割付コードを知る方法 (Concealment)	

介入 (Intervention)		
項目(Item)	日本語(Japanese)	英語(English)
群数 (No. of arms)	2	
介入の目的 (Purpose of intervention)	治療・ケア/Treatment	
介入の種類 (Type of intervention)	医薬品/Medicine	
介入1 (Interventions/Control_1)	標準的降圧療法群: 標準的降圧療法群の目標は、ニカルジピン静脈投与を行い，無作為化後24時間にわたってSBPを180 mmHg未満に維持することである。	Standard treatment group: The goal for the standard BP reduction group is to reduce and maintain SBP<180 mmHg for 24 hours after randomization, with IV nicardipine.
介入2 (Interventions/Control_2)	積極的降圧療法群: 積極的降圧療法群の目標は、ニカルジピン静脈投与を行い，無作為化後24時間にわたってSBPを140 mmHg未満に維持することである。	Intensive treatment group: The goal for the intensive BP reduction group is to reduce and maintain SBP <140 mmHg for 24 hours after randomization, with IV nicardipine.
介入3 (Interventions/Control_3)		
介入4 (Interventions/Control_4)		
介入5 (Interventions/Control_5)		
介入6 (Interventions/Control_6)		
介入7 (Interventions/Control_7)		
介入8 (Interventions/Control_8)		
介入9 (Interventions/Control_9)		
介入10 (Interventions/Control_10)		

適格性 (Eligibility)		
項目(Item)	日本語(Japanese)	英語(English)
年齢(下限) (Age-lower limit)	18 歳/years-old 以上/<=	
年齢(上限) (Age-upper limit)	90 歳/years-old 未満/>	
性別 (Gender)	男女両方/Male and Female	
選択基準 (Key inclusion criteria)	1.発症後3時間以内にニカルジピン静脈内投与を開始することができる症例 2.言語障害、運動機能障害、認知障害および／または注視障害、視力障害または無視を含め，脳卒中に合致する臨床徴候が認められる症例 3.ED到着時のGCSの合計スコア(言語反応、	1.IV nicardipine can be initiated within 3 hours of symptom onset 2.Clinical signs consistent with the diagnosis of stroke, including impairment of language, motor function, cognition, and/or gaze, vision, or neglect 3.Total GCS score(aggregate of verbal, eye, &

	開眼および運動反応のスコアの合計値）が5点以上の症例 4.CTで脳実質内出血が認められ、手動測定による血腫量が60 cc未満である症例 5.ニカルジピン投与前に無作為化した患者の場合：入院時SBPが180mmHg以上240未満で、無作為化の時点でSBP180mmHg未満に自然に下がっていない症例 ニカルジピン投与後に無作為化した患者の場合：入院時SBPが180mmHg超240未満で、無作為化の時点でSBP140mmHg未満に自然に下がっていない症例 6.患者本人、代諾者または近親者によるインフォームドコンセントが得られる	motor response scores) of 5 or greater at ED arrival 4.CT scan demonstrates intraparenchymal hematoma with manual hematoma volume measurement <60 cc 5.For subjects randomized prior to infusion start: Admission SBP greater than 180 mmHg but less than 240 mmHg AND WITHOUT spontaneous SBP reduction to below 180 mmHg at the time of randomization OR For subjects randomized after infusion start: Admission SBP greater than 180 mmHg but less than 240 mmHg AND WITHOUT SBP reduction to below 140 mmHg at the time of randomization 6.Informed consent obtained by subject, legally authorized representative, or next of kin
除外基準 (Key exclusion criteria)	1.既知の脳腫瘍、AVMまたは動脈瘤によるICHの症例 2.脳内血腫が外傷によるものと考えられる症例 3.ICHが橋や小脳といったテント下で発生している症例 4.脳実質内出血を伴うIVHで、血液が一側側脳室に充満しているか、または両側側脳室の半分以上を満たしている症例 5.緊急外科的減圧術を受ける症例 6.妊娠中、分娩後30日以内、あるいは授乳中の症例 7.過去5日以内にワルファリンを服用し、かつPT-INR>4の症例 8.血小板数が50,000/mm3未満の症例 9.ニカルジピンに対する過敏症の既往がある症例 10.発症前に歩行や日常生活に介助を要する障害を持っている症例 11.積極的なICU管理を発症前に望んでいなかった症例 12.他の介入的臨床試験に参加中の症例	1.ICH is due to previously known neoplasms, AVM, or aneurysms 2.Intracerebral hematoma considered to be related to trauma 3.ICH located in infratentorial regions such as pons or cerebellum 4.IVH associated with intraparenchymal hemorrhage and blood completely fills one lateral ventricle or more than half of both ventricles 5.Patient to receive immediate surgical evacuation 6.Current pregnancy, parturition within previous 30 days or active lactation 7.Use of warfarin within the last 5 days and INR >4 8.A platelet count less than 50,000/mm3 9.Known sensitivity to nicardipine 10.Pre-morbid disability requiring assistance in ambulation or activities of daily living 11.Subjects living will precludes aggressive ICU management 12.Subject is currently participating in another interventional clinical trial
目標参加者数 (Target sample size)	1280	

責任研究者 (Research contact person)		
項目(Item)	日本語(Japanese)	英語(English)
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所属部署 (Division name)	神経内科，脳神経外科，放射線科部門	Department of Neurology Professor of Neurology, Neurosurgery, and Radiology
住所 (Address)	Minneapolis, Minnesota, United States, 55455	Minneapolis, Minnesota, United States, 55455

試験問い合わせ窓口(Public contact)		
項目(Item)	日本語(Japanese)	英語(English)

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部署名 (Division name)	脳血管内科	Department of Cerebrovascular Medicine
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電話 (TEL)	06-6833-5012	
試験のホームページURL (Homepage URL)	http://www.atach-2.com/	
Email (Email)	toyoda@hsp.ncvc.go.jp	

実施責任組織 (Sponsor)		
項目(Item)	日本語(Japanese)	英語(English)
実施責任組織 (Name of primary sponsor)	ミネソタ大学	University of Minnesota - Clinical and Translational Science Institute

実施責任組織とは、「試験の計画、解析と結果公表、研究費調達を含めた実施のための運営管理に対して責任を持つ組織」です。英語名でスポンサーとありますが、通常イメージする資金提供者のことではございません。従いまして、「なし」という記載はありえません。

研究費提供組織(Funding Source)		
項目(Item)	日本語(Japanese)	英語(English)
研究費提供組織 (Source of funding)	財団法人 循環器病研究振興財団 (米国国立衛生研究所)	Japan Cardiovascular Research Foundation(National Institutes of Health)
組織の区分 (Category of Org.)	財団/Non profit foundation	
研究費拠出国 (Nation of funding)		

その他の関連組織 (Other related organizations)		
項目(Item)	日本語(Japanese)	英語(English)
共同実施組織 (Name of secondary sponsor(s))		
その他の研究費提供組織 (Name of secondary funder(s))		

他機関から発行された試験ID (Secondary IDs)		
項目(Item)	日本語(Japanese)	英語(English)
他機関から発行された試験ID (Secondary IDs)	はい/YES	

試験ID1 (Study ID_1)	NCT01176565 (Clinical Trials.gov)	
ID発行機関1 (Org. issuing International ID_1)	米国国立衛生研究所	National Institutes of Health (NIH)
試験ID2 (Study ID_2)		
ID発行機関2 (Org. issuing International ID_2)		
治験届 (IND to MHLW)		

試験実施施設 (Institutions)		
項目(Item)	日本語(Japanese)	英語(English)
試験実施施設名称 (Institutions)	国立循環器病研究センター(脳血管内科，脳神経内科)，中村記念病院(脳神経外科)，広南病院(脳血管内科)，杏林大学(脳神経外科)，聖マリアンナ医科大学(神経内科)，(国)名古屋医療センター(神経内科)，神戸市立医療センター中央市民病院(神経内科)，川崎医科大学(脳卒中医学)，国立九州医療センター(脳血管内科)，岐阜大学(脳神経外科)，東京都済生会中央病院(神経内科、脳神経外科)， 虎の門病院(神経内科)，鹿児島医療センター(脳血管内科)，慶応大学(神経内科)， 聖マリアンナ医科大学東横病院(脳卒中科)，稲城市立病院(神経内科)	

試験進捗状況 (Progress)		
項目(Item)	日本語(Japanese)	英語(English)
試験進捗状況 (Recruitment status)	一般募集中/Open public recruiting (参加医療機関受診により、基準を満たせば被験者となれる)	
プロトコル確定日 (Date of protocol fixation)	2010/10/20	
登録・組入れ開始(予定)日 (Anticipated trial start date)	2011/10	
フォロー終了(予定)日 (Last follow-up date)		
入力終了(予定)日 (Date of closure to data entry)		
データ固定(予定)日 (Date trial data considered complete")		
解析終了(予定)日 (Date analysis concluded)		

関連情報 (Related information)		
項目(Item)	日本語(Japanese)	英語(English)
プロトコル掲載URL (URL releasing protocol)	http://www.atach-2.com/	

試験結果の公開状況 (Publication of results)	未公表/Unpublished
結果掲載URL (URL releasing results)	
主な結果 (Results)	
その他関連情報 (Other related information)	

管理情報		
項目(Item)	日本語(Japanese)	英語(English)
登録日 (Date of registration)	2011/10/14	
最終情報更新日 (Date of last update)	2011/10/12 12:12:28	

閲覧ページへのリンク	
日本語URL	https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000007737&type=summary&language=J
英語URL	https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000007737&type=summary&language=E

戻る

神経疾患最新の治療

2012-2014

編集
小林祥泰 島根大学
水澤英洋 東京医科歯科大学

オンラインアクセス権付き

巻頭トピックス

1. 脳血管内治療の最先端
2. 未破裂脳動脈瘤に対する薬物治療
3. rt-PA による血栓溶解療法の検証と展望
4. 脳血管性アパシーの治療
5. アルツハイマー病の標準的治療と先端治療
6. てんかん診療の最先端
7. 神経 Behcet 病，Sweet 病の治療
8. 脳原発悪性リンパ腫治療の発展
9. 視神経脊髄炎（NMO）
10. 神経サルコイドーシスの治療
11. デュシェンヌ型筋ジストロフィーに対するエクソン・スキップ療法

南江堂

3 rt-PAによる血栓溶解療法の検証と展望

豊田一則

A rt-PA静注療法の4つの問題点

脳梗塞急性期内科治療の標的として，現時点では損傷神経細胞の修復よりも脳循環保持，閉塞動脈の再開による神経細胞損傷の抑止に主眼が置かれる．遺伝子組み換えによる組織プラスミノーゲンアクチベータ（recombinant tissue-type plasminogen activator：rt-PA，一般名：alteplase）を用いた超急性期の血栓溶解療法は，この目的をかなえ得る代表的治療法と言える．米国に10年近く遅れて2005年に国内承認されたこのrt-PA静注療法も，承認後6年を過ぎて国内での推定使用件数が40,000例を超え，今や標準治療として定着してきた．同時に，現状の治療法に対する問題点も明らかになってきた．すなわち，①0.6 mg/kgの投与量は適切か，②発症3時間以内の治療可能時間は適切か，③超急性期の唯一の治療法か，④alteplaseしか使えないのか，などである．本項では特に最初の2つの課題を検証し，今後の展望を解説する．

B 「0.6 mg/kg」は適切か？—国内外の成績の比較

rt-PAの国際標準投与量であるalteplase 0.9 mg/kg体重の根拠は，1990年代に行われたいくつかの大規模臨床試験での投与量が次第に0.9 mg/kgに収斂し，この量を用いた米国NINDS（National Institute of Neurological Disorders and Stroke）主導による多施設共同臨床試験が成功した点によるところが大きい[1]．一方日本では，独自の投与量である0.6 mg/kgを用いて，第Ⅲ相試験J-ACT（Japan Alteplase Clinical Trial）[2]が実施され，その成功に基づいて同量での国内承認に至った．投与量設定根拠に，急性心筋梗塞における同薬の投与量の国内外での違いや，1990年代初頭の国内臨床試験におけるrt-PA（duteplase）投与量が挙げられるが，そもそも日本人が疫学的に頭蓋内出血を発症しやすく，rt-PAの治療合併症としての頭蓋内出血発症を抑えようという考えが底流にあったと推し量れる．

国内承認条件の1つとして，規制当局から承認後2年間の全例使用成績調査が求められた．これに応え，全国の医療機関に広く協力を求めた観察研究J-MARS（Japan post-Marketing Alteplase Registration Study）が実施された[3]．2005年からの2年間に，1,100施設で8,313例にrt-PA静注療法が施行されたと考えられ，そのうち942施設7,492例［女性2,836例，中央値72歳，治療前NIH Stroke Scale（NIHSS）中央値15］のデータを安全性の解析に，また発症前および3ヵ月後のmodified Rankin Scale（mRS）が明らかな4,944例を有効性の解析に用いた．この成果発表に先行して，筆者らは国内10施設共同の観察研究SAMURAI（Stroke Acute Management with Urgent Risk-factor Assessment and Improvement）rt-PA Registry〈http://samurai.stroke-ncvc.jp/index.html〉でのrt-PA静注療法施行600例（女性223例，72±12歳，治療前NIHSS中央値13）の治療成績をまとめた[4]．両研究の安全性評価として治療後36時間以内の症候性頭蓋内出血発現率と3ヵ月後の死亡率を図1に，有効性評価として3ヵ月後のmRSを図2に，それぞれNINDSでの試験[1]，J-ACT[2]，欧州における大規模市販後調査SITS-MOST（Safe Implementation of Thrombolysis in Stroke-MOnitoring Study：6,483例，女性2,581例，中央値68歳，NIHSS中央値12）[5]の成績と対比させて示す．J-MARSはSITS-MOSTやSAMURAIと比べて，症候性頭蓋内出血がやや多いが絶対的な発現率は低く，死亡率はSITS-MOSTとほぼ同等であった．またJ-MARSとSAMURAIにおける全患者を対象とした3ヵ月後のmRS 0-1の患者（完全自立に復する患者）はともに33％であったが，欧州での患者適応基準に合わせて80歳以下，治療前NIHSS 25未満，糖尿病と脳梗塞既往の合併例以外などの条件を満たす患者に限ると，各々39％，41％となった．これ

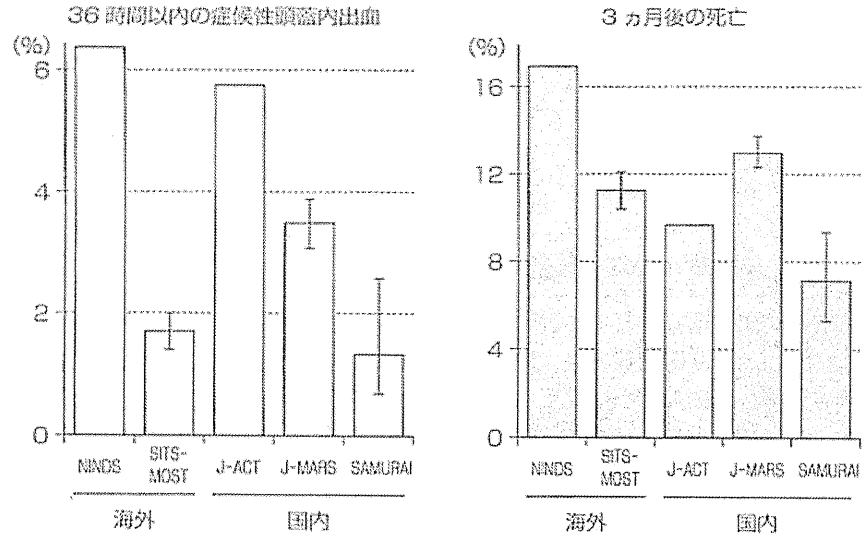

図1◈rt-PA静注療法の安全性―国内外の臨床試験の比較
NIHSS 4以上の増悪をもって「症候性」と定義した．ただしNINDSは軽度の増悪も症候性とみなしている．

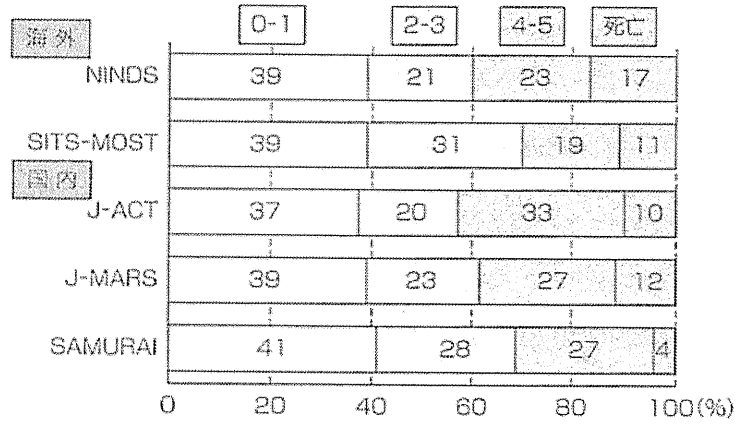

図2◈ rt-PA静注療法の有効性―国内外の臨床試験の比較
3ヵ月後のmodified Rankin Scaleを示す．J-MARS，SAMURAIは，欧州の適応基準に合う患者に限った成績を表す．

らの頻度は，alteplase 0.9 mg/kgを用いたSITS-MOSTの成績と比べて遜色がなかった．国内でのalteplase 0.6 mg/kgによる治療が，欧米と同等の有効性をもつことが示唆された．

この結果は，日本人にとって0.6 mg/kgが閉塞脳動脈を再開通させるに十分な量であることを示しているのであろうか．第Ⅳ相試験J-ACTⅡでは，MR angiography（MRA）で中大脳動脈主幹部（M1）ないし分枝（M2）の閉塞を認めた脳梗塞患者58例を対象に，rt-PA静注療法後の閉塞動脈の再開通所見と転帰との関係が調べられた（図3）[6]．発症6時間後における中大脳動脈の完全ないし部分再開通患者は51.7%，24時間後で69.0%を占め，再開通患者で3ヵ月後に完全自立患者（mRS 0-1）が有意に多かった．初期重症度やCTでの早期虚血所見などを含めた背景要因で補正した後も，6時間後（オッズ比6.030，95% CI 1.730～21.011）や24時間後（21.231，3.318～135.859）の再開通所見が3ヵ月後の完全自立に独立して有意に関係した．登録患者をM1起始後

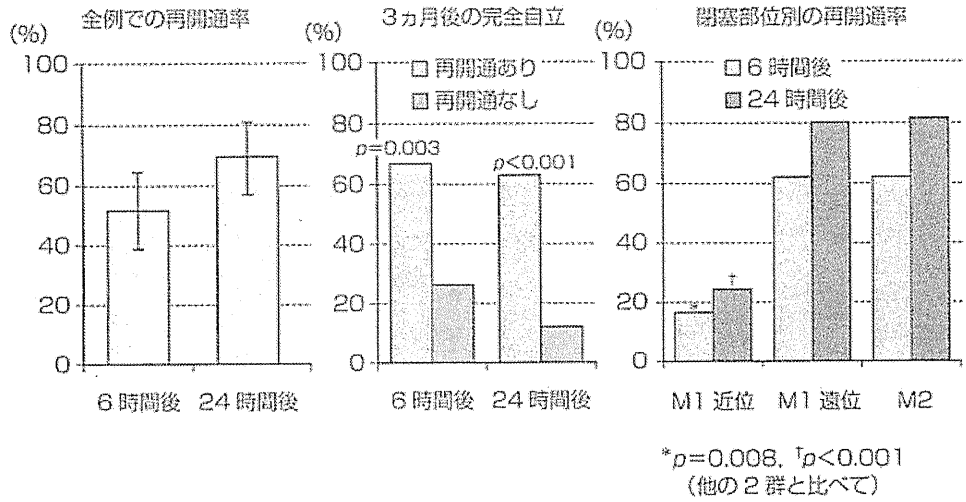

図3◈閉塞中大脳動脈の再開通率と転帰：J-ACT Ⅱ

(文献6, 7より改変)

5 mm未満の近位部閉塞，5 mm以遠の閉塞，M2閉塞の3群に分けると，M1近位部閉塞群の再開通率が他群に比べて有意に低く，M1近位部閉塞が早期再開通しないことが3ヵ月後に完全自立しないこと（オッズ比0.082，95% CI 0.008～0.812）に，独立して有意に関連した[7]．海外での再開通の評価はMRAよりも超音波で行われることが多く，単純な比較は困難であるが，J-ACT Ⅱの成績は0.6 mg/kgのalteplaseが一定の割合で早期再開通をもたらすことを示している．しかしながら，日本人に0.9 mg/kgを用いた場合に，より良い成績が得られる可能性もある．両投与量を直接比べる試験の機会があれば，この課題への最適な回答が得られるであろう．

C 「3時間以内」は適切か？—治療可能時間の延長

「発症3時間以内の治療開始」は，rt-PA使用時に特に重要な規則として厳守されている．本来虚血侵襲の程度には個体差があり，治療可能時間を一律に定めることは困難であるが，治療を標準化しある程度の安全性を確保するうえでは，何らかの時間設定が必要であったろう．「3時間」の根拠は，3時間以内に投与開始可能な患者を対象としたNINDS試験が治療の有効性を証明し得た一方で[1]，6時間以内を対象としたECASS Ⅰ（European Cooperative Acute Stroke Study Ⅰ），ECASS Ⅱ，ATLANTIS（Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke，ただしATLANTIS part Bは5時間以内）で確実な有効性を示せなかったことに由来する．これらの試験成績の統合解析を行うと，3時間を過ぎても4.5時間までは有意に良好な成績を得ることができ，また6時間までは良好な転帰のオッズ比が1を超えることが示された[8]．Cochrane reviewも，6時間までの治療開始によって3～6ヵ月後の死亡ないし自立できない状態（mRS 3-6）が有意に減ったと報告している（オッズ比0.84，95% CI 0.75～0.95）[9]．上述の統合解析にさらに後述するECASS Ⅲ[10]，EPITHET（Echoplanar Imaging Thrombolysis Evaluation Trial）[11]を加えた新たな統合解析の結果を，図4に示す[12]．この結果によれば，発症3～4.5時間のrt-PA群は偽薬群に比べて，有意に3ヵ月後の完全自立者（オッズ比1.34，95% CI 1.06～1.68）や複合評価での転帰良好患者（1.32，1.09～1.61）が多く，4.5～6時間においては両群の有意差を認めなかった．

これらの背景に基づき，欧州では発症後3～4.5時間の治療開始例の成績を観察研究（SITS-ISTR：Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry）[13]と介入試験（ECASS Ⅲ）[10]で調べた．SITS-ISTRでは，欧州でのrt-PA静注療法承認後に多施設共通のデータベースに登録された患者のうち3～4.5時間に治療開始された664例を，3

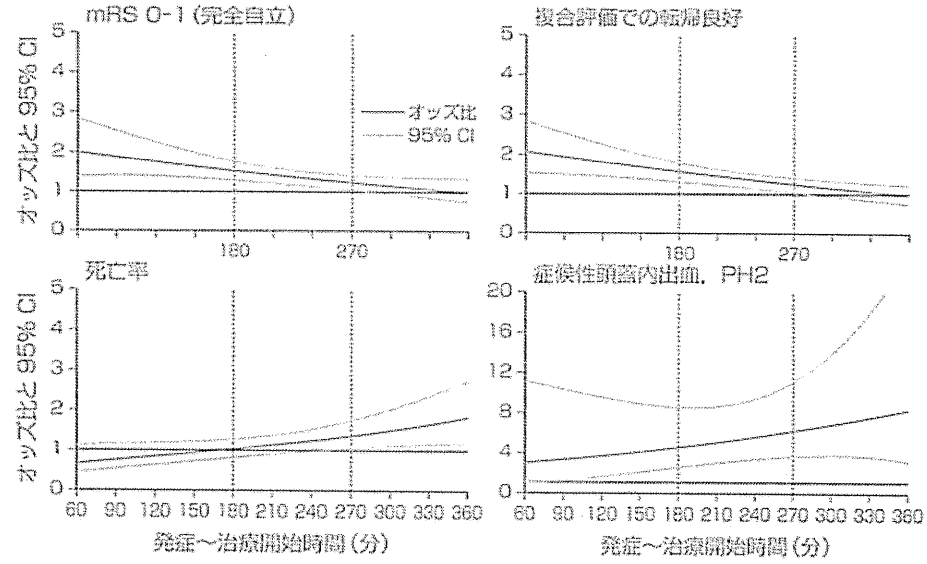

図4◈発症~治療開始時間と3ヵ月後の転帰—統合解析結果
NINDS試験, ECASS Ⅰ, Ⅱ, Ⅲ, ATLANTIS, EPITHETの統合解析.

(文献12より改変)

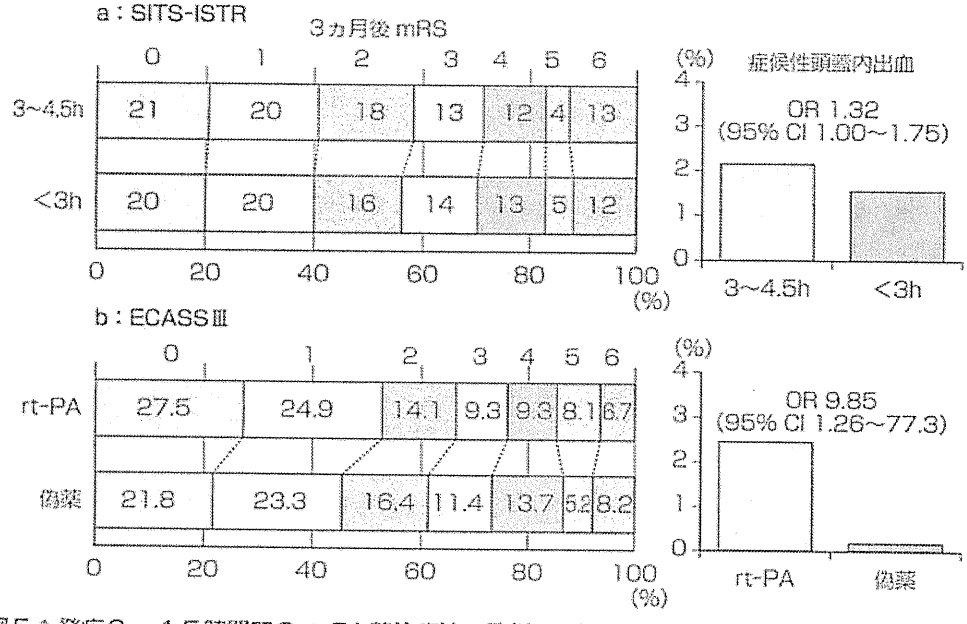

図5◈発症3~4.5時間でのrt-PA静注療法—欧州での知見

(文献10, 13より改変)

時間以内に治療開始された11,865例と比べた. 前者は後者に比べて有意に若く, 治療前のNIHSS値が有意に低いなど, 背景因子に多少の差があるものの, 症候性頭蓋内出血の頻度や3ヵ月後のmRSで示された患者自立度や死亡率に, 有意な差を認めなかった(図5a). ECASS Ⅲでは3~4.5時間に治療を始められる821例をrt-PA治療群と偽薬群に無作為に割り付けた. rt-PA群で治療前のNIHSS値が有意に低く脳卒中既往例が有意に少ないなど, 2群がやや不均質であったものの, 3ヵ月後に完全自立に至った患者(mRS 0-1)はrt-PA群で有意に多かった(52.4%

表1◆ペナンブラの評価を行ったrt-PA静注療法の臨床試験

試験名	rt-PAの種類	治療開始時間	試験デザイン	患者選択におけるDPM所見の利用	患者数	主要評価項目	主な成績
EPITHET	アルテプラーゼ	3～6h	第Ⅱ相，RCT，rt-PA対偽薬	患者の割り付けにDPMを参照せず	100	初回DWIと90日目T2WIで比べた梗塞の増大	DPMをもつ患者で，rt-PAは梗塞の増大をやや抑え，再灌流を有意に増やした
DEFUSE	アルテプラーゼ	3～6h	第Ⅱ相，実薬のみ	患者登録にDPMを参照せず	74	PWIでの早期再灌流，臨床転帰	DPMをもつ患者で，早期再灌流が転帰良好に関連した
DIAS	デスモテプラーゼ	3～9h	第Ⅱ相，5段階用量の実薬と偽薬の比較	MRIで20%以上のDPMをもつ患者を登録	102	sICHの頻度，PWIでの早期再灌流，90日後の臨床上の改善	実薬群が再灌流が多く臨床転帰も良好な傾向．特に高用量（125 μg/kg）群が有望
DEDAS	デスモテプラーゼ	3～9h	第Ⅱ相，2段階用量の実薬と偽薬の比較	MRIで20%以上のDPMをもつ患者を登録	37	DIASと同じ	DIASと同様．特に高用量（125 μg/kg）群が有望
DIAS-2	デスモテプラーゼ	3～9h	第Ⅲ相，RCT，2段階用量の実薬と偽薬の比較	MRIまたはCTで20%以上のDPMをもつ患者を登録	186	90日後の臨床上の改善	rt-PA 2群とも偽薬群より優れた効果を示さず，特に高用量（125 μg/kg）群で死亡が増えた

DPM：diffusion perfusion mismatch，DWI：拡散強調画像，PWI：灌流画像，T2WI：T2強調画像，
sICH：症候性頭蓋内出血

（文献14より改変）

対45.2%，オッズ比1.34，95% CI 1.02～1.76，図5b）．rt-PA群では症候性頭蓋内出血の発症率も偽薬群に比べて有意に高いが，その値は2.4%と低く，両群間の死亡率にも差を認めなかった．このECASS Ⅲの成績を根拠に，2008年から2010年にかけて欧州，米国，カナダ，豪州などでガイドラインが改訂され，発症4.5時間以内のrt-PA静注療法開始が推奨されるに至った．日本でも治療可能時間を見直すべく，日本脳卒中学会から厚生労働省へ提言が行われている．さらに，現在発症6時間以内のrt-PA静注療法の有効性を調べるIST-3（Third International Stroke Trial）が英国などを中心に行われている．

個別化医療の立場から考えれば，治療対象患者を発症からの経過時間で選ぶよりも，個々の症例の画像所見から治療可能領域や易出血域の範囲を判断して選ぶほうが，合理的に思える．MRI拡散強調画像（diffusion-weighted image：DWI）での高信号病変は完全虚血域を，灌流画像（perfusion-weighted image：PWI）での高信号病変は灌流異常域を表し，両者の差をdiffusion perfusion mismatch（DPM）と呼ぶ．このDPMの領域内に，速やかに血流が再開すれば梗塞を免れるが，血流再開がない場合は梗塞に陥る，不完全な虚血部位（いわゆるペナンブラ）が存在すると考えられる．そしてペナンブラの多寡によって発症後3時間を過ぎてもrt-PA静注療法の効果が期待される患者を抽出する試みがなされている（表1）[14]．このうちEPITHET[11]とDEFUSE[15]は，DPMをもつ患者においてのみ，再灌流（PWIでの高信号病変の軽減）や転帰の改善が期待できることを示し，DPMを基準に患者を抽出して第Ⅲ相試験を行う可能性を考察している．DIAS[16]，DEDAS[17]，DIAS-2[18]は，いずれもデスモテプラーゼと呼ばれる新世代rt-PAを用いている．デスモテプラーゼは南米の吸血コウモリの唾液か

ら発見された蛋白を遺伝子工学で合成し，高いフィブリン親和性を示す．治療可能時間を一気に発症後9時間まで延ばすことが期待されたが，第Ⅲ相試験（DIAS-2）でrt-PA群の有効性が証明できなかった．この不成功の原因として，約2割の患者のDPM評価にMRIでなくCTを用いたことや患者数が比較的少なかったことに加え，DPMの評価の難しさも指摘すべきであろう．特に灌流画像の撮像法の標準化が必要であり，現在DPMを自動的に計測するオンライン上のパッケージが利用可能である（Acute Stroke Imaging Standardization Group：ASIST-Japan〈http://asist.umin.jp/〉）．EPITHETの成果を土台に，MRIでDPMを有する発症3～9時間，ないし睡眠中発症の脳梗塞患者を対象とした第Ⅲ相国際多施設共同無作為化臨床試験EXTEND（Extending the time for Thrombolysis in Emergency Neurological Deficits）が豪州を中心に組まれており，筆者らも国内多施設での試験参加をめざしている．

D その他の問題点

投与量と治療可能時間を中心に，日本のrt-PA静注療法を検証した．他に，冒頭に挙げた問題点として，「唯一の治療法か」という問いに対しては，rt-PA治療に後続する，あるいはrt-PA禁忌例への治療法として，2010年に経皮経管的脳血栓回収機器MERCIの使用が，また2011年に同じくPENUMBRAの使用が承認され，発症後8時間以内の超急性期脳梗塞患者への治療の幅が広がった．今後も，多種多様な脳血栓回収・吸引機器の開発・承認が予想される．従来は診断機器であった経頭蓋超音波照射をrt-PA治療時に併用する超音波血栓溶解療法も，臨床応用をめざして開発が進んでいる．薬物治療の併用として，脳保護薬edaravoneはすでに高頻度に併用され，またrt-PA治療後24時間以内は禁忌と定められている抗血栓療法に関しても，対象患者や治療法を工夫しての併用の臨床試験が，今後組まれる可能性がある．

現在国際的に脳梗塞患者に用いられるrt-PAはalteplaseのみであるが，よりフィブリン親和性の高いrt-PAを用いれば，さらに安全で有効な治療効果を得ることが期待できる．前述したデスモテプラーゼが，その1つとして期待されている．他に，テネクテプラーゼ，レテプラーゼなど，rt-PAの一部を改変した薬剤も開発されている．

治療可能時間が延長し，併用治療の開発が進んだとしても，適切な患者をより早くより確実に治療すべきというrt-PA静注療法の鉄則は変わらない．一般住民や救急隊員への啓発による脳卒中早期発見・迅速受診の推進，病院内ないし広域医療圏での治療環境の整備など，社会医学的に取り組むべき課題も多い．法制化を目指した動きが進む「脳卒中対策基本法」が，課題解決の追い風となるであろう．

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Early Ischemic Change on CT Versus Diffusion-Weighted Imaging for Patients With Stroke Receiving Intravenous Recombinant Tissue-Type Plasminogen Activator Therapy

Stroke Acute Management With Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry

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Background and Purpose—Alberta Stroke Programme Early CT Score (ASPECTS) is a quantitative topographical score to evaluate early ischemic change in the middle cerebral arterial territory on CT as well as on diffusion-weighted imaging (DWI). The aim of the present study was to elucidate the relationship between CT-ASPECTS and DWI-ASPECTS for patients with hyperacute stroke and their associations with outcomes after recombinant tissue-type plasminogen activator therapy based on a multicenter registry.

Methods—ASPECTS was assessed on both CT and DWI before intravenous 0.6 mg/kg alteplase in 360 patients with stroke (119 women, 71±11 years old). The outcomes were symptomatic intracerebral hemorrhage within 36 hours and independence at 3 months defined by a modified Rankin Scale score of 0 to 2.

Results—DWI-ASPECTS was positively correlated with CT-ASPECTS (ρ=0.511, P<0.001) and was lower than CT-ASPECTS (median 8 [interquartile range, 6 to 9] versus 9 [8 to 10], P<0.001). Higher baseline National Institutes of Health Stroke Scale score (standardized partial regression coefficient [β] 0.061, P<0.001) and cardioembolic stroke (β 0.35, P<0.001) were related to this discrepancy. The area under the receiver operating characteristic curve for predicting sICH (12 patients) using ASPECTS was 0.673 (95% CI, 0.503 to 0.807) by CT and 0.764 (95% CI, 0.635 to 0.858) by DWI (P=0.275). The area for predicting independence at 3 months (192 patients) was 0.621 (0.564 to 0.674) by CT and 0.639 (0.580 to 0.694) by DWI (P=0.535).

Conclusions—For patients with hyperacute stroke, DWI-ASPECTS scored approximately 1 point lower than CT-ASPECTS. Both CT-ASPECTS and DWI-ASPECTS were useful predictors of symptomatic intracerebral hemorrhage and independence at 3 months after recombinant tissue-type plasminogen activator. (***Stroke.* 2011;42:2196-2200.)**

Key Words: acute stroke ■ diffusion-weighted MRI ■ early ischemic sign ■ thrombolysis

Early ischemic change (EIC) of the brain is predictive of the benefit from thrombolysis.[1–3] EIC on CT has been assessed by using the one third of cerebral hemisphere rule, and patients with extensive EIC are contraindicated for administration of intravenous recombinant tissue-type plasminogen activator (rtPA) within 3 to 4.5 hours of onset of acute ischemic stroke.[4–6] The Alberta Stroke Programme Early CT Score (ASPECTS) was successfully developed to improve reliability for the detection of EIC on CT imaging.[7] However, EIC on CT is subtle and has poor intra- and interrater reliabilities.[8]

MRI with diffusion-weighted imaging (DWI) is better than CT for detection of acute ischemic stroke. MRI could be used as the first-line modality for the emergent imaging of patients with acute stroke.[9,10] ASPECTS has been recently applied to

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assess EIC on DWI.[11,12] We reported that pretreatment ASPECTS on DWI was independently predictive of functional and vital outcomes at 3 months after rtPA therapy from single-center and multicenter registries.[13,14] To our knowledge, EIC on CT has been compared with that on MRI before rtPA therapy using ASPECTS only in a few studies[15,16]; 1 small study, involving 22 patients with stroke, reported that ASPECTS on DWI seemed to be useful for predicting neurological deterioration after thrombolysis.[16] The aim of the present study was to elucidate the relationship between pretreatment ASPECTS assessed using CT and DWI before rtPA therapy and their associations with outcomes after stroke.

Subjects and Methods

The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry was conducted using a multicenter hospital-based retrospective observational design. The details of this study have been described previously.[14,17] In brief, a total of 600 consecutive patients with acute ischemic stroke receiving intravenous rtPA were registered from October 2005 (when intravenous alteplase therapy was approved in Japan) through July 2008 in 10 stroke centers in Japan. Patient eligibility for alteplase therapy was determined based on the Japanese guideline for intravenous rtPA therapy, which followed the inclusion and exclusion criteria used in the National Institute of Neurological Disorders and Stroke study and the Japan Alteplase Clinical Trial (J-ACT).[18,19] According to the Japanese guidelines,[20] patients with CT-documented extensive EIC (size is not defined) were not eligible for the treatment. Because the guidelines do not refer to EIC on DWI, the eligibility of patients having large EIC on DWI depended on each physician's decision. Each local ethics committee approved the retrospective collection of clinical data from the database and submission of the data to our central office. Each patient received a single alteplase dose of 0.6 mg/kg (the recommended dose in Japanese guidelines and the approved labeling) intravenously with 10% given as a bolus within 3 hours of stroke onset followed by a continuous intravenous infusion of the remainder over 1 hour.

Baseline data, including sex, age, comorbidities (hypertension, diabetes, hyperlipidemia, and congestive heart failure), blood pressure on admission, time from onset to treatment, neurological deficits using the National Institutes of Health Stroke Scale score, and stroke subtype according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) categories,[21] were collected retrospectively from medical charts for all patients.

Assessment of ASPECTS on CT and DWI

Before rtPA infusion, MRI studies, including DWI and MR angiography, were begun principally after CT. Time of starting CT and MRI were collected from medical charts. Administration of rtPA was begun approximately 10 minutes after MRI. CT scans were performed in almost all centers according to a standard CT scan protocol (5- to 10-mm slice thickness without contrast enhancement, 120 kV, high tube current, low speed scan with ≥2 seconds/rotation, contrast-favored algorithm, inferior orbitomeatal baseline, filmed at appropriate window width of ≥80 Hounsfield units). MRI scans were performed on a 1.5-T scanner. MRI protocols were not entirely uniform in each center, but all included an axial DWI using a single-shot echoplanar imaging (b=1000 s/mm^2, 5- to 6-mm-thick slices). The time required to perform CT was a few minutes and that of MRI was 10 to 15 minutes. ASPECTS assessed using DWI (DWI-ASPECTS) as well as original ASPECTS based on CT (CT-ASPECTS) was examined by each investigator in each center without using a central reading system. Thus, the reading results reflect real-life conditions. At least 2 experienced vascular neurologists or neurosurgeons in each stroke center evaluated the initial DWI and CT images to calculate quantitative EIC using ASPECTS later as a post hoc analysis. The interrater agreement of ASPECTS in our study group assessed using a sample of 76 CT and DWI images was ρ=0.634 for CT (P<0.001) and ρ=0.818 for DWI (P<0.001, Spearman rank test). Arterial occlusion was (principally) assessed on the initial MR angiography.

Table 1. Baseline Characteristics

	n=360
Women	119 (33.1)
Age, y	71±11
Hypertension	215 (60.2)
Diabetes mellitus	63 (17.6)
Dyslipidemia	71 (19.8)
Congestive heart failure	20 (5.7)
Pretreatment systolic blood pressure, mm Hg	151±21
Pretreatment diastolic blood pressure, mm Hg	82±15
Baseline NIHSS	12 (7–18)
CT-ASPECTS	9 (8–10)
DWI-ASPECTS	8 (6–9)
Arterial occlusion site	
Internal carotid artery	58 (16.1)
Middle cerebral artery trunk (M1)	119 (33.1)
Middle cerebral artery branch (M2 or M3)	81 (22.5)
Not occluded*	102 (28.3)
Stroke subtype	
Cardioembolism	217 (60.3)
Atherothrombotic stroke	52 (14.4)
Lacune	21 (5.8)
Other	70 (19.5)
Onset to treatment time, min	140 (120–165)
Time delay of MRI after CT, min (n=323)	19 (12–29)

Data are no. of patients (%), median (interquartile range) for discontinuous variables, and mean±SD for continuous variables.

NIHSS indicates National Institutes of Health Stroke Scale score; ASPECTS, Alberta Stroke Programme Early CT Score; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; CT, computed tomography; M1, middle cerebral artery trunk (horizonal segment); M2, middle cerebral artery branch (sylvian segment); M3, middle cerebral artery branch (cortical segment).

*Including patients who have insufficient-quality MR angiography.

Outcomes

The outcomes were symptomatic intracerebral hemorrhage (sICH) within the initial 36 hours and independence at 3 months corresponding to a modified Rankin Scale score of 0 to 2. Intracerebral hemorrhage was defined as CT evidence of new parenchymal hemorrhage of Type I or Type II within the initial 36 hours[2] and was assessed by at least 2 experienced examiners. sICH was defined as a parenchymal intracerebral hemorrhage associated with neurological deterioration corresponding to an increase of ≥4 points from the baseline National Institutes of Health Stroke Scale score.

Statistical Analysis

Statistical analysis was performed using the JMP 8.0 statistical software (SAS Institute Inc, Cary, NC). The relationship between CT-ASPECTS and DWI-ASPECTS was assessed by Spearman rank test, the Bland and Altman plot, and an interrater correlation coefficient. Multiple linear regression was performed to identify the predictors for the discrepancy between CT-ASPECTS and DWI-ASPECTS based on the characteristics in Table 1. CT-ASPECTS and DWI-ASPECTS in patients with middle cerebral artery occlusion were compared with those in patients without by the Mann–Whitney U test. Sensitivity and specificity of EIC on each region of

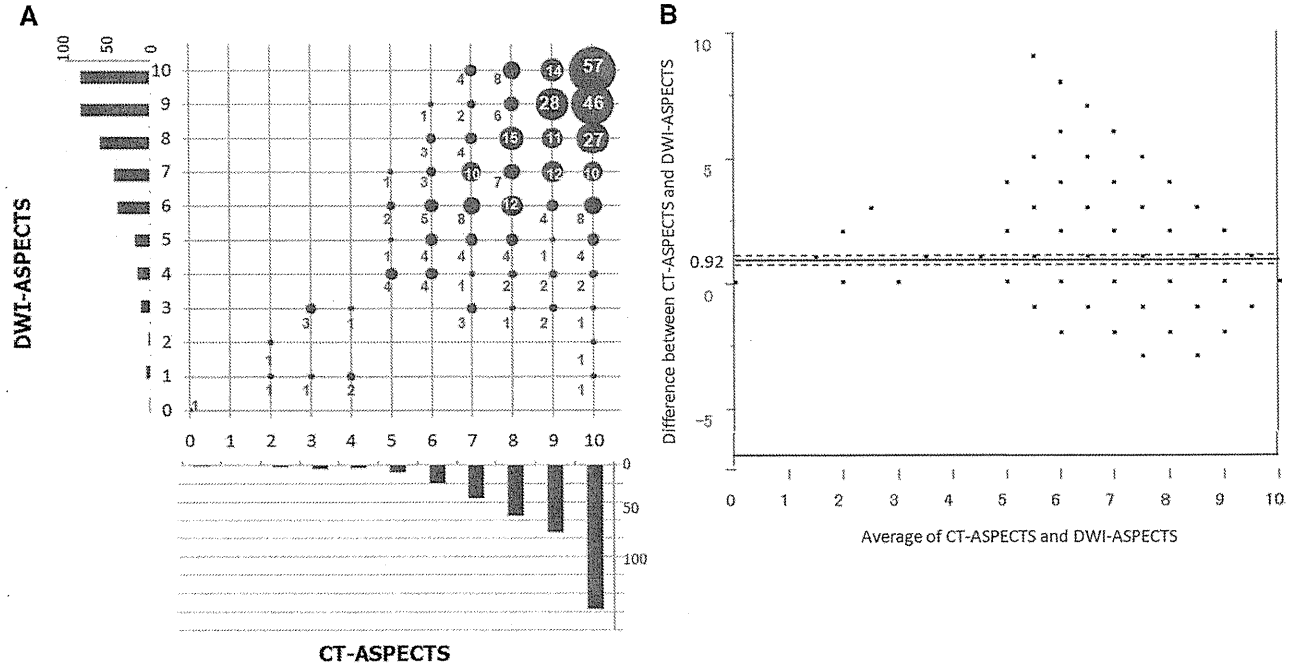

Figure 1. Number of patients assessed using CT-ASPECTS and DWI-ASPECTS (**A**). Bland and Altman plot of CT-ASPECTS and DWI-ASPECTS. The mean difference between CT-ASPECTS and DWI-ASPECTS was +0.92. The horizontal line showed the mean difference in scores and the dotted lines showed the 95% CI (**B**). ASPECTS indicates Alberta Stroke Programme Early CT Score; DWI, diffusion-weighted imaging; CT, computed tomography.

CT-ASPECTS were assessed when setting DWI-ASPECTS as a standard. To evaluate the predictive ability of the CT-ASPECTS and DWI-ASPECTS for each outcome, receiver operating characteristic curves were constructed. The area under the receiver operating characteristic curve was used as a scalar measure to assess the performance of prognostic risk scores. The comparison of area under the receiver operating characteristic curves was conducted by nonparametric method.[22] Statistical significance was established at $P<0.05$.

Results

Of the total of 600 consecutive patients registered, the following 240 patients were deemed ineligible for the study: 109 patients who had a history of ischemic stroke; 20 who had premorbid modified Rankin Scale scores of 3 to 5; 58 who were not performed MRI due to contraindications, unsteadiness, or time limitation; 6 who had CT or DWI images of insufficient quality to evaluate EIC; 43 who had vertebrobasilar, posterior cerebral arterial, or anterior cerebral arterial territory strokes; and 3 who had missing data on 3-month modified Rankin Scale scores. Finally, 360 patients (241 men, 71±11 years old) were included in the study. Baseline clinical characteristics of the patients are presented in Table 1. The median National Institutes of Health Stroke Scale score was 12 (interquartile range, 7 to 18). Time delay between CT and MRI was identified in 323 patients (89.7%); the median delay was 19 minutes (interquartile range, 12 to 29).

The pretreatment DWI-ASPECTS was positively correlated with CT-ASPECTS ($\rho=0.511$, $P<0.001$, Spearman rank test; Figure 1A). An interrater correlation coefficient between CT-ASPECTS and DWI-ASPECTS was 0.535. DWI-ASPECTS (median, 8; interquartile range, 6 to 9) was lower than CT-ASPECTS (9; 8 to 10; $P<0.001$). Figure 1B shows the Bland and Altman plot. The mean difference between CT-ASPECTS and DWI-ASPECTS was 0.92 (95% CI, 0.74 to 1.10). On multiple linear regression analysis, baseline National Institutes of Health Stroke Scale (standardized partial regression coefficient [β] 0.061, $P<0.001$) and cardioembolism (β 0.35, $P<0.001$) were related to the discrepancy between CT-ASPECTS and DWI-ASPECTS. CT-ASPECTS was ≥8 in 286 patients (79.4%); of these, 21 patients (7.3%) had DWI-ASPECTS of ≤5. Of these 21 patients, 2 patients had sICH. CT-ASPECTS and DWI-ASPECTS (median, 9; interquartile range, 7 to 10 and 8; 6 to 9, respectively) in patients with middle cerebral artery occlusion were lower than those in patients without (median, 10; interquartile range, 9 to 10 and 9; 9 to 10, respectively; $P<0.001$ for both).

The sensitivity and specificity of EIC on each region of CT-ASPECTS when using DWI-ASPECTS as the gold standard are shown in Table 2. The sensitivities of EICs in the caudate and internal capsule regions (13.0% and 18.0%, respectively) and the specificity of EIC in the lentiform nucleus (86.2%) were relatively low on CT.

Of 360 patients, 76 (21.1%) had any intracerebral hemorrhage, 12 (3.3%) had sICH, and 192 (53.3%) were independent (modified Rankin Scale 0 to 2). For prediction of sICH, the area under the receiver operating characteristic curve was 0.673 (95% CI, 0.503 to 0.807) for CT-ASPECTS and 0.764 (0.635 to 0.858) for DWI-ASPECTS ($P=0.275$; Figure 2A). For prediction of independence at 3 months, the area under the receiver operating characteristic curve was 0.621 (0.564 to 0.674) for CT-ASPECTS and 0.639 (0.580 to 0.694) for DWI-ASPECTS ($P=0.535$; Figure 2B).

Discussion

In this study, DWI-ASPECTS was positively related with CT-ASPECTS, scored lower than CT-ASPECTS, and was as

Table 2. Sensitivity and Specificity of Early Ischemic Change on Each Region of ASPECTS

	Frequency of EIC, %				
	CT	DWI	Both	Sensitivity, %	Specificity, %
Caudate (C)	2.2	12.8	1.7	13.0	99.4
Lentiform nucleus (L)	22.2	27.8	12.2	44.0	86.2
Internal capsule (IC)	5.0	13.9	2.5	18.0	97.1
Insular ribbon (I)	32.5	45.3	25.8	57.1	87.8
M1	11.4	21.7	9.7	44.9	97.8
M2	19.7	26.1	13.3	51.1	91.4
M3	8.9	15.6	6.1	39.3	96.7
M4	7.2	14.2	5.3	37.3	97.7
M5	17.5	31.1	12.5	40.2	92.7
M6	7.8	18.6	6.4	34.3	98.3

ASPECTS indicates Alberta Stroke Programme Early CT Score; DWI, diffusion-weighted imaging; CT, computed tomography; EIC, early ischemic change; M1, anterior MCA (middle cerebral artery) cortex; M2, MCA cortex lateral to insular ribbon; M3, posterior MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories, respectively, approximately 2 cm superior to M1, M2, and M3, respectively, rostral to basal ganglia.

useful as CT-ASPECTS for predicting functional outcomes in patients with hyperacute stroke who were scheduled to receive rtPA therapy. We elucidated the relationship between DWI-ASPECTS and CT-ASPECTS before rtPA therapy and their associations with outcomes after therapy. We followed much a previous study design by Barber et al[15] involving 100 patients within 6 hours of stroke onset. The strength of our study compared with the previous 1 was the larger sample size, shorter time interval between stroke onset and imaging examination, and shorter time interval between CT and DWI.

This study demonstrates that DWI-ASPECTS scored approximately 1 point lower than CT-ASPECTS in patients with stroke within 3 hours of onset. Previously, the reported difference of ASPECTS in both methods was 0.43 on average based on the previously mentioned study by Barber et al[15] and 1 when using the median based on another study involving 30 patients within 24 hours of stroke onset.[23] The time delay of MRI after CT, 102 minutes on average in the former study and 4.4 hours when using the median in the latter study, was proposed as a major reason for the discrepancy in ASPECTS.[15,23] Because the time delay was much smaller in the present study, the discrepancy in ASPECTS appears to be mainly due to the superior ability of DWI to delineate the extension of EIC as compared with CT.

The multivariate analysis indicated that when stroke subtype was cardioembolic and when the initial neurological deficits were severe, CT had the tendency to underestimate extension of EIC than DWI. The time delay of MRI after CT was not related to this discrepancy. Among regions of interest, the sensitivities of EICs in the caudate and internal capsule regions and the specificity of EIC in the lentiform nucleus were low on CT as compared with DWI. Thus, ASPECTS in the 2 modalities may not coincide, particularly in patients with severe cardioembolic stroke whose EICs lie extensively in the basal ganglia. CT seems to have a limitation for delineation of attenuation changes in the caudate and internal capsule regions as compared with that of sulcal effacement, focal cortical swelling, and loss of gray–white differentiation in the cortex because of the low sensitivity. The probable reason for the low specificity in the lentiform in the basal ganglia may be reversed discrepancy between CT and DWI.[24] Reversed discrepancy was identified mainly in the basal ganglia, and its pathophysiology may be pseudonormalization of apparent diffusion coefficient in EIC by early spontaneous reperfusion.[24] A critical limitation in our Table 2 was that the analysis was referenced to DWI, which incorporates both reversible and irreversible ischemia. The analysis should be fundamentally referenced to follow-up imaging, which represents final tissue status. However, our patients were treated with rtPA and natural courses of final tissue status could not be assessed.

Another unique finding in this study was comparison of CT-ASPECTS and DWI-ASPECTS as an outcome predictor. The area under the receiver operating characteristic curves for predicting outcomes with DWI-ASPECTS were somewhat,

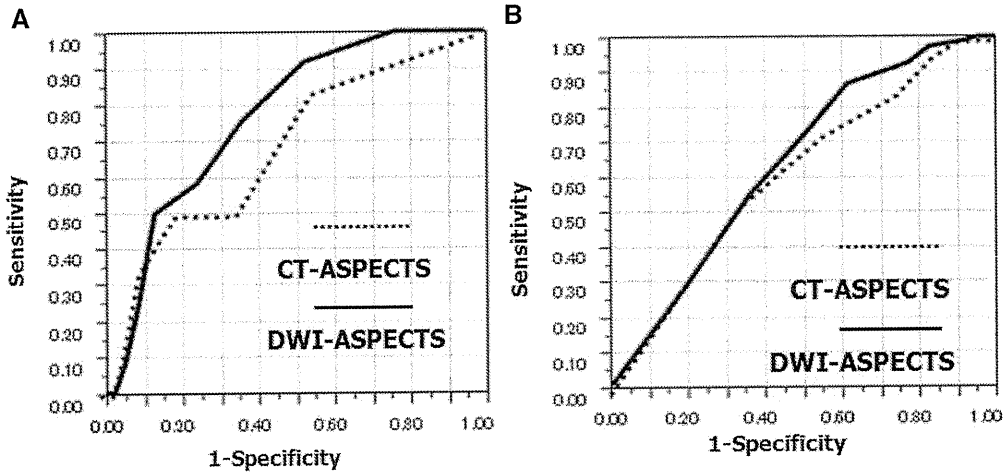

Figure 2. Receiver operating characteristic (ROC) curves of ASPECTS (CT or DWI) for predicting symptomatic intracerebral hemorrhage (**A**). ROC curves of ASPECTS (CT or DWI) for predicting modified Rankin Scale scores of 0 to 2 (**B**). ASPECTS indicates Alberta Stroke Programme Early CT Score; DWI, diffusion-weighted imaging; CT, computed tomography.

although not significantly, higher than those with CT-ASPECTS. DWI-ASPECTS appears to be at least equivalent to CT-ASPECTS in predicting sICH and stroke outcomes.

This study has several limitations. First, this was an observational study and patient eligibility for rtPA was determined according to each patient's situation, although the determination was principally based on the Japanese guidelines.[20] These guidelines might have contributed to selection bias. Second, all the patients were treated with 0.6 mg/kg alteplase. Thus, the clinical values of CT-ASPECTS and DWI-ASPECTS in patients treated with 0.9 mg/kg alteplase were not ascertained. Third, although we tried to perform CT and MRI as quickly as possible, onset to treatment time might have been somewhat longer than if only 1 of the examinations had been done. Finally, the present analysis was done only for patients without extensive EIC; this selection bias affects statistical results.

Our findings support the use of DWI-ASPECTS as well as CT-ASPECTS in predicting clinical outcomes after rtPA therapy. In addition, DWI-ASPECTS in our cohorts showed higher interrater reliability as compared with CT-ASPECTS as was reported in previous reports.[25,26] DWI-ASPECTS is a promising scoring system to evaluate EIC for predicting reliable clinical outcomes in future clinical stroke trials.

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Disclosures

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Low-Dose Intravenous Recombinant Tissue-Type Plasminogen Activator Therapy for Patients With Stroke Outside European Indications

Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry

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Background and Purpose—The purpose of this study was to determine the safety and efficacy of intravenous recombinant tissue-type plasminogen activator (0.6 mg/kg alteplase) within 3 hours of stroke onset in Japanese patients outside the indications in the European license.

Methods—Of the 600 patients who were treated with recombinant tissue-type plasminogen activator, 422 met the inclusion criteria of the European license (IN group) and 178 did not (OUT group).

Results—The OUT group was inversely associated with any intracerebral hemorrhage (adjusted OR, 0.50; 95% CI, 0.29–0.84), positively associated with an unfavorable outcome (2.48; 1.55–3.94) and mortality (2.04; 1.02–4.04), and not associated with symptomatic intracerebral hemorrhage (0.53; 0.11–1.79) or complete independency (0.65; 0.40–1.03) after multivariate adjustment.

Conclusions—Functional and vital outcomes 3 months after low-dose recombinant tissue-type plasminogen activator in patients outside the European indications were less favorable compared with those included in the indications; however, the risk of intracerebral hemorrhage was not. **(*Stroke*. 2012;43:253-255.)**

Key Words: acute stroke ■ diabetes mellitus ■ elderly patients ■ intracerebral hemorrhage ■ outcomes ■ thrombolysis

Patients with severe stroke as indicated by a baseline National Institutes of Health Stroke Scale (NIHSS) score of ≥25, those >80 years old, and those with any history of prior stroke and concomitant diabetes were excluded from a European postmarketing monitoring study for intravenous recombinant tissue-type plasminogen activator (rtPA) therapy (the Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy [SITS-MOST] registry) without sufficient rationale.[1] European regulatory agencies do not advocate rtPA therapy for patients having such exclusion items. Using our multicenter registry,[2] this study documented the safety and efficacy of low-dose intravenous rtPA (0.6 mg/kg) in patients with stroke outside the European indications as compared with those who fulfilled the SITS-MOST criteria.

Patients and Methods

Patients were derived from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry.[2] Patient eligibility for alteplase was determined based on the Japanese guideline[3] stating that patients ≥75 years old, those with NIHSS score ≥23, those with a history of prior stroke, and those with poorly controlled diabetes are to be carefully considered but not excluded. Other exclusion criteria are almost identical between the European and Japanese indications. Each patient received alteplase (0.6 mg/kg) intravenously with 10% given as a bolus within 3 hours of stroke onset and the remainder delivered through continuous intravenous infusion over 1 hour. Patients not meeting the inclusion criteria of the European license were categorized into the OUT group and those who did were categorized into the IN group.

Outcomes included: any and symptomatic intracerebral hemorrhage (ICH) within the initial 36 hours, complete independence

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The online-only Data Supplement is available at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.631176/-/DC1.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.111.631176**

Table. Safety and Efficacy Outcomes

			Age		NIHSS		Prior Stroke Plus Diabetes	
	IN Group (N=422)	OUT Group (N=178)	≤80 Y (N=471)	>80 Y (N=129)	<25 (N=560)	≥25 (N=40)	Absent (N=575)	Present (N=25)
Any ICH within 36 h, no. (%)	93 (22.0)	26 (14.6)	96 (20.4)	23 (17.8)	113 (20.2)	6 (15.0)	116 (20.2)	2 (8.0)
Multivariate OR (95% CI)	1	0.50 (0.29–0.84)*	1	0.83 (0.46–1.46)	1	0.62 (0.22–1.46)	1	0.32 (0.05–1.16)
Symptomatic ICH, no. (%)	13 (3.1)	3 (1.7)	15 (3.2)	1 (0.8)	15 (2.7)	1 (2.5)	15 (2.6)	1 (4.0)
Multivariate OR (95% CI)	1	0.53 (0.11–1.79)	1	0.27 (0.01–1.47)	1	1.17 (0.06–6.88)	1	1.32 (0.07–7.70)
mRS 0–1, no. (%) (N=532)§	161 (40.5)	35 (26.1)	173 (39.4)	23 (24.7)	191 (38.2)	5 (15.6)	189 (36.8)	7 (38.9)
Multivariate OR (95% CI)	1	0.65 (0.40–1.03)	1	0.58 (0.31–1.04)	1	0.40 (0.13–1.05)	1	0.97 (0.32–2.91)
mRS 5–6, no. (%)	68 (16.1)	69 (38.8)	86 (18.3)	51 (39.5)	117 (20.9)	20 (50.0)	128 (22.3)	9 (36.0)
Multivariate OR (95% CI)	1	2.48 (1.55–3.94)‡	1	2.36 (1.36–4.09)†	1	3.23 (1.51–6.97)†	1	2.35 (0.81–6.44)
Mortality, no. (%)	20 (4.7)	23 (12.9)	25 (5.3)	18 (14.0)	34 (6.1)	9 (22.5)	41 (7.1)	2 (8.0)
Multivariate OR (95% CI)	1	2.04 (1.02–4.04)*	1	2.00 (0.93–4.24)	1	3.75 (1.45–9.09)†	1	1.54 (0.23–6.24)

NIHSS indicates National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; CI, confidence interval; OR, odds ratio.
*$P<0.05$.
†$P<0.01$.
‡$P<0.001$.
§Assessed for patients who had premorbid mRS 0–1.

(modified Rankin Scale score 0–1), unfavorable outcome (modified Rankin Scale score 5–6) at 3 months, and death within 3 months. Symptomatic ICH was defined as that associated with neurological deterioration corresponding to an increase of ≥4 points from the baseline NIHSS score.

To evaluate the independent effect of the OUT group and each exclusion criterion on the clinical outcomes, a multivariate logistic regression model was estimated adjusting for sex, hypertension, dyslipidemia, atrial fibrillation, onset-to-treatment time, Alberta Stroke Programme Early CT Score, and internal carotid artery occlusion. The model was adjusted for: patients >80 years using NIHSS score, prior stroke, and diabetes; patients with NIHSS score ≥25, using age, prior stroke, and diabetes; and patients with prior stroke plus diabetes using age and NIHSS score.

Results

Of the 600 patients, 178 (85 men; age, 81.7±8.6 years) were categorized into the OUT group and the remaining 422 (292 men; 67.7±10.5 years) into the IN group. A higher percentage of patients in the OUT group were female, older, hypertensive, diabetic, and had higher initial NIHSS scores and internal carotid artery occlusion compared with the IN group (Supplemental Table I; http://stroke.ahajournals.org). Of the OUT group, 129 patients were >80 years old, 40 had severe stroke with an NIHSS score ≥25, and 25 had prior stroke plus diabetes.

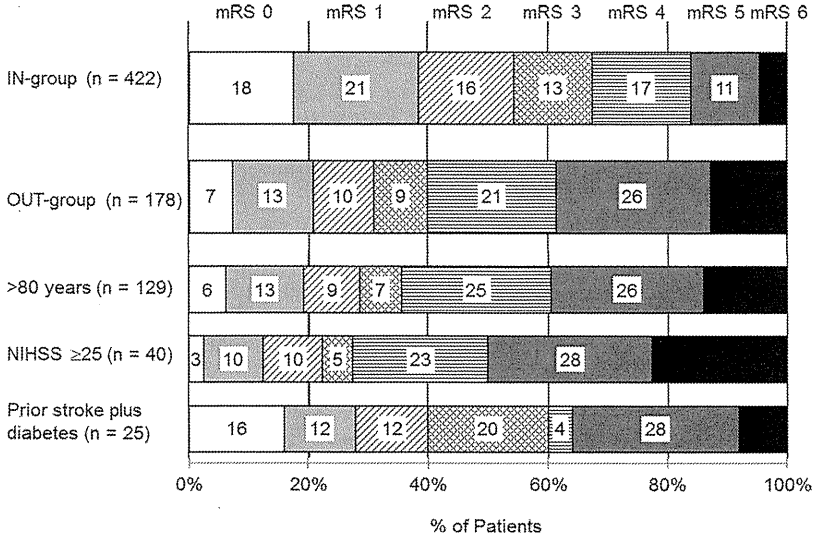

Figure. Modified Rankin Scale (mRS) distribution at 3 months.