, major systemic bleeding rate
5. Exploratory endpoint: DWI, GRE
6. Imaging CRO & Imaging core lab & IIRC

Primary outcome

- Safety and Efficacy of Novel Neuroprotective agent

- rtPA 표준 치료 시 NA주 투여 후 24시간 시점에 촬영한 뇌 CT 영상에서 유럽급성뇌졸중협력연구 (ECASS) I 과 II 기준에 따른 실질혈종 (Parenchymal hematoma)의 발생 비율

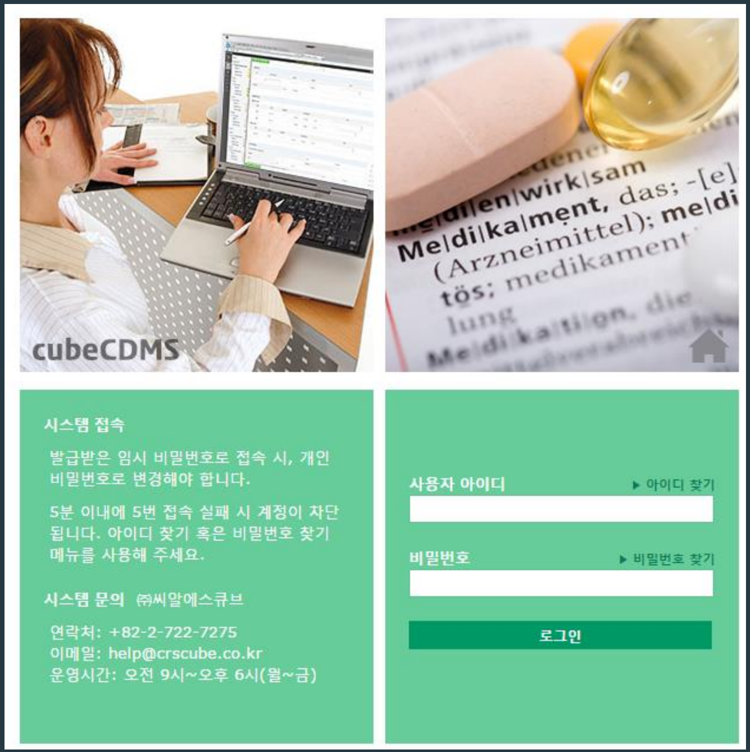
→ Consultant for appropriate imaging protocol and analysis for evaluation of drug safety and efficacy

Secondary outcome

- 5일 이내에 발생한 모든 두개내 출혈의 발생 비율
- 5일 이내에 DWI 영상에 확인된 뇌경색 크기의 증가 비율
- 5일 이내에 DWI 영상에 확인된 뇌경색의 재발 비율
- 5일 이내에 GRE 영상에 확인된 출혈의 발생 건수 및 크기
- GRE와 DWI 영상을 통해 확인된 뇌출혈과 뇌경색의 변화 비율

eCRF (clinical report form)

- Outcomes
  - ✓ Hemorrhagic transformation
  - ✓ Infarction



Outcomes

1. Hemorrhagic transformation: BBB stabilizer → Prevent HT

   1) Definition and classification → ECASS (4 classification)

   2) Imaging modality: CT & MR

   3) MR: GRE (SWI vs GRE)

      → The same imaging machine after Phantom

   4) Measurement

      → Quantitative In-house Software

Outcomes

2. Acute infarct

   1) Definition : DWI restricted lesion

   2) Presence or Absence

   3) Anatomic location

   4) Measurement: DWI (b1000 with ADC)

   5) Semi- automated In-house software

Outcomes

3. New infarct or recurred infarct

1) Definition

→ New DWI restricted lesions on follow-up outside the region of the acutely symptomatic lesion and which is not detected on initial DWI.

→ Although new DWI restriction occurs on follow-up image after no DWI restriction on initial images, the lesion is defined as No New infarction in case of occurrence in the perfusion territory which is the same with initial perfusion deficit.

Outcomes

3. New infarct or recurred infarct

   2) Imaging modality: DWI

   3) Measurement: The entire infarct core volume on F/U using In-house analysis software

Outcomes

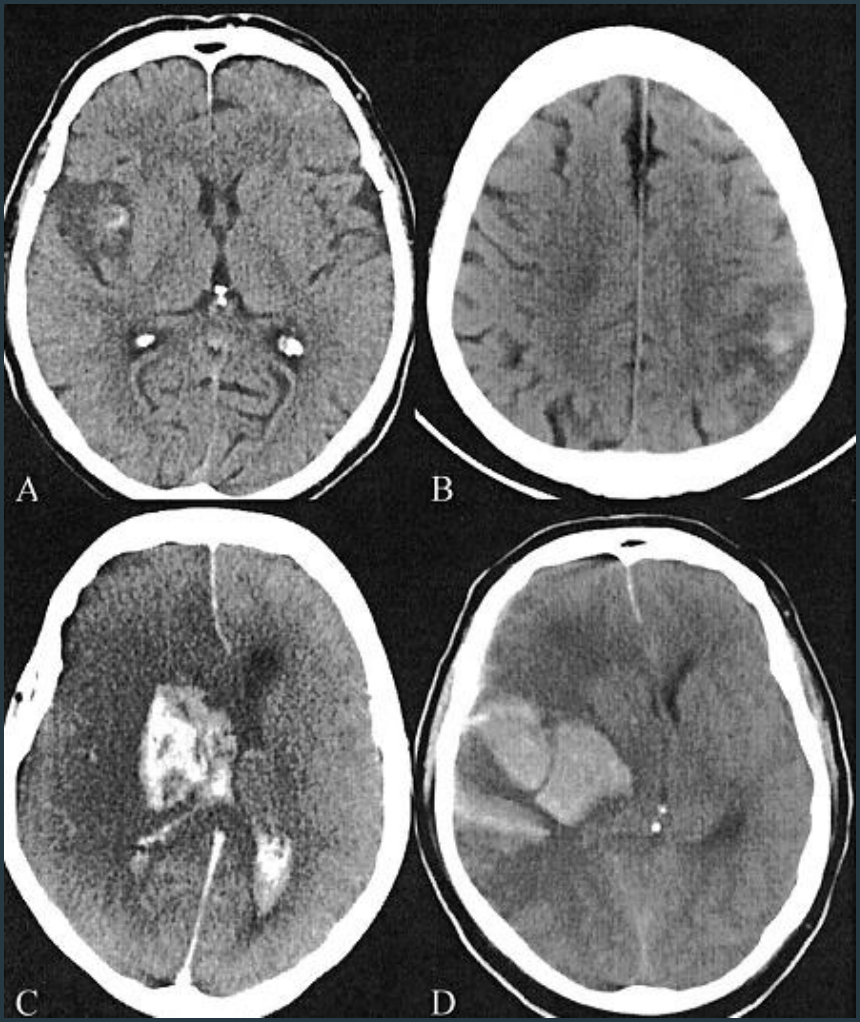
4. Steno-occlusion

   1) Definition: Revascularization

   2) Imaging modality: CTA, MRA

   3) Scoring: mTICI

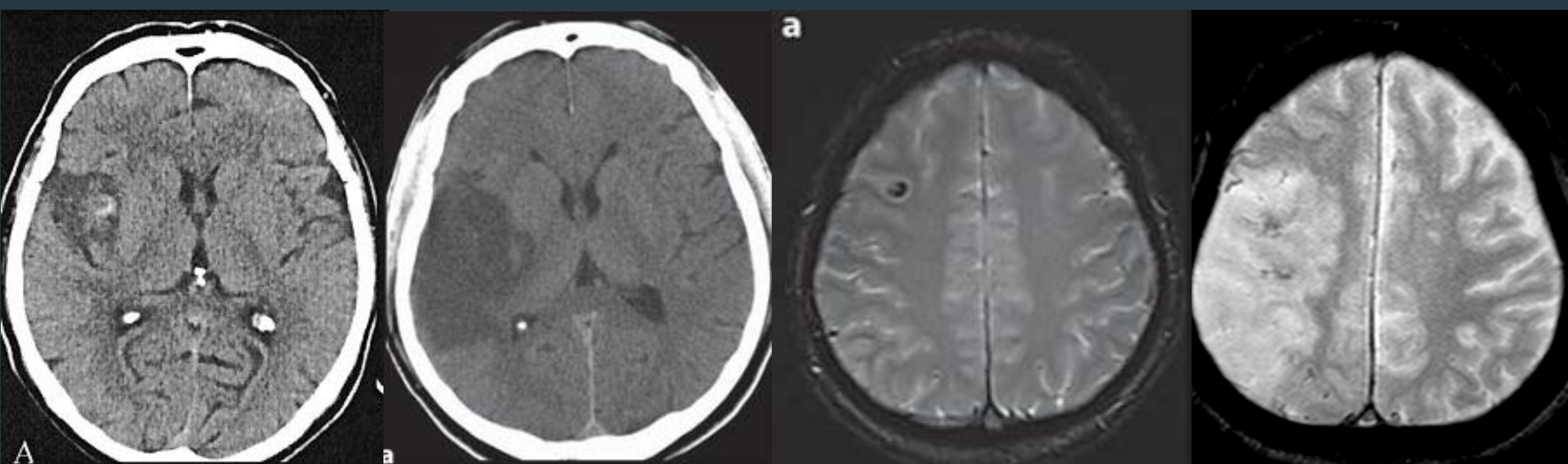
Hemorrhagic transformation Classification



ECASS I, II
Berger C et al. Stroke 2001

Hemorrhagic infarct type 1 (HI-1)

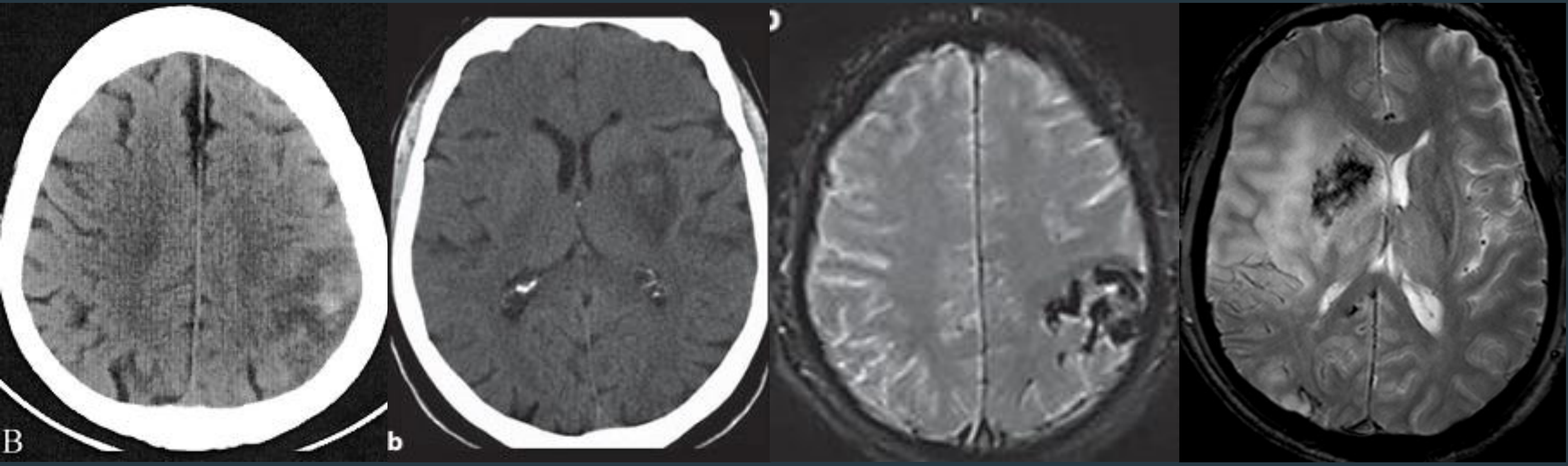
- ✓ *Small petechiae along the margins of the infarct*
- ✓ *Smaller than 10 mm*



Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra

Hemorrhagic infarct type 2 (HI-2)

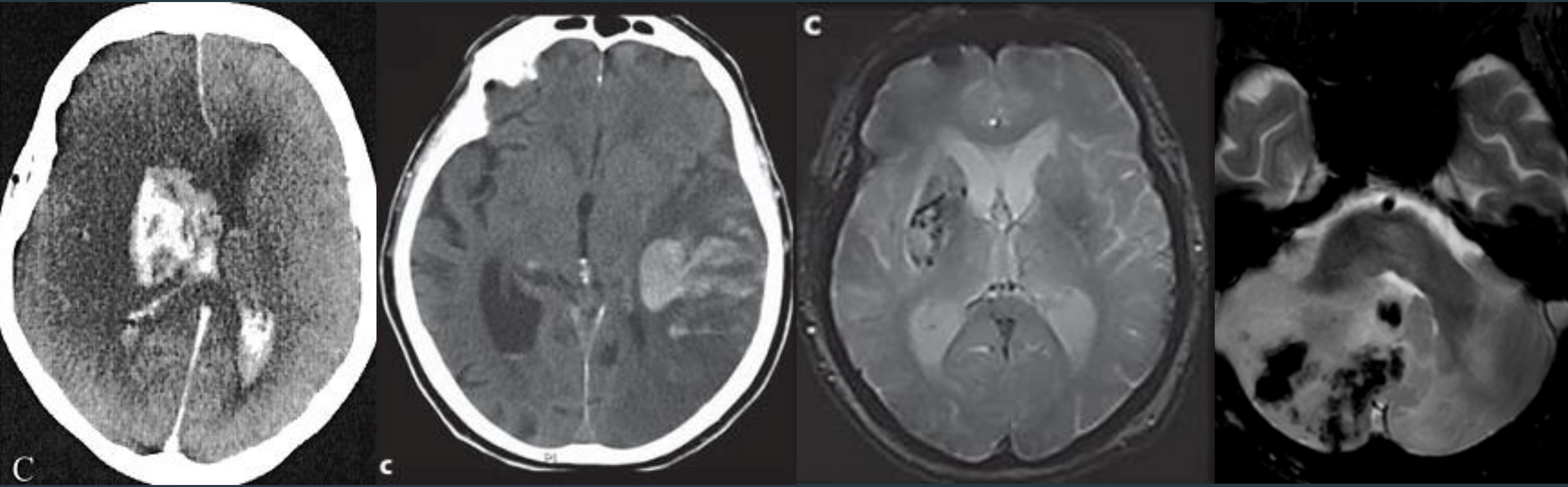
- ✓ *More confluent petechiae within the infarcted area but without space-occupying effect*
- ✓ *> 10 mm*



Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra

Parenchymal hematoma type 1 (PH-1)

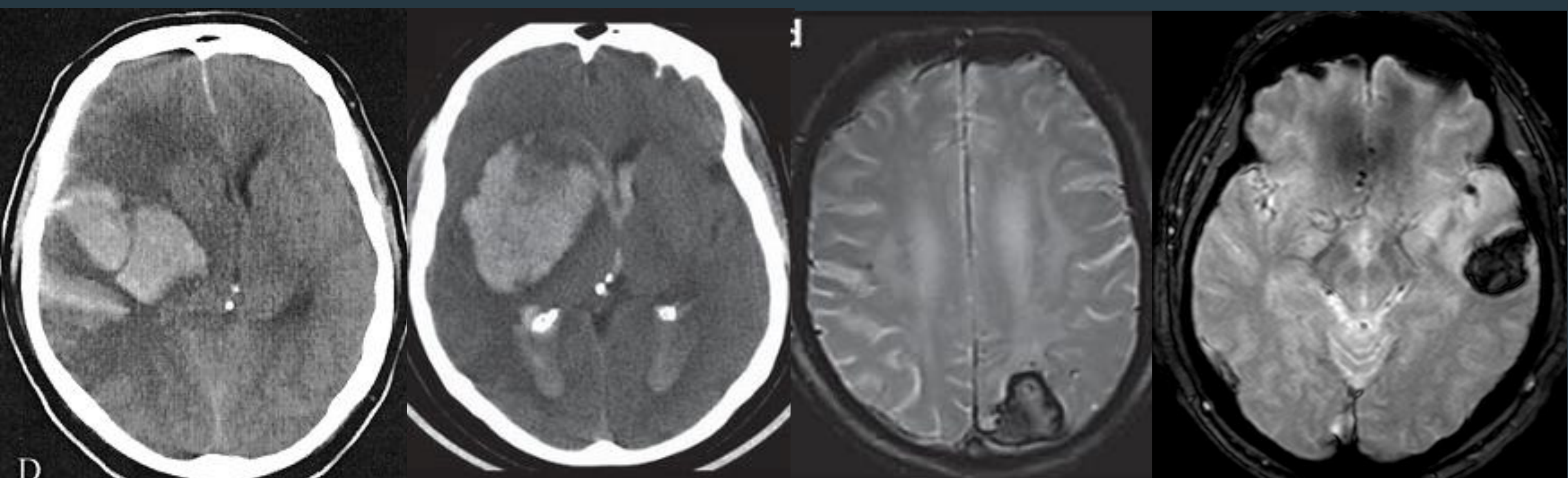
- ✓ *Hematoma in ≤ 30 % of the infarcted area with some slight space-occupying effect*
- ✓ *Round-shaped hypointensity (sometimes central hyperintensity)*



Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra

Parenchymal hematoma type 2 (PH-2)

- ✓ *Dense hematoma > 30 % of the infarcted area*
  with substantial space-occupying effect
  or as any hemorrhagic lesion outside the infarted area
- ✓ *Round-shaped hypointensity (possible central hyperintensity)*



Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra

CT vs MR

1. Upward shift
2. Overestimation of PH
3. Variability

   (Inter- & Intra-)

Comparison of CT and Three MR Sequences for Detecting and Categorizing Early (48 Hours) Hemorrhagic Transformation in Hyperacute Ischemic Stroke

Marie-Cécile Arnould, Cécile B. Grandin, André Peeters, Guy Cosnard, and Thierry P. Duprez

BACKGROUND AND PURPOSE: **Our goal was to compare the sensitivity of CT and three MR sequences in detecting and categorizing early (48 hours) hemorrhagic transformation (HT) in hyperacute ischemic stroke.**

METHODS: **Twenty-five consecutive patients with hyperacute ischemic stroke (<6 hours) without MR signs of cerebral bleeding at admission were included. Twenty-one underwent thrombolytic therapy. A standardized follow-up protocol, performed 48 hours after admission, combined brain CT scan and MR examination (1.5 T) including fast spin-echo–fluid-attenuated inversion recovery (FSE-FLAIR), echo-planar spin-echo (EPI-SE) T2-weighted, and EPI-gradient-recalled echo (GRE) T2*-weighted sequences. Both CT scans and MR images were obtained within as short a time span as possible between techniques (mean delay, 64 minutes). CT scans and MR images were independently rated as negative or positive for bleeding and categorized for bleeding severity (five classes) by two blinded observers. Prevalence of positive cases, intra- and interobserver agreement, and shifts in bleeding categorization between respective modalities and sequences were assessed.**

RESULTS: **Twelve patients (48%) were rated positive for HT on the basis of findings of at least one technique or sequence. From this subset of bleeding patients, seven (58%) had positive CT findings, nine (75%) had positive FSE-FLAIR and EPI-SE T2-weighted findings, and 12 (100%) had positive EPI-GRE T2*-weighted findings. CT had lower intra- and interobserver agreement for positivity than did MR imaging. Among the seven patients with positive CT and MR findings, only two had convergent ratings for bleeding category based on findings of two modalities. The five remaining had upward grading from CT to MR, which varied according to pulse sequence.**

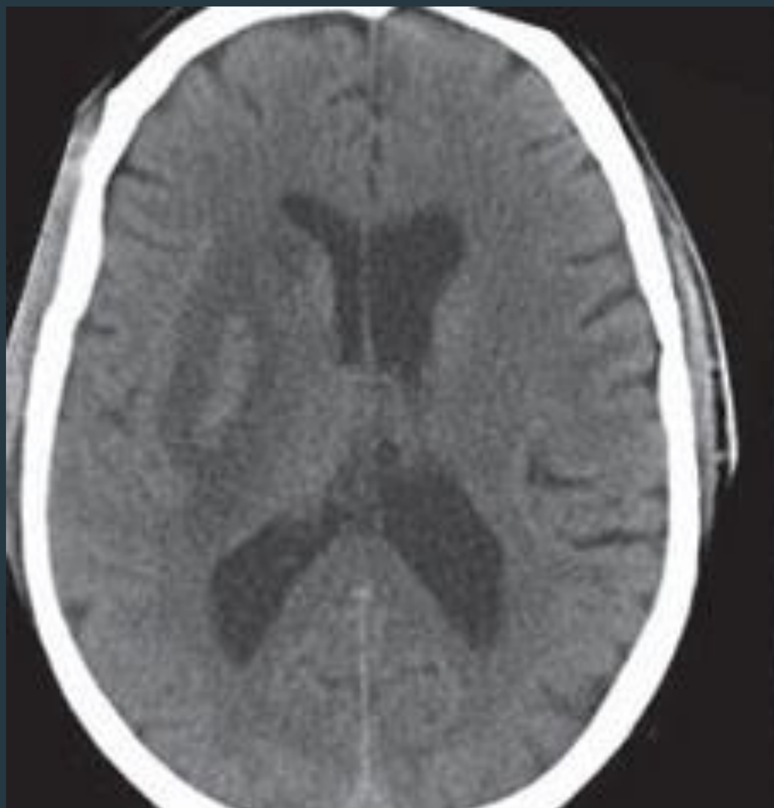
CONCLUSION: **MR imaging depicted more hemorrhages and had higher intra- and interobserver agreement than did CT. The EPI-GRE T2*-weighted sequence demonstrated highest sensitivity. Equivocal upward shifts in bleeding categorization were observed from CT to MR imaging and between MR images.**

Arnould et al. AJNR 2004

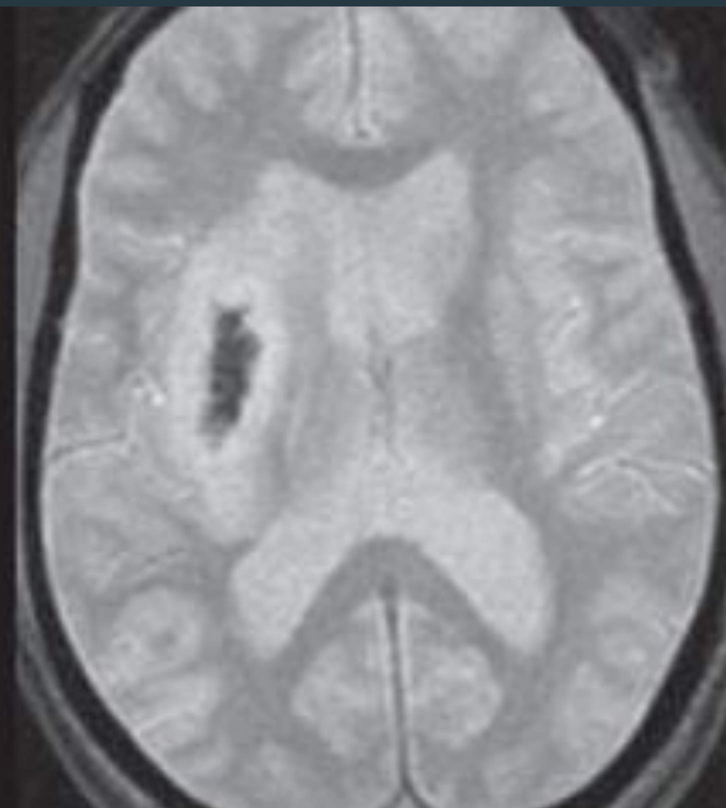
Independent image review committee (IIRC)

1. Mock training (모의고사) : around 20 ~ 30 cases
   1) Inter-observer agreement
   2) Reliability

2. Reading (수능)→ Actually, Independent



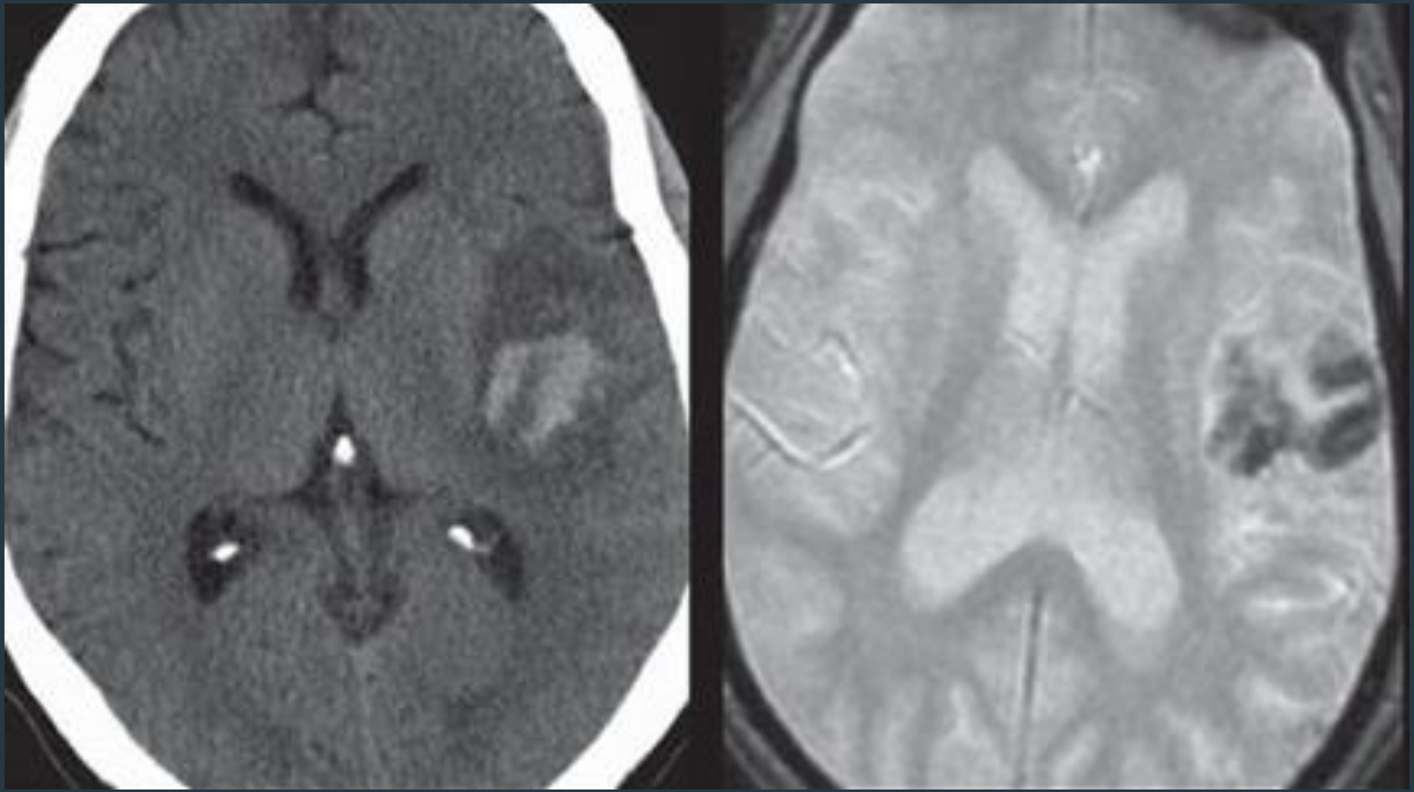
HI 2



PH 1

→ HI 2?

Renou et al. Cerebrovascular Dis 2010



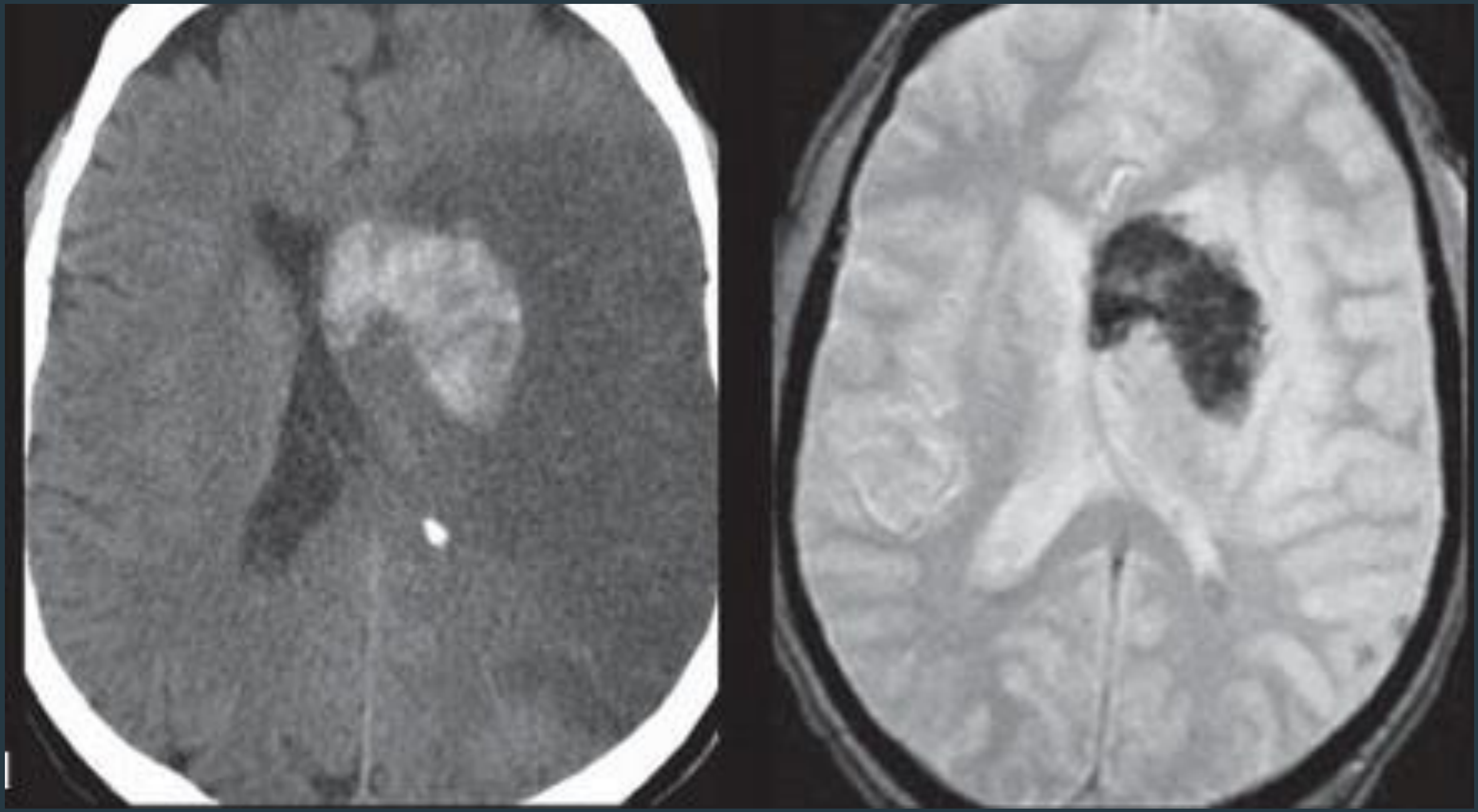
PH 1

→ PH1/HI 2?

HI 2

HI 2?

Renou et al. Cerebrovascular Dis 2010



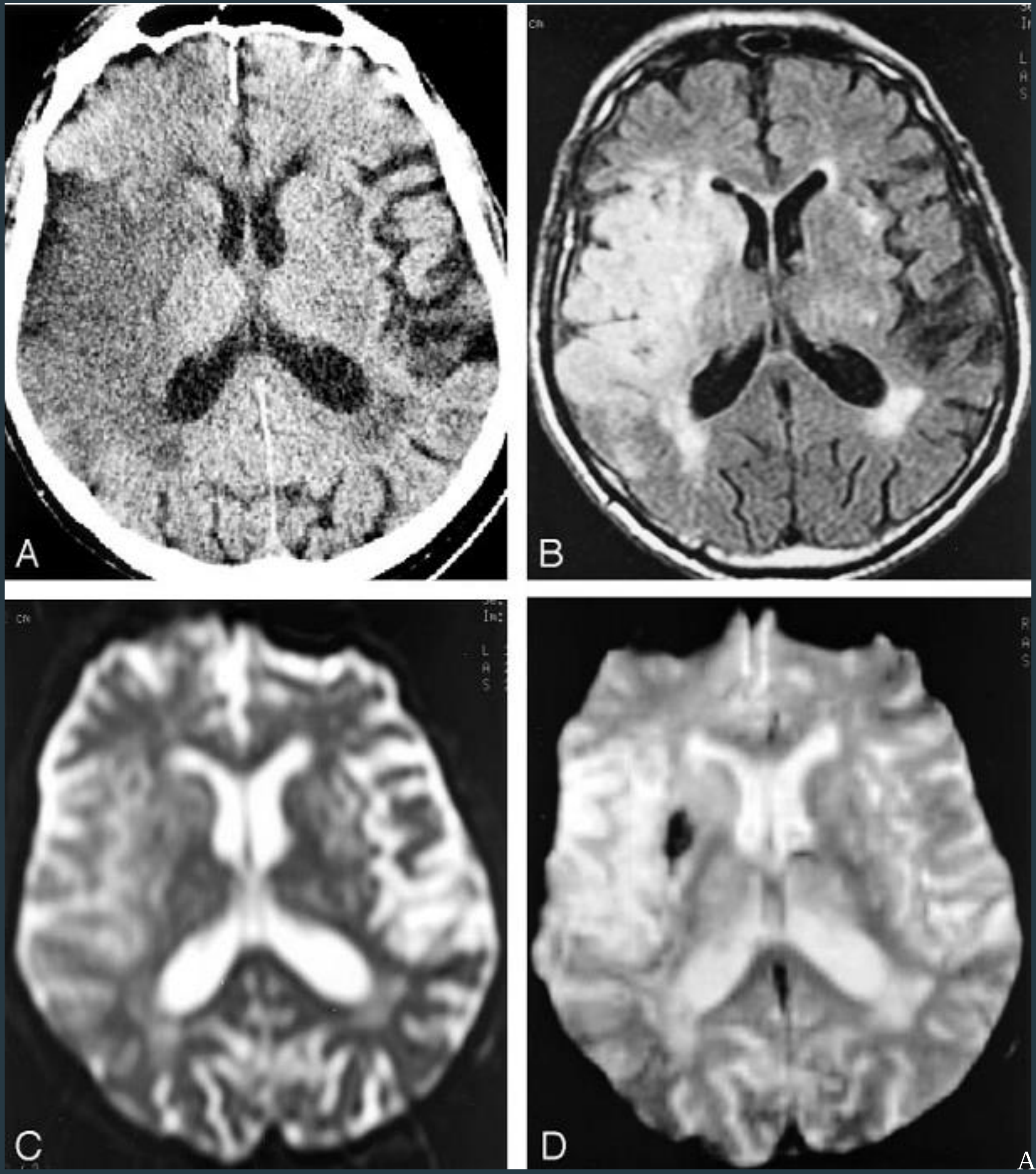
PH 1

PH 2

→ PH1?

Renou et al. Cerebrovascular Dis 2010

0



HI 2

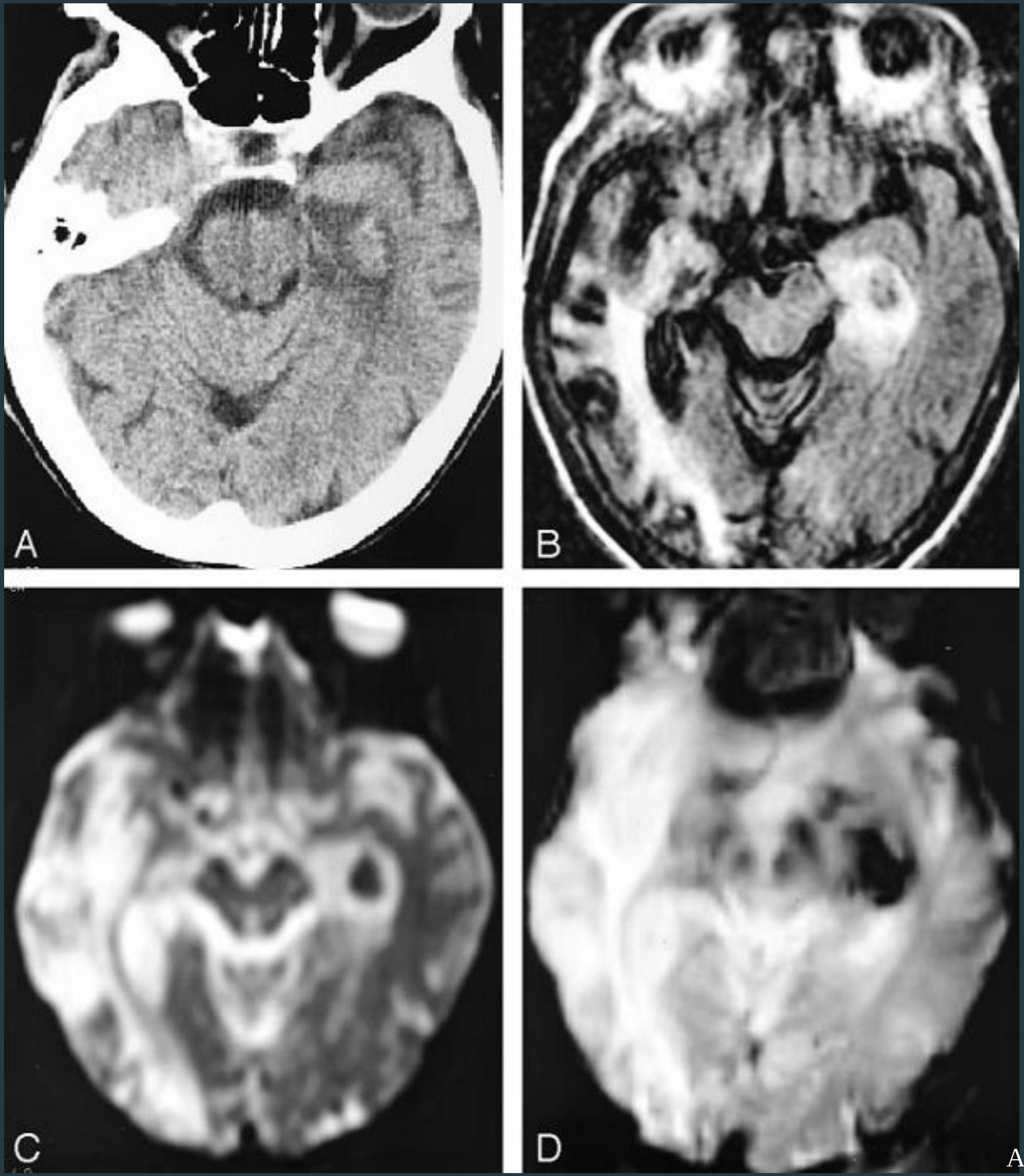
Confluent petechiae

Arnould et al. AJNR 2004

HI 1

Extended debate

Spared tissue vs petechial HT



PH 2

>30 %

Arnould et al. AJNR 2004

Infarct core volume segmentation

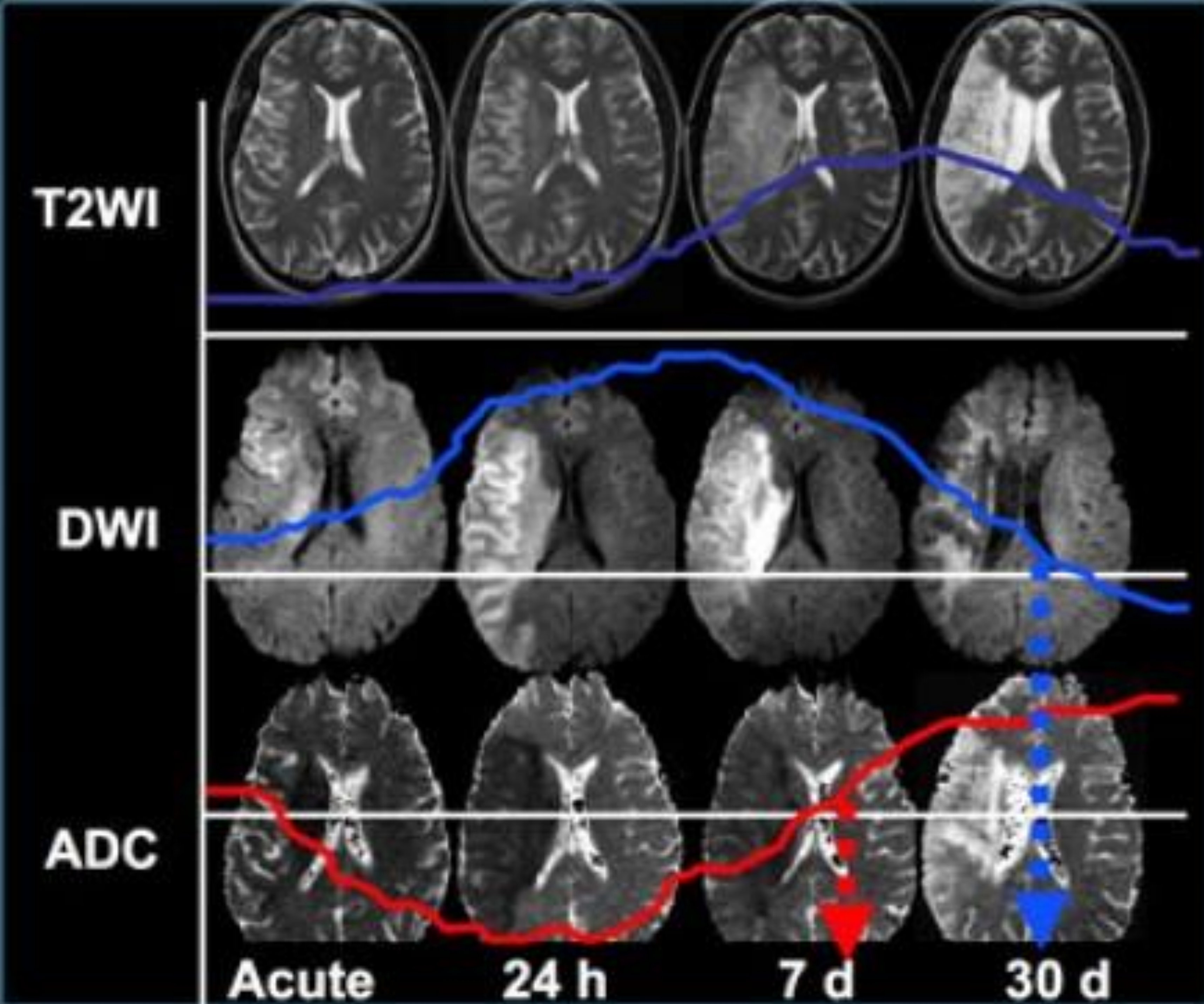
- ECASS I, II (JAMA 1995, Lancet 1998), ATLANTIS (JAMA 1999)
  - CT (infarction≒hypodensity, hemorrhage or not)
  - IV tPA beneficial? within 6 hrs of the onset of stroke
  - Try a time window of upto 6 hrs → Fail

- DIAS (Desmoteplase In Acute ischemic Stroke phase II, Stroke 2005)
  - MR (infarct lesion volume ≒ DWI abnormality)
  - IV Desmoteplase within 3 to 9 hrs improves outcome

- DEDAS (Dose Escalation study of Desmoteplase in Acute ischemic Stroke, Stroke 2006)
  - MR (infarct lesion volume ≒ DWI lesion)
  - CT (hemorrhage for exclusion)
  - IV Desmoteplase within 3 to 9 hrs improves outcome

Infarct core volume segmentation

- DIAS-2 (Desmoteplase In Acute ischemic Stroke phase III, Lancet Neurol 2009)
  - ➢MR (infarct lesion volume ≒ DWI abnormality), CT
- DEFUSE (Diffuseion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study, Ann Neurol 2006)
  - ➢MR (infarct lesion volume ≒ DWI high SI + ADC confirm)
- EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial, Lancet Neurol 2008)
  - ➢MR (infarct lesion volume ≒ DWI volume, no comment about ADC)
- DEFUSE 2 (Lancet Neurol 2012)- MRI can identify
  - ➢RAPID software
  - ➢MR (infarct lesion volume ≒ less than ADC 600×100^{-6} mm^2/s)


T2WI
DWI
ADC
Acute
24 h
7 d
30 d

Infarct core/ volume

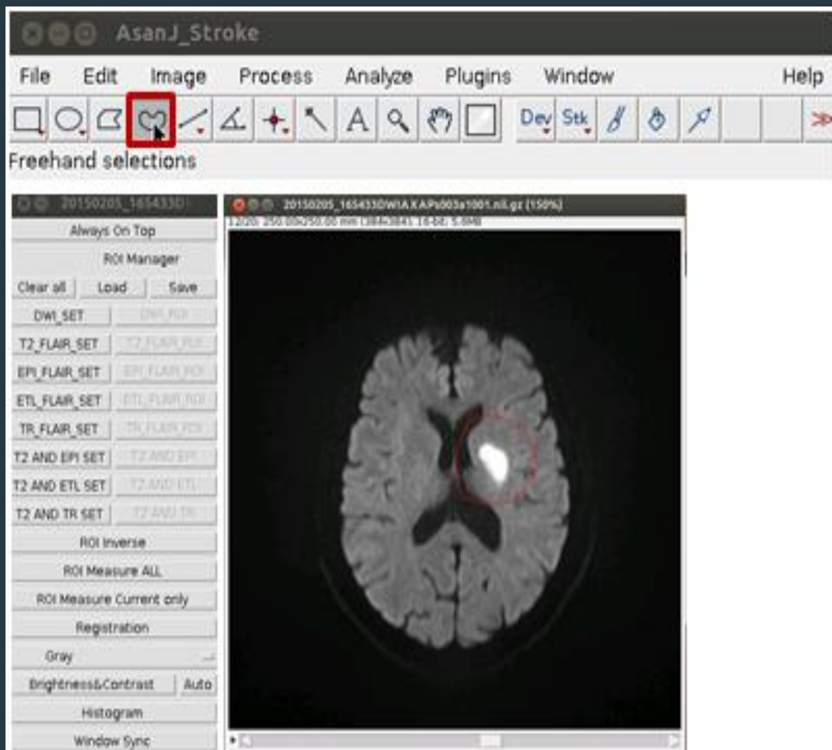
- ➢ DWI high SI
- ➢ ADC low SI
- ➢ FLAIR high SI
- ➢ ADC pseudonormalization

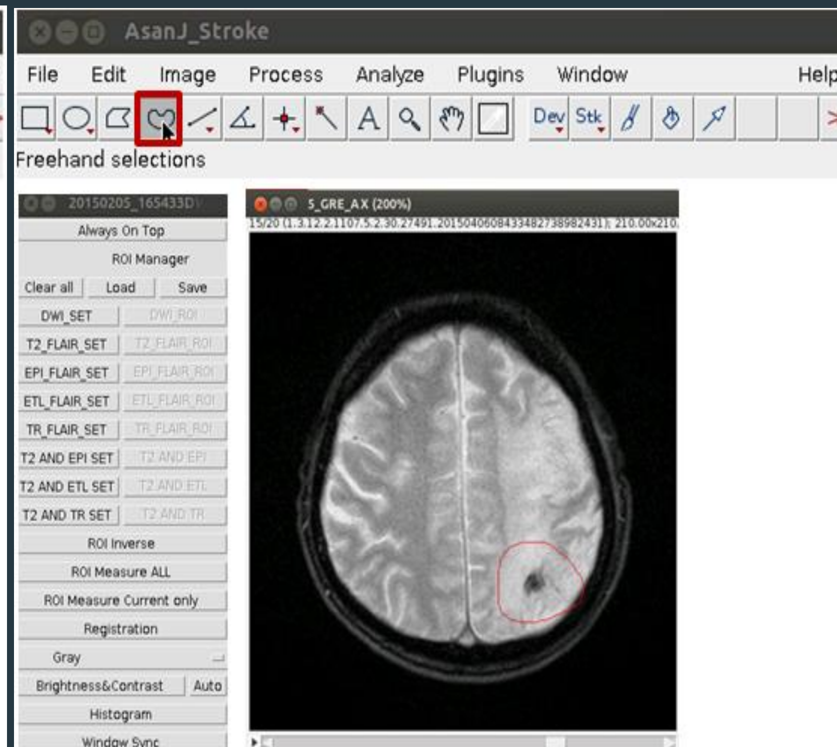
(B.C.) who was not blinded to treatment. Regions of interest were manually drawn using careful windowing to outline the maximal visual extent of the acute DWI (B1000 trace-weighted) lesion with reference to the apparent diffusion coefficient image to avoid regions of T2 shine-through. The B1000 image was used as the primary template because quantitative apparent diffusion coefficient thresholds tend not to accurately outline the visually evident lesion and have been shown to vary with time after stroke onset and perfusion status.

→ Infarction volume is measured based on DWI high SI with reference to ADC

Toshiyasu Ogata et al. Stroke 2013

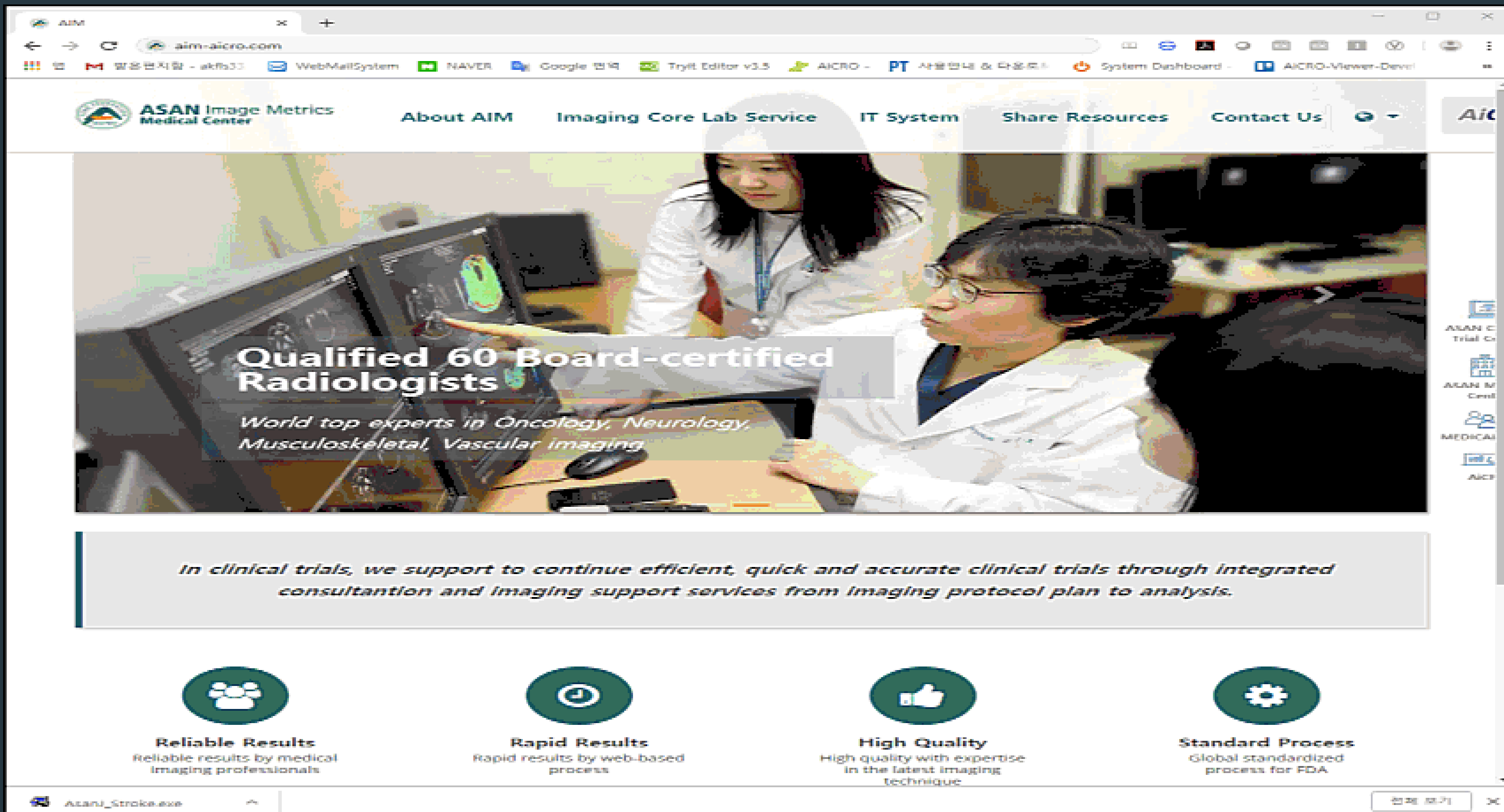
Infarct core/Hemorrhage volume





Datasharing.aim-aicro.com/strokevolumetry

분석 소프트웨어



Datasharing.aim-aicro.com/strokevolumetry

Revascularization, Reperfusion, Recanalization

Trial nickname	Revascularization			Reperfusion			Recanalization		
	Imaging	Time interval	Definition	Imaging	Time interval	Definition	Imaging	Time interval	Definition
DAWN				DSA	Post-procedure	mTICI (2b-3)	CTA or MRA	24 hours	No, Partial, or Complete
DEFUSE 3				1) CTP or MRP, 2) DSA	1) 24 hours, 2) Post-procedure	1) Reduction (>90%) in perfusion lesion volume with Tmax > 6s, 2) mTICI (2b-3)	CTA or MRA	24 hours	Complete or not
PISTE				DSA	Post-procedure	mTICI (2b-3)	CTA or MRA	24 hours	IST-3 CTA score
ASTER	DSA	Post-procedure	mTICI (2b-3)						
THERAPY									
THRACE									
SWIFT PRIME	DSA	Post-procedure	mTICI (2b-3)	CTP or MRP	27 hours	Reduction (≥90%) in perfusion lesion volume			
REVASCAT	DSA	Post-procedure	mTICI (2b-3)				CTA or MRA	24 hours	Patent or Occluded
ESCAPE				DSA	Post-procedure	TICI (2b-3)	CTA	2-8 hours	mAOL (2-3)
EXTEND-IA				CTP or MRP	24 hours	RAPID (Reduction [%] in perfusion lesion volume with T max > 6 s)	CTA or MRA,	24 hours	TIMI (2-3)
MR CLEAN				DSA	Post-procedure	mTICI (2b-3)	CTA or MRA	24 hours	mAOL (2-3)
MR RESCUE	CTA or MRA	7 days	TICI (2a-3)	CTP or MRP	7 days	Reduction (≥90%) in perfusion lesion volume with Tmax > 6s			
SYNTHESIS									
IMS III				DSA	Post-procedure	TICI (2-3)	CTA > MRA	24 hours	Partial or Complete recanalization
SWIFT							DSA	Post-procedure	TIMI (2-3)
TREVO 2				DSA	Post-procedure	TICI (2-3)			

Recommendations on Angiographic Revascularization Grading Standards for Acute Ischemic Stroke

A Consensus Statement

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See related article, p 2509

Intra-arterial therapy (IAT) for acute ischemic stroke (AIS) has dramatically evolved during the past decade to include aspiration and stent-retriever devices. Recent randomized controlled trials have demonstrated the superior revascularization efficacy of stent-retrievers compared with the first-generation Merci device.[1,2] Additionally, the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) 2, the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and the Interventional Management of Stroke (IMS) III trials have confirmed the importance of early revascularization for achieving better clinical outcome.[3–5] Despite these data, the current heterogeneity in cerebral angiographic revascularization grading (CARG) poses a major obstacle to further advances in stroke therapy. To date, several CARG scales have been used to measure the success of IAT.[6–14] Even when the same scale is used in different studies, it is applied using varying operational criteria, which further confounds the interpretation of this key metric.[10] The lack of a uniform grading approach limits comparison of revascularization rates across clinical trials and hinders the

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This statement is also endorsed by Cerebrovascular Coalition (CVC), Stroke Imaging Repository (STIR) Consortium and Stroke Treatment Academic Industry Roundtable (STAIR) group.

A list of all STAIR Participant Endorsees is given in the Appendix.

Guest Editor for this article was Bruce Ovbiagele, MD, MSc, MAS.

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Revascularization, Reperfusion, Recanalization

- Revascularization, recanalization and reperfusion: interchangeably.
- Revascularization reflects all treatment-related flow improvement, including local arterial recanalization and reperfusion of the downstream territory.
- Recanalization is required for antegrade tissue reperfusion but may not be necessary for reperfusion in distal regions (36, 37).
- Revascularization and reperfusion seem to be interchangeable terms while recanalization seems to focus on the restoration of proximal vessel patency.

Zaidat OO et al. Neurology 2012 and Stroke 2013

mTICI

Table 2: Varying definitions of TICI grades in the literature

Category	Definition
Grade 0	No flow No canalization Complete occlusion No recanalization/reperfusion
Grade 1	Minimal recanalization (<20%) Minimal flow (very slow) without significant flow distal to the occlusion site Limited or no reperfusion Distal movement of thrombus without reperfusion Perfusion past initial occlusion, but limited distal branch Filling
Grade 2	Partial recanalization—recanalization of some but not all of the occluded arteries Incomplete recanalization/reperfusion Near-normal flow, with flow distal to the occlusion but not filling the distal branches normally
Grade 2a	Perfusion of <50% of the MCA distribution Partial filling of the entire vascular territory Partial perfusion with incomplete distal filling of <50% of expected territory Partial filling of the entire vascular territory
Grade 2b	Partial perfusion with incomplete distal branch filling of ≥50–99% of the expected territory Complete filling, but the filling is slower than normal Perfusion of half or greater of the vascular distribution of the occluded artery
Grade 2c	Near-complete perfusion without clearly visible thrombus but with delay in contrast run-off
Grade 3	Full perfusion with filling of all distal branches, including M3, M4 Normal flow Partial recanalization with >50% reperfusion Full perfusion with normal filling of distal branches in a normal hemodynamic fashion
Grade 4	Complete recanalization/reperfusion

Table 2. Modified Treatment in Cerebral Ischemia Scale

mTICI Grades	Definitions
Grade 0	No perfusion
Grade 1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade 2a	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory)
Grade 2b	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and their territories)
Grade 3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

MCA indicates middle cerebral artery; and mTICI, Modified Treatment in Cerebral Ischemia Scale.

J.E.Fugate et al. AJNR 2013

Osama O. Zaidat et al. Stroke 2013

Table S3. Arterial Occlusive Lesion (AOL) Rating Scale[8]

Score	Definition
0	No recanalization of the primary occlusion lesion
I	Incomplete or partial recanalization of the primary occlusion lesion with no distal flow
II	Incomplete or partial recanalization of the primary occlusion lesion with any distal flow
III	Complete recanalization of the primary occlusion with any distal flow

Table S4. Thrombolysis in Cerebral Infarction (TICI) Rating Scale[3]

Score	Definition
0	No perfusion
1	Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion
2a	Perfusion of less than 2/3 of the vascular distribution of the occluded artery
2b	Perfusion of 2/3 or greater of the vascular distribution of the occluded artery
3	Full perfusion with filling of all distal branches

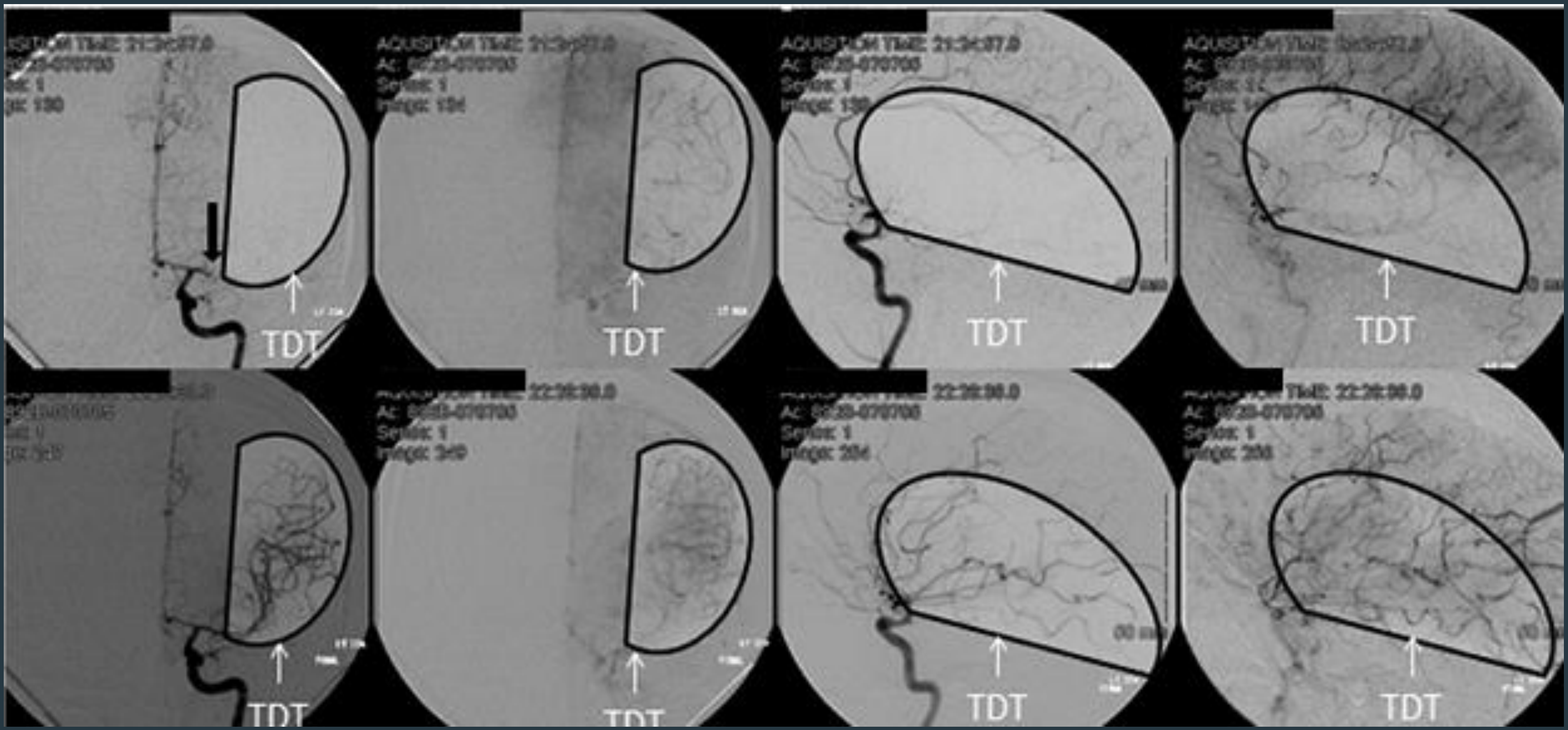
Table S5. Thrombolysis in Myocardial Ischemia (TIMI) Rating Scale[7]

Score	Definition
0	No perfusion: absence of any antegrade flow beyond a coronary occlusion
1	Penetration without perfusion: faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed
2	Partial reperfusion: delayed or sluggish antegrade flow with complete filling of the distal territory
3	Complete perfusion: normal flow which fills the distal coronary bed completely

TICI 0

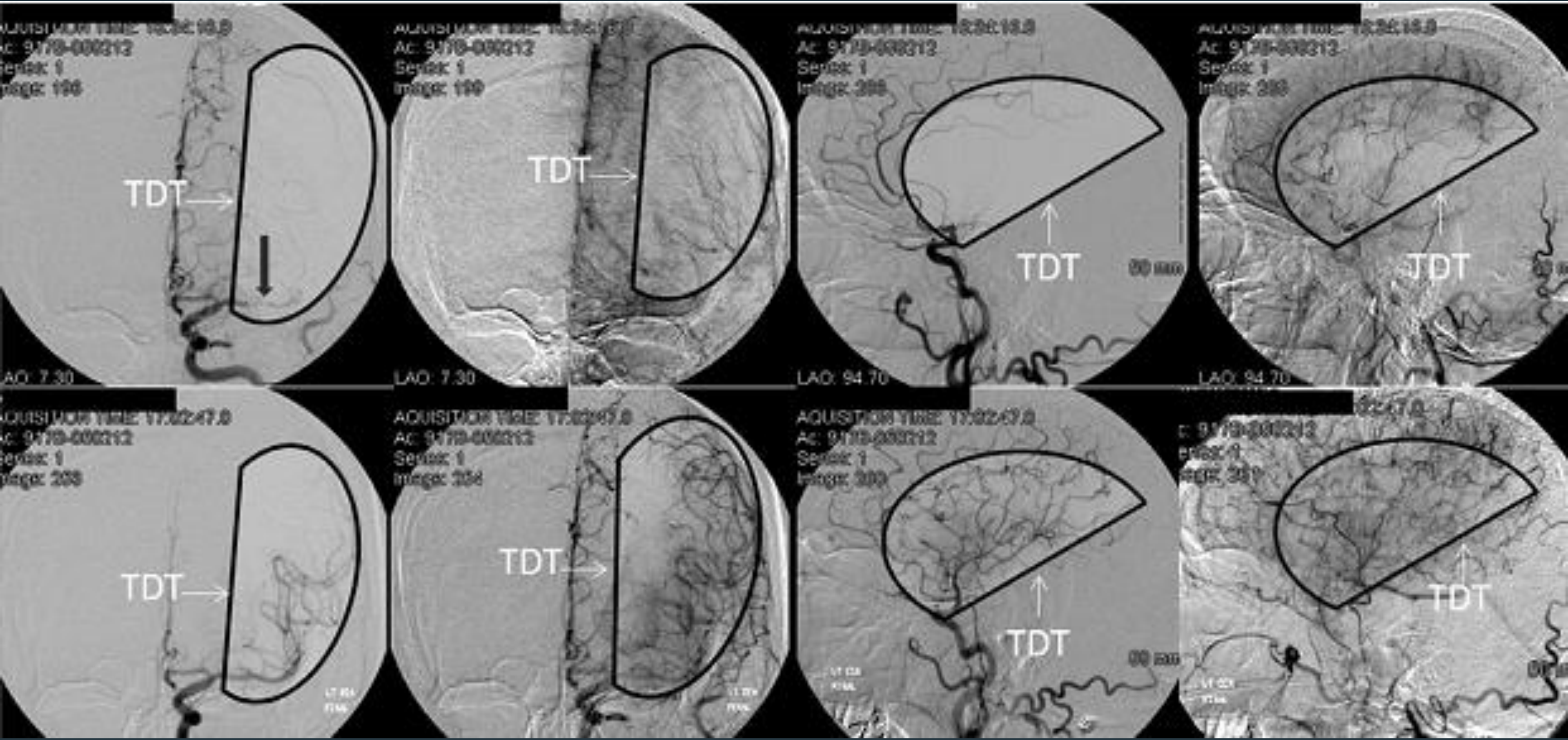
TICI 2a

TICI 0



TICI 2b

TICI 1


TDT
TDT
TDT
TDT
LAO: 7.30
LAO: 7.30
LAO: 94.70
LAO: 94.70
TDT
TDT
TDT
TDT

TICI 3

기준안

- 뇌졸중 치료 약물 임상시험에서의 영상 바이오마커의 기준안을 제시한다.

1. 뇌졸중 영상 바이오마커 표준화 팬텀
2. 뇌졸중 영상 바이오마커 분석 소프트웨어
3. 뇌졸중 영상 바이오마커의 촬영, 전송, 분석 등의 기준

뇌졸중 영상 적합 팬텀

1. CT 팬텀: 미국 표준 팬텀인 AAPM CT Performance phantom 혹은 ACR Phantom으로 표준화 가능

2. DWI MR 팬텀: QIBA 팬텀이 글로벌 스탠다드 (단점: 촬영의 불편, 해상도 평가 어려움, GRE추가 평가 불가, 비싼 가격 US $ 4,000)

3. GRE MR 팬텀: NIST/ISMRM system 팬텀 (NIST에 의한 내부 물질 공인, 비싼 가격 US $ 20,000)

뇌졸중 영상 적합 팬텀

NIST/ISMRM system phantom
NIST/RSNA/NCI diffusion phantom
NIST/UCSF/NCI system phantom
T1 array
Fiducial array
Resolution inset
T2 array
Slice profile inset
Proton density array
Wide range of diffusion
Fat suppression with T1 relaxation phantom
No Fat suppression
Spectral Fat suppression
Heavy Mineral oil
Olive oil
Heavy Mineral oil
Olive oil
Signal from silicone shell is suppressed.

뇌졸중 영상 적합 팬텀

서울아산병원 Asan Medical Center

영상바이오마커 선정
내부 물질 협의
팬텀 디자인

KRISS 한국표준과학연구원

내부 물질 협의
팬텀 주문 제작
표준물질 공식인증

센터소개

의료융합표준센터는 2025년 세계적으로 의료측정표준 분야의 연구를 선도하는 대표적인 연구센터가 되기 위하여 기본 물리량에 소급한 의료기기 측정표준 확립, 의료영상 정량화를 통하여 재현성과 신뢰성이 확보된 영상 측정기술 개발, 정밀측정 기술을 기반으로 새로운 의료진단 및 치료기술 개발 연구를 통해 의료 빅데이터 명품화를 추구하고 있습니다.

전자 신문

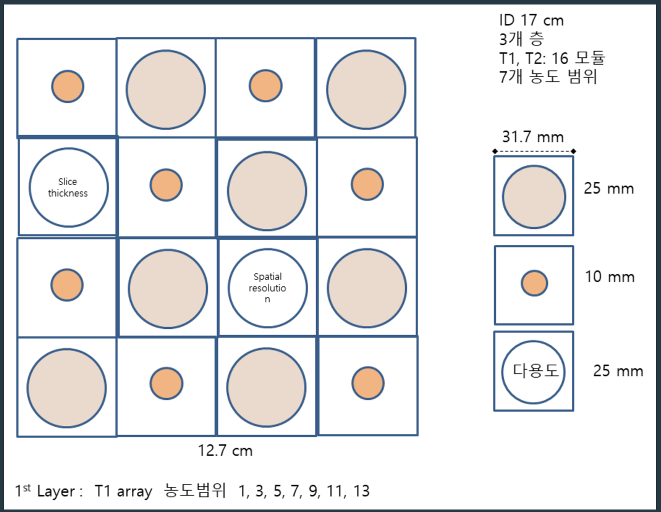
표준연, 의료기기 성능 평가하는 모듈형 팬텀 세계 첫 개발

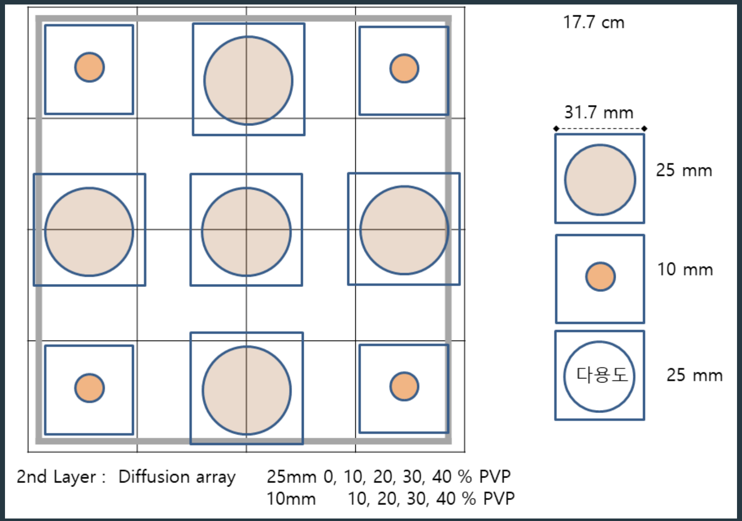
<조효민 한국표준과학연구원 의료융합측정표준센터 박사가 새로 개발한 'MOMA 팬텀' 모듈 물성을 시험하고 있다.>

뇌졸중 영상 적합 팬텀

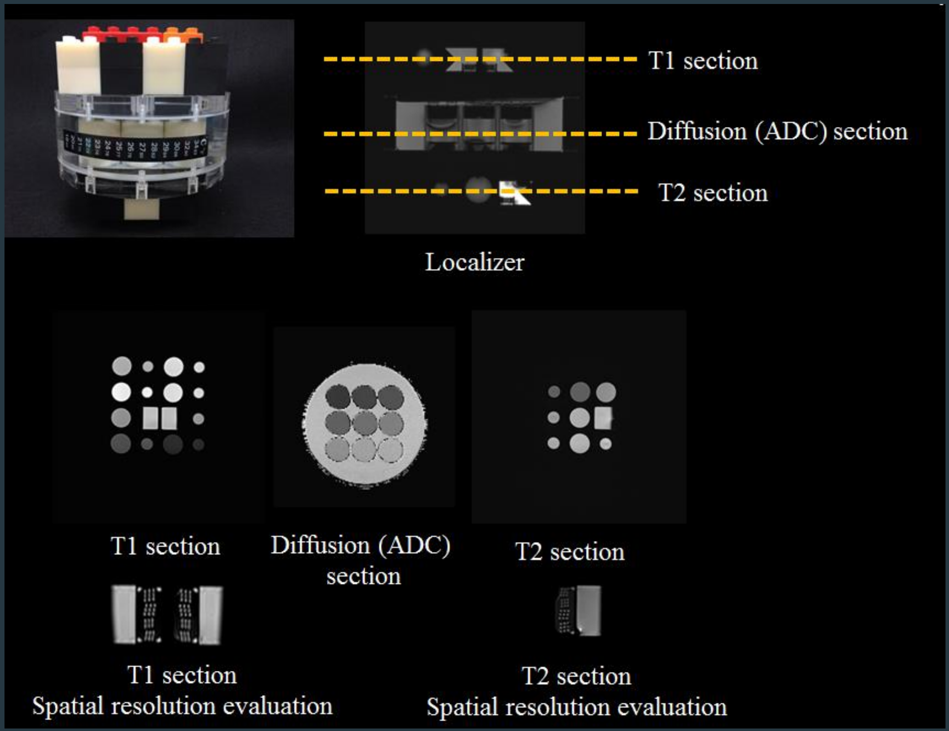
- 뇌졸중 표준화 팬텀을 위한 영상바이오마커 선정: DWI, GRE (T2*), T1
- K-Stroke-Block (KSB) 팬텀과 QIBA 및 NIST/ISMRM system 팬텀과의 차별점

1. Spatial resolution 측정 가능
2. Cost-effective 팬텀
3. GRE 동시 측정 가능 팬텀
4. 레고블럭방식의 팬텀: 다양한 영상 바이오마커 선정 및 조합 가능





뇌졸중 영상 적합 팬텀



NIST (National Institute of Standards and Technology) 공인 물질

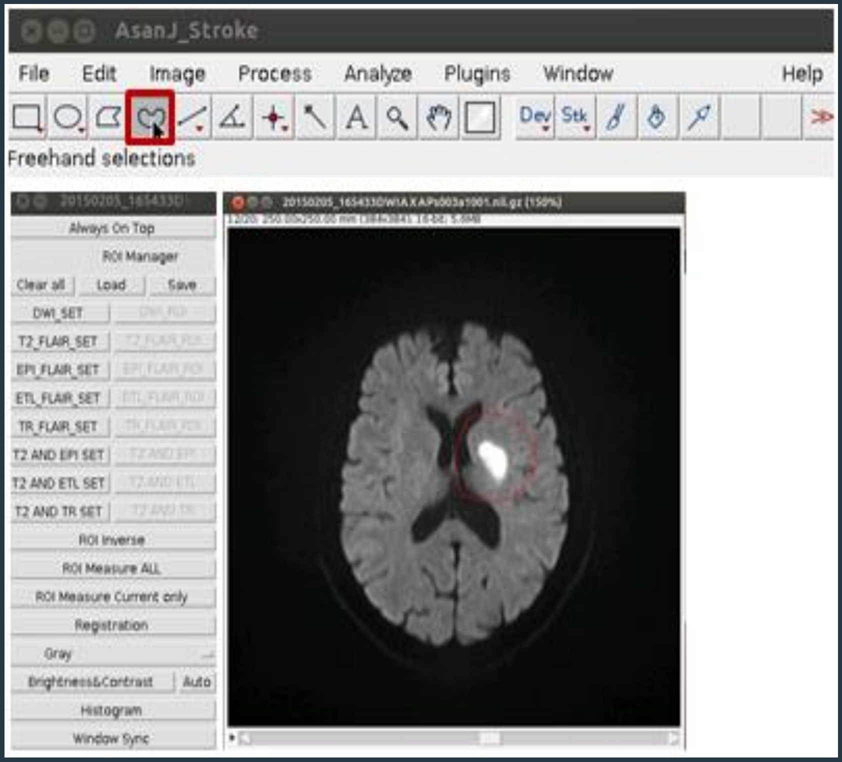
가격 경쟁력 (미국 제품의 반값)

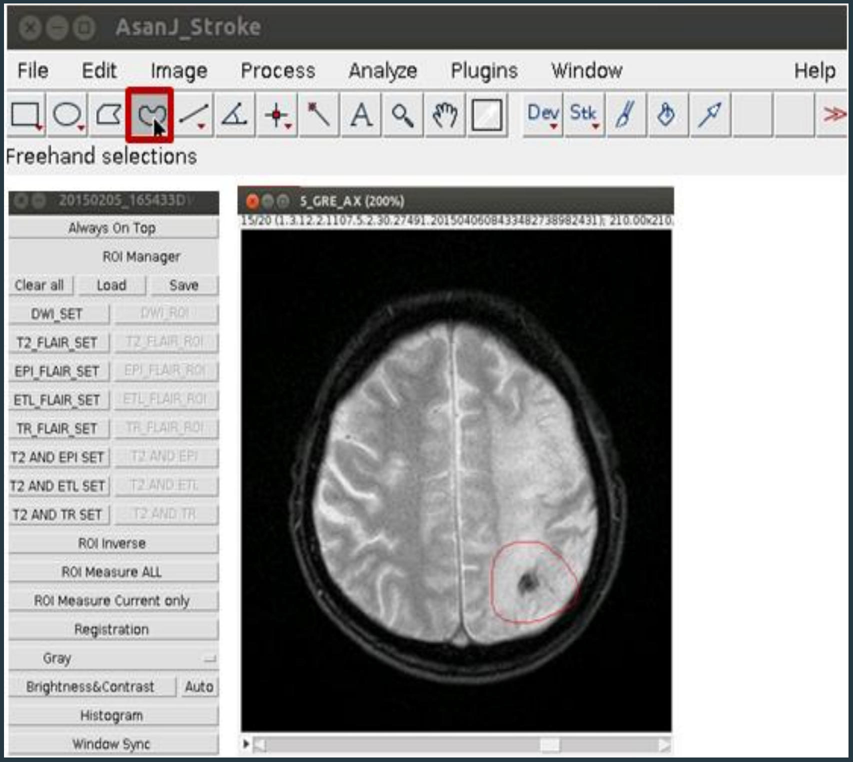
조립이 용이하고 맞춤형 디자인 가능

분석 소프트웨어

1. 국내: 소프트웨어 개발이 진행중 (자동 정량화 분석 소프트웨어가 주류, DWI-PWI mismatch 위주, 해외 소프트웨어에 비해 가격이 낮으나 개별 연구자에게는 여전히 높을 수도 있음.)
2. 해외: 다수의 글로벌 회사 및 연구자들이 다양한 분석 소프트웨어를 판매 (편리한 UI, 고가)

분석 소프트웨어





Datasharing.aim-aicro.com/strokevolumetry

기준안

급성 뇌졸중 임상시험 영상의 글로벌 동향

조사 보고서

2018. 10

제작: 서울아산병원 영상의학과/
울산대학교 의과대학/

국문표기: 본 보고서는 정부(식품의약품안전처, 18182임상평402)의 용역연구개발사업의 지원을 받아 수행된 연구임.
영문표기: This work was supported by the grant of Ministry of Food and Drug Safety (18182MFDS402).

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급성 뇌졸중 영상촬영 프로토콜 표준화 및 팬텀 품질평가를 위한 기준안

(1차년도용)

2018.10

제작: 서울아산병원 영상의학과/
울산대학교 의과대학/

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2018. 10

제작: 서울아산병원 영상의학과/

울산대학교 의과대학/

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영문표기: This work was supported by the grant of Ministry of Food and Drug Safety (18182MFDS402).

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Guideline

Guidance for Industry

Standards for Clinical Trial Imaging Endpoints

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Dr. Rafel Rieves at 301-796-2050 or (CBER) Office of Communication, Outreach, and Development at 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2011
Clinical/Medical

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08/08/11

Clinical Trial Imaging Endpoint Process Standards

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2018
Clinical/Medical

Guideline

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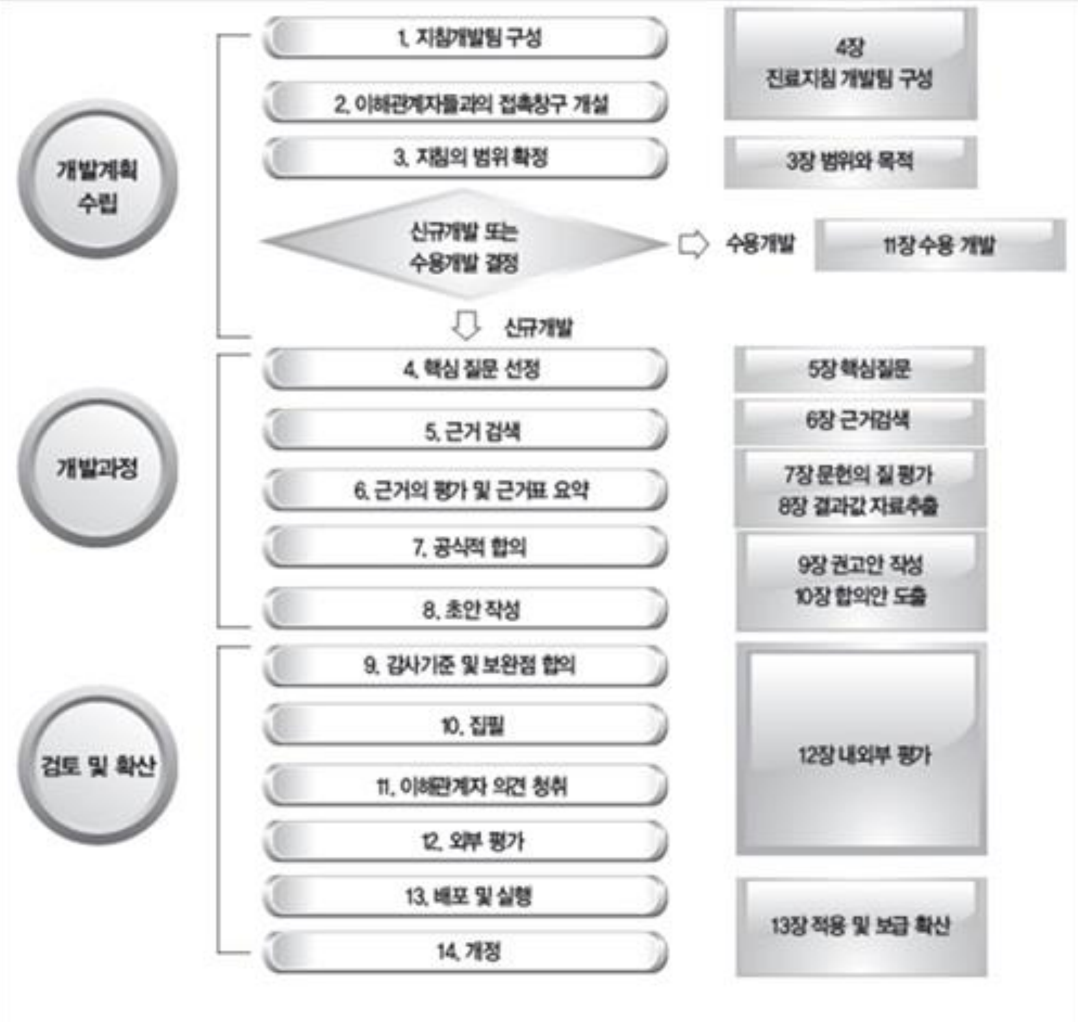
기준안



〈그림2-1〉 지침 개발 과정

기준안

- 근거 (문헌) 검색 및 문헌의 질 평가
- 핵심 질문 선정
- Delphi 합의 도출

- 대한신경두경부영상의학회
- 대한신경중재치료의학회
- mfds.stroke.imaging@gmail.com

기준안

- Infarct core를 반영하는 영상: CT, MR (DWI, PWI-CTP)
- Hemorrhagic transformation/Hematoma를 반영하는 영상: CT, MR (GRE)
- Steno-occlusion을 반영하는 영상: CTA, MRA, DSA
- 영상 촬영 기준 및 팬텀 사용
- 최소한의 Standardization
- Independent centralized reading and analysis

Standardization

- The process of implementing and developing technical standards based on the consensus of different parties

1. Technical Standards: Imaging Protocols
2. Different Parties: Vendors, Scanners, Softwares
3. Consensus: Figuring out common protocols for all vendors, scanners, softwares → Standardization

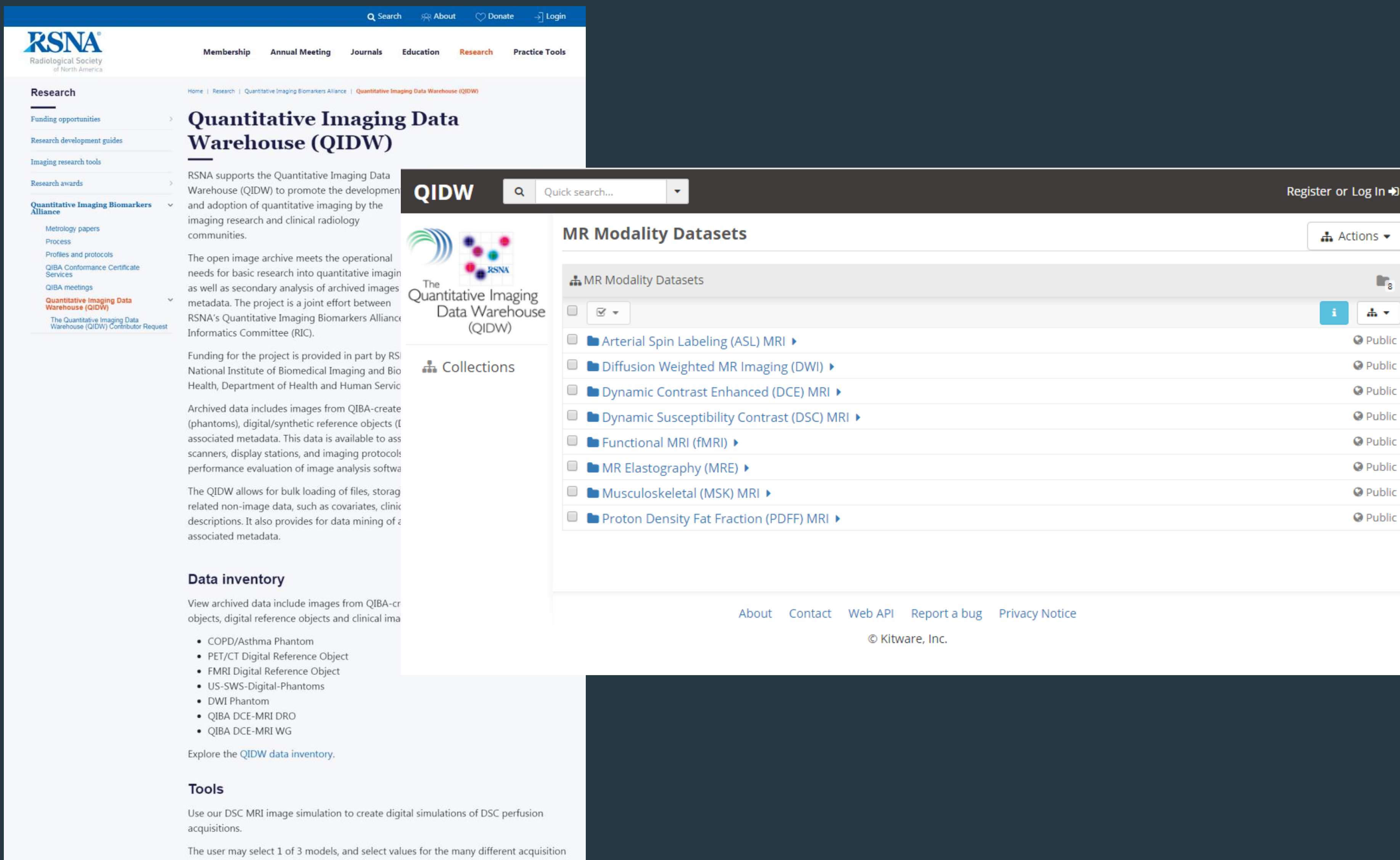
Courtesy of 김인성 Ph.D.

Standardization

- National-wide Standardization: QIBA
- Trial-specific standardization: Study-specific with reference to QIBA

Courtesy of 김인성 Ph.D.

Standardization



Standardization

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in optimizing the quality of imaging data obtained in clinical trials intended to support approval of drugs and biological products.[2] This guidance focuses on imaging acquisition, display, archiving, and interpretation process standards that we regard as important when imaging is used to assess a trial's primary endpoint or a component of that endpoint.

Considerable standardization already exists in clinical imaging. There are a variety of sources, including picture archiving and communication systems and the Digital Imaging and Communications in Medicine (DICOM) formats for the handling and transmission of clinical

Standardization, while important for all clinically used measures, becomes essential for an imaging endpoint used in a clinical trial to reduce variability and to ensure interpretability of the results. The extent of trial-specific standardization may vary depending upon how standardized

in a manner that complies with a trial's protocol, that the quality of imaging data is maintained within and among clinical sites, and that a verifiable record of the imaging process is created. Minimization of imaging process variability may importantly enhance a clinical trial's ability to detect drug treatment effects.

Standardization, while important for all clinically used measures, becomes essential for an imaging endpoint used in a clinical trial to reduce variability and to ensure interpretability of the results. The extent of trial-specific standardization may vary depending upon how standardized the local imaging procedures are (e.g., routine bone X-rays (relatively standardized) versus bone mineral density (more variability across sites)). This guidance does not address approaches for

Clinical Trial Imaging Endpoint Process Standards Guidance for Industry. FDA 2018

Standardization

F. **What Procedures Should Be Standardized for an Imaging-Based Clinical Trial Primary Endpoint?**

No single set of detailed imaging process standards is readily applicable to every clinical trial because the trials differ in design and objectives. When usual medical practice imaging process standards are acceptable in a trial, the plans for the use of such standards should be stated in the clinical protocol. Determinations on what to standardize beyond these expectations should be driven by consideration of the imaging processes that might introduce variability and inaccuracy to the endpoint and by consideration of the other items outlined below. When determining the

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Standardization

- Imaging modality availability and the modality's technical performance variation across trial sites
- Performance features of the imaging modality at the trial sites or any other locations where subjects may undergo imaging
- Qualifications of the imaging technologists and any special technological needs for the trial
- Proposed imaging measures' reliance on phantoms and/or calibration standards to ensure consistency and imaging quality control among clinical sites
- Any unique image acquisition features of the trial design, including subject positioning, anatomical coverage of imaging, use of contrast, timing of imaging, importance of subject sedation, and scanner settings for image acquisition
- Image quality control standards, including those specifying the need for repeat imaging to obtain interpretable images

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Standardization

- Procedures for imaging display and interpretation, including technical variations in reader display stations
- Nature of the primary endpoint image measurement, including the importance of training image readers in trial-specific quantification methods
- Extent that image archiving could be important to the trial's conduct, monitoring, and data auditing
- Potential for imaging modality upgrades or modality failures, as well as the potential variation in imaging drugs (such as contrast agents) across trial sites
- Precedent for use of the imaging-based primary endpoint measure in investigational drug development, especially previously observed imaging methodological problems

Clinical Trial Imaging Endpoint Process Standards Guidance for Industry. FDA 2018

Standardization in Acute Ischemic Stroke

- QIBA (Quantitative Imaging Biomarkers Alliance)
- Oncology imaging

- Urgent circumstance in acute ischemic stroke
- Balancing between standardization and critical pathway

Standardization in Acute Ischemic Stroke

- Stroke Imaging Research (STIR) group in Stroke Treatment Academy Industry Roundtable (STAIR)의 Acute Stroke Imaging Research Roadmap II & III (2013, 2016)
- 뇌졸중 임상시험에 있어서 영상 획득과 해석에 대한 Consensus 및 권고안 제시
- 뇌졸중 임상시험의 영상 조건: Speed, Standardization, Quality control, Reproducibility, Centralization

Standardization in Acute Ischemic Stroke

Table 1. General Requirements for Imaging in Stroke Clinical Trials

Speed: In therapeutic trials, the benefits of additional imaging should be balanced against potential treatment delay; workflow should be optimized on the basis of best practice

Standardization: Acquisition parameters and perfusion post processing should be standardized (by common software processing at centers or centralized processing) and should conform to minimum, protocol-defined, common standards

Quality control: A well-defined image quality control process should be implemented to ensure that the predefined study imaging protocol is respected and to minimize the number of protocol violations

Reproducibility: If imaging is used to define patient selection then either a system for standardized central image processing and automated analysis, or appropriate training for neuroimaging raters at participating centers, should be undertaken. Imaging methods should have demonstrated acceptable interobserver and across-center reliability

Centralization: Central analysis of imaging outcomes should be conducted as the reference standard in multicenter trials. A system for standardized central image processing and interpretation, blinded to clinical information and local investigator decision, should be implemented

STIR and VISTA Imaging Investigators. Stroke 2013

Standardization in Acute Ischemic Stroke

Special Report

Acute Stroke Imaging Research Roadmap III Imaging Selection and Outcomes in Acute Stroke Reperfusion Clinical Trials

Consensus Recommendations and Further Research Priorities

***Conclusions*—**Recent positive acute stroke endovascular clinical trials have demonstrated the added value of neurovascular imaging. The optimal imaging profile for endovascular treatment includes large vessel occlusion, smaller core, good collaterals, and large penumbra. However, equivalent definitions for the imaging profile parameters across modalities are needed, and a standardization effort is warranted, potentially leveraging the pooled data resulting from the recent positive endovascular trials. **(*Stroke*. 2016;47:1389-1398. DOI: 10.1161/STROKEAHA.115.012364.)**

Max Wintermark, MD, MAS; for the Stroke Imaging Research (STIR) and VISTA-Imaging Investigators*

***Background and Purpose*—**The Stroke Imaging Research (STIR) group, the Imaging Working Group of StrokeNet, the American Society of Neuroradiology, and the Foundation of the American Society of Neuroradiology sponsored an imaging session and workshop during the Stroke Treatment Academy Industry Roundtable (STAIR) IX on October 5 to 6, 2015 in Washington, DC. The purpose of this roadmap was to focus on the role of imaging in future research and clinical trials.

***Methods*—**This forum brought together stroke neurologists, neuroradiologists, neuroimaging research scientists, members of the National Institute of Neurological Disorders and Stroke (NINDS), industry representatives, and members of the US Food and Drug Administration to discuss STIR priorities in the light of an unprecedented series of positive acute stroke endovascular therapy clinical trials.

***Results*—**The imaging session summarized and compared the imaging components of the recent positive endovascular trials and proposed opportunities for pooled analyses. The imaging workshop developed consensus recommendations for optimal imaging methods for the acquisition and analysis of core, mismatch, and collaterals across multiple modalities, and also a standardized approach for measuring the final infarct volume in prospective clinical trials.

STIR and VISTA Imaging Investigators. Stroke 2016

Summary

- **IIRC: Consultant, Study design, Image analysis, Central reading**
- **Reading outcomes: Infarct, HT, Revascularization**
- **기준안 & Guidelines & Standardization**

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경청해 주셔서 감사합니다.