2. 「超急性期脳出血への降圧療法に関する研究」

(1) パイロット研究

本研究は平成20年度に終了し、原著論文として掲載された(Itabashi R, et al: J Hypertens 2008;26:2016-2021）。研究結果は、平成20年度報告書に記載されている。

(2) 全国webアンケート調査

本研究は平成21年度までに終了し、原著論文として掲載された(Koga M, et al: Hypertens Res 2009;32:759-764）。研究結果は、平成20年度および21年度報告書に記載されている。

調査結果でニカルジピンが国内の大半の施設で急性期脳出血患者に用いられていたことは、同薬の添付文書での急性期脳出血患者への使用を制限する内容と合致しない。同薬は欧米のガイドラインで急性期脳出血患者への主要推奨薬に挙げられており、EBMの観点や脳卒中治療の国際的標準化の観点からも、添付文書の見直しが必要と考えた。2008年10月に日本脳卒中学会、日本脳神経外科学会、日本高血圧学会の三学会合同で、厚生労働省医薬食品局へ禁忌事項記載見直しの要望書を提出し、2009年9月に日本脳卒中学会から厚生労働省へ再度の見直し要望を意見提出していただいた。2011年3月末の段階で、見直し作業中との情報を得た。

(3) 急性期脳出血症例に対する降圧療法の安全性と有効性に関する多施設共同研究

2011年3月末までに188例(目標症例数の94%)を登録した。中間解析結果を古賀がEuropean Stroke Conference 2011や第36回日本脳卒中学会総会シンポジウムで発表する。この結果は、**資料2-a**にも詳述されている。概要を記す。

独立データモニタリング委員（九州大学病態機能内科 北園孝成教授、熊本大学神経内科 平野照之講師)による安全性の評価は、55例到達時（2010年1月）、101例到達時（2010年6月）、171例到達時（2011年1月）に行われた。いずれも研究は安全に行われており、研究の継続が可能という評価結果であった。分担研究者の同意を得て、目標の200例に到達するまで研究を続ける。

平成23年4月17日までにデータを収集した182例を中間解析した。その背景要因と臨床像を表に示す。

≪登録患者の背景要因、臨床像≫

女性		76 例 (42%)
年齢		66±12 歳
治療前収縮期血圧		203±16 mmHg 200 [189-214.8]
出血部位：被殻		98 例 (54%)
	視床	64 例 (35%)
	皮質下	9 例 (5%)
	混合性	9 例 (5%)
	尾状核	1 例 (1%)
	その他	1 例 (1%)

患者数（%）、中央値[IQR]、平均±SD

治療開始前の頭部CTで評価した血腫量は中央値11.0ml（IQR5.9-19.3）、降圧開始24時間後は12.1ml（6.1-25.9）（$p<0.0001$, Wilcoxon符号付順位検定）であった。治療前NIHSSは中央値13（IQR8-18）、降圧開始72時間後は10（5-15）（$p<0.0001$）であった。

治療開始24時間以内に脳外科手術を5例が受けた。内訳は4例が開頭血腫除去術で、1例が脳室ドレナージ術であっ

た。72時間～7日に2例が手術を受け、1例は脳室ドレナージ術で、もう1例は穿頭血腫吸引術であった。

主要評価項目である治療開始から72時間以内のNIHSS4以上の症状進行は8例（4.4%）（200例での予測値：90%信頼区間 27.0-38.4%）、24時間以内のニカルジピン中断を要する副作用は1例（0.5%）（200例での予測値: 90%信頼区間 3.1-8.9%）に認めた。副次評価項目である降圧目標域血圧値に到達した時間は中央値30分（IQR15-45）で、179例（98.4%）は2時間以内に降圧目標を達成した。目標到達後に目標域を逸脱したのは5048計測中1076計測（21.3%）であった。治療開始24時間後の33%以上の血腫拡大は29例（15.9%）（200例での予測値:90%信頼区間 18.6-29.0%）であった。発症3ヶ月後までフォローアップが終了した147例中、3ヶ月後までの死亡は4例（2.7%）で、3ヶ月後の転帰不良（mRS 4-6）は56例（37.6%）であった。他に以下の有害事象（72時間以内）を認めた。

≪72時間以内の有害事象≫

24-72 時間の血腫拡大	9 例 (4.9%)
脳出血再発	1 例 (0.5%)
脳梗塞	0 例
静脈炎 (24 時間以降)	8 例 (4.4%)
頻脈 (24 時間以降)	1 例 (0.5%)
昇圧が必要な血圧低下	0 例
その他 *	6 例 (3.3%)

* 過度降圧によるニカルジピン中断1例、肺炎3例、症候性癲癇1例、総ビリルビン上昇1例

(4) 米国 ATACH 試験主任研究者との研究打ち合わせ・合同会議

ATACHの主要研究者であるPalesch教授から国循峰松一夫副院長（当時、部長）に、第Ⅲ相試験ATACH 2への国内多施設の共同参加の打診があり、2008年5月に国循でPalesch教授と豊田、国循先進医療・治験推進部山本晴子部長（当時、室長）がATACH本試験（ATACH 2）の計画の説明を受けた。

≪2008年10月初年度第3回班会議≫

2008年10月の初年度第3回班会議（東京）にQureshi教授とPalesch教授が出席し、ATACH 2を日米共同で行う意義と問題点を班員全体で討議した。ATACHパイロット研究の最終報告が2009年2月のInternational Stroke Conference (San Diego)でQureshi教授によって報告され、豊田が聴講するとともに、現地でQureshi教授、Palesch教授と再度の情報交換を行った。その後2010年2月に米国サンアントニオで意見交換会、2010年7月に米国サンフランシスコで日本側有志との会議が開かれ、豊田・古賀らが参加した。

2010年にATACHパイロット試験の成績が、論文掲載された（Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators: Crit Care Med 2010;38: 637-648; Qureshi AI, et al: Arch Neurol 2010;67: 570-576）。収縮期血圧が180 mmHgを超える天幕上脳出血患者を、ニカルジピンの持続静注で140-180 mmHgないし110-140 mmHgの範囲へ降圧する2群に無作為に振り分け、その有効性と安全性を調べる第Ⅲ相試験ATACH 2に対して、米国国立衛生研究所（NIH）からの研究助成が決定し、2011年に米国で試験が開始された。国内でも、本研究班の参加研究者を含む施設が試験参加を表明し、2011年1月にQureshi教授を大阪に招いて説明会が開かれた。

3. 「急性脳主幹動脈閉塞症の実態に関する後ろ向き多施設共同研究」

研究結果を、分担研究者の山上や研究協力者の遠藤がWorld Stroke Congress 2010などで発表した。その概要を記す。主要所見を**資料3-a**に示す。

発症24時間以内に来院した急性期脳梗塞5213例のうち、主幹脳動脈閉塞を伴う1170例(女性42%、74±12歳)を登録した。閉塞部位は内頸動脈31%、中大脳動脈52%、脳底動脈7.6%。病型は心原性脳塞栓症が68%であった。3時間未満来院は59%、NIHSS中央値16（四分位値 8-21）。再開通治療としてrt-PA静注を23%、血管内治療を12%、両者の併用を2.5%が受けた。評価項目の症候性頭蓋内出血を5.3%に、90日もしくは退院時mRS 0-2を29%、mRS 5-6を39%、死亡を16%に認めた。多変量解析の結果を表に記す。

≪症候性頭蓋内出血に関連する要因≫

	OR	95%CI	P値
NIHSS, 1 点毎	1.05	1.01 – 1.08	<0.01
心原性脳塞栓症	3.77	1.68 – 10.1	<0.01

≪mRS 0-2に関連する要因≫

	OR	95%CI	P値
年齢、10 歳毎	0.59	0.51 – 0.68	<0.01
NIHSS, 1 点毎	0.84	0.82 – 0.86	<0.01
内頸動脈閉塞	0.41	0.27 – 0.62	0.01
再開通治療	2.07	1.41 – 3.06	<0.01

≪mRS 5-6に関連する要因≫

	OR	95%CI	P値
年齢、10 歳毎	1.71	1.48 – 1.99	<0.01
NIHSS, 1 点毎	1.14	1.12 – 1.17	<0.01
内頸動脈閉塞	3.14	2.27 – 4.37	<0.01

≪死亡に関連する要因≫

	OR	95%CI	P値
年齢、10 歳毎	1.32	1.10 – 1.58	<0.01
NIHSS, 1 点毎	1.10	1.08 – 1.12	<0.01
内頸動脈閉塞	2.94	2.05 – 4.22	0.01
再開通治療	0.62	0.41 – 0.93	0.02

閉塞血管別に検討すると、内頸動脈閉塞例での mRS 0-2 は 15%、mRS 5-6 は 60%と治療成績が際立って不良であり、この患者群においては再開通治療と転帰に有意な関連を認めなかった。

この登録症例を用いて、分担研究者の古賀が早期に来院しながら再開通治療を受けなかった患者に関連する要因を調べ、World Stroke Congress 2010 などで発表した。発症 150 分以内に来院した 603 例（女性 257 例、74±13 歳）のうち 51%に当たる 306 例が、再開通治療を受けなかった。多変量解析によって、高齢、発症 120 分以降の来院、内頸動脈閉塞の 3 項目が再開通治療を受けなかった患者に有意に関連する要因であった。

4.「急性期脳出血患者への抗凝固療法再開に関する多施設共同観察研究」

(1) 全国アンケート調査

本研究は平成 21 年度に終了し、研究結果を、研究協力者の前田が International Stroke Conference 2011 などで発表した。研究結果は、平成 21 年度報告書に記載されている。全結果を**資料 4-a** に示す。

(2)多施設共同前向き登録研究

2011 年 1 月末時点で、31 例が登録された。うち 29 例について、2011 年 3 月末時点で、患者背景などの入院時評価項目が中央事務局に報告された。研究協力者の前田が纏めた中間報告の概要を示す。

≪登録患者の背景要因・臨床像≫

男性	20 例（69%）
年齢	73±8 歳
既往症	
（塞栓・血栓性疾患）	
脳梗塞	11 例（39%）
TIA	0 例（0%）
脳以外の塞栓症	2 例（7%）
深部静脈血栓症	1 例（3%）
（出血性疾患）	
頭蓋内出血	2 例（7%）
頭蓋外	0 例（0%）
（心疾患）	
冠動脈疾患	2 例（7%）
発作性心房細動	1 例（3%）
慢性心房細動	14 例（48%）
心筋症	4 例（14%）
機械弁置換術後	1 例（3%）
出血部位	
皮質下	3（10%）
被殻	6（21%）
視床	9（31%）
脳幹	6（21%）
小脳	3（10%）
混合（複数部位）	1（3%）
その他	1（3%）
血腫量	6.7 ml（IQR：1.7-15.7）
来院時 NIHSS	9（IQR：3-18）
来院時 PT-INR	2.04（IQR：1.835-2.86）

≪PT-INR 是正方法≫

入院時 PT-INR 是正あり	26 例（90%）
PT-INR 是正の方法	
ビタミン K 単独	14 例（54%）
PCC 単独	3 例（11%）
ビタミン K と PCC 併用	9 例（35%）

FFP、第Ⅶ凝固因子製剤の使用症例は無し。

≪PT-INR の推移≫

・入院時に PT-INR 是正あり（26 例）

来院時 NIHSS	2.24（IQR：1.8475-2.96）
是正後初回 PT-INR	1.55（IQR：1.28-2.145）
24 時間後 PT-INR	1.19（IQR：1.08-1.34）

・入院時に PT-INR 是正なし（3 例）

来院時 NIHSS	1.92（1.08-2.04）
24 時間後 PT-INR	データ未回収

2011 年度末時点で 28 症例について、入院後の抗凝固療法再開の有無、入院中の合併症などが中央事務局に報告された。

≪抗凝固療法再開（解析対象：28 例）≫

抗凝固療法を再開した例	20 例（71%）
抗凝固療法再開までの日数	3 日（IQR 2-6）
再開時の薬剤	
ヘパリン単独	9 例（45%）
ワルファリン単独	7 例（35%）
両者の併用	4 例（20%）

≪入院後の合併症（解析対象：28 例）≫

・抗凝固療法を再開した例（20 例）

（塞栓・血栓性疾患）	
脳梗塞	1 例（5%）
TIA	0 例（0%）
脳以外の塞栓症	0 例（0%）
深部静脈血栓症	0 例（0%）
（出血性疾患）	
頭蓋内出血	1 例（5%）
消化管出血	1 例（5%）
尿路出血	0 例（0%）
治療が必要な鼻出血	1 例（5%）

・抗凝固療法を再開しなかった例（8 例）

（塞栓・血栓性疾患）	
脳梗塞	1 例（13%）
TIA	0 例（0%）
脳以外の塞栓症	0 例（0%）
深部静脈血栓症	0 例（0%）
（出血性疾患）	
頭蓋内出血	0 例（0%）
消化管出血	1 例（13%）
尿路出血	0 例（0%）
治療が必要な鼻出血	0 例（0%）

3 ヶ月後、および 1 年後の予後調査については、データの回収後に解析を行う必要がある。また、目標症例数（100 例）に到達するため、症例登録期間を 2012 年 3 月末まで延長することを予定している。

STROKE ACUTE MANAGEMENT WITH URGENT RISK-FACTOR ASSESSMENT AND IMPROVEMENT

SAMURAI

D．考察：
研究成果の意義および今後の発展

1. 「わが国独自の低用量 rt-PA 静注療法の適正性を証明した。」

国際的標準用量である 0.9 mg/kg は科学的根拠に富むと言えず、安全性や医療経済効果を考えても、0.6 mg/kg は実用的な用量と思われる。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。

2. 「超急性期脳出血患者への降圧治療の安全性を証明し、この主題に関する薬剤添付文書・ガイドライン改定を提言するとともに、国際試験企画に貢献した。」

全国アンケート調査成果の論文発表は、急性期降圧薬の選択における国内添付文書と現場での診療内容の乖離を明らかにし、乖離の是正を促す契機となった。アンケート調査での多数意見の妥当性を検証する前向き観察研究の中間解析結果も、肯定的な成績を挙げ、現在進行中の厚生労働省での添付文書見直し作業に続けることが出来た。研究結果をもとに、日本蘇生協議会等による心肺蘇生ガイドラインの作成に神経蘇生作業部会委員として携わり、急性期脳出血の治療推奨を定めた。本研究は、国際共同臨床試験 ATACH2 にわが国の参加する上での、大きな原動力となった。

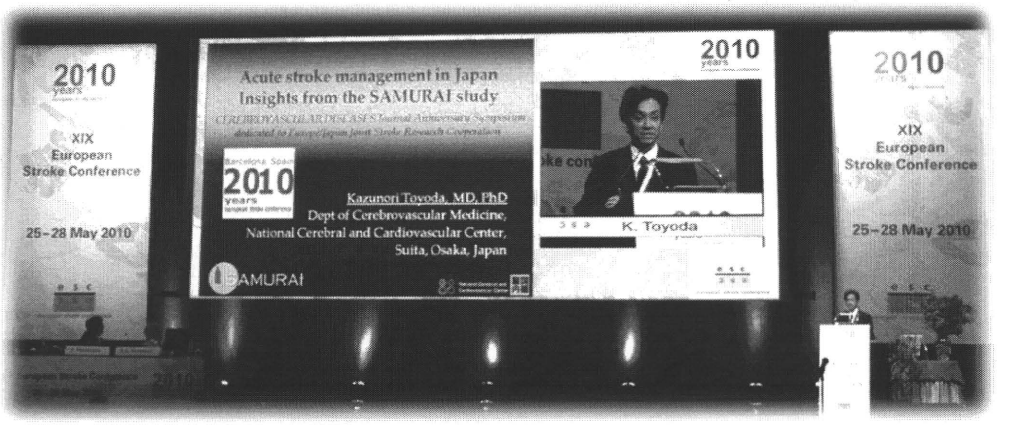
3. 「抗凝固療法中の脳出血に関する診療基準の不統一という問題点を明らかにした。基準統一のための観察研究・介入試験を企画遂行する。」

2011 年には新たな抗凝固薬ダビガトランも薬事承認され、抗凝固療法の新展開に対応した治療中の脳出血の予防・救急治療法を確立すべく、本研究を進展させる予定である。

4. 「国内での新治療（MERCI）承認のための基礎資料として貢献し、いわゆるデバイスラグを防いだ。」

現在主幹脳動脈閉塞患者の急性期治療手段として、新たな血管内治療機器などの国内承認が検討されている。そのうち 2010 年に承認された経皮経管的脳血栓回収機器 MERCI の承認にあたって、従来治療成績を判断する資料にも用いられた。

≪国際学会での招請講演：19th European Stroke Conference, Barcelona, 2010≫



5. 「研究成果の情報発信に努め、とくに海外研究者との交流の契機となった。」

SAMURAI rt-PA Registry の論文発表（Stroke 誌、2009 年）に対して、とくに民族的に近いアジア諸国から質問・意見が多く寄せられた。主任研究者の豊田は、2010 年に 3 つの国際学会で、この研究成果に基づく特別講演・シンポジウム発表に招聘され、わが国の血栓溶解療法を広く紹介する機会を得た（19th European Stroke Conference, Barcelona, Spain; Tiantan International Stroke Conference 2010, Beijing, China; 7th World Stroke Congress, Seoul, Korea）。

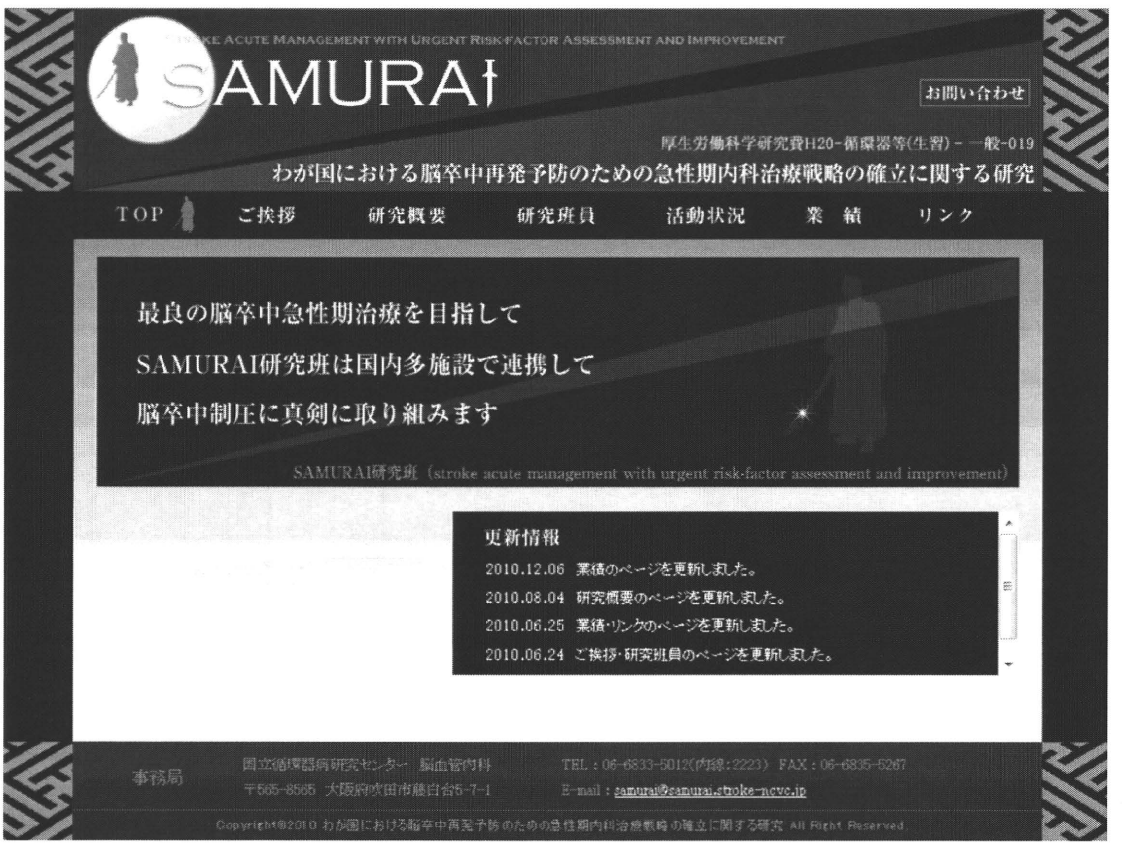
分担研究者が多くの国際学会・国内学会で、研究成果を発表した。**資料 5b, c** に発表内容の一覧と演題抄録を纏める。

豪州の Geoffrey Donnan 教授（National Stroke Research Institute）、Stephen Davis 教授（Royal Melbourne Hospital）が主宰する、MRI 上灌流・拡散ミスマッチのある発症 3〜9 時間の虚血性脳卒中症例に対して rt-PA もしくは偽薬に無作為に割り付ける第Ⅲ相国際多施設共同無作為化臨床試験 EXtending the time for Thrombolysis in Emergency Neurological Deficits（EXTEND）に、わが国の参加を呼びかけられる契機となった。

6. 「国内各地で医師やコメディカル、救急隊員、国民への啓発資料として用いた。」

ホームページ<http://samurai.stroke-ncvc.jp >や公開講座などで、医療者や国民に情報を公開した。

≪本研究班のホームページ扉頁≫



7. 「ガイドラインの作成や厚生労働省検討会での提言に貢献した。」

心肺蘇生ガイドラインの作成に携わった。厚生労働省「救急医療の今後のあり方に関する検討会」に委員として参加し、脳卒中救急医療への提言を行った。

8. 「現行治療の限界を示したことで、治療法改善を目的に基礎研究者と情報交換できた。今後のトランスレーショナル・リサーチを企画する契機となった。」

国循研究所など基礎部門との連携に努めた。

E．結論

4つの多施設共同研究を企画、遂行した。急性期脳梗塞患者へのわが国独自の低用量rt-PA静注療法の有効性と安全性、主幹動脈閉塞を伴う急性期脳梗塞患者へのrt-PA静注療法を含めた急性期治療の効果、日本人に多い病型である超急性期脳出血への降圧療法の必要性、抗凝固療法中に発症した脳出血患者への対応など、いずれも未解決の問題に対して一定の研究成果を得、論文発表をはじめとする情報発信を積極的に行った。

本研究班の理念と成果を、平成23年度からの新たな研究班である「急性期脳卒中への内科複合治療の確立に関する研究」（H23－循環器等（生習）－一般－010）において、さらに発展させ、わが国における脳卒中医学の向上に役立てたい。

F．健康危険情報：　なし

G．研究発表

1.　論文発表

Nezu T, Koga M, Kimura K, et al: Pre-treatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. Neurology 2010; 75:555-561（共同研究1-(2)のサブ解析）

Naganuma M, Koga M, Shiokawa Y, et al: Reduced estimated glomerular filtration rate is associated with stroke outcomes after intravenous rt-PA: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. Cerebrovasc Dis 2011;31:123-129　（共同研究1-(2)のサブ解析）

Nezu T, Koga M, Nakagawara J, et al: Early ischemic change on CT versus DWI for stroke patients receiving intravenous rt-PA therapy: SAMURAI rt-PA Registry. Stroke 2011, in press（共同研究1-(2)のサブ解析）

Koga M, Kimura K, Shibasaki K, et al: $CHADS_2$ score is associated with 3-month clinical outcomes after intravenous rt-PA therapy in stroke patients with atrial fibrillation: SAMURAI rt-PA Registry. J Neurol Sci 2011, Epub ahead of print（共同研究1-(2)のサブ解析）

牧原典子、岡田　靖、古賀政利、他：rt-PA静注療法施行症例におけるスタチンの頭蓋内出血および転帰に及ぼす影響：Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry、臨床神経学 2010;40:225-231　（共同研究1-(2)のサブ解析）

その他、「研究成果の刊行に関する一覧表」を参照

2. 学会発表

Toyoda K: Acute stroke management in Japan: insights from the SAMURAI study. 19th European Stroke Conference, Barcelona, Spain 2010/5/26-28 （招請シンポジウム講演）

Toyoda K: Intravenous low-dose rt-PA for ischemic stroke: messages from SAMURAI rt-PA Registry. 10th Tiantan International Stroke Conference 2010, Beijing, China 2010/6/25-27（招請シンポジウム講演）

Toyoda K: Intravenous low-dose rt-PA for ischemic stroke: SAMURAI rt-PA Registry. 7th World Stroke Congress, Seoul, Korea 2010/10/13-16（招請講演）

豊田一則：日本発の大規模観察研究：SAMURAI 研究。第 36 回日本脳卒中学会総会 京都 2011/7/30-8/1（招請シンポジウム講演）

古賀政利、山上 宏、岡田 靖、他：急性期脳出血患者に対するニカルジピン静注による降圧療法：多施設共同前向き観察研究（中間報告）。第 36 回日本脳卒中学会総会 京都 2011/7/30-8/1（シンポジウム講演）

その他、「**資料5a,b**：本研究成果の学会発表一覧、演題抄録」を参照

H. 知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得： なし
2. 実用新案登録： なし
3. その他： なし

多施設共同研究　関連資料

1：rt-PA患者登録研究

1-a.　サブ解析：早期虚血変化（Neurology 掲載論文）

1-b.　サブ解析：早期虚血変化（Stroke掲載予定論文要旨）

1-c.　サブ解析：腎機能障害（Cerebrovascular Diseases 掲載論文）

1-d. サブ解析：血液透析（European Neurology 掲載予定論文要旨）

1-e. サブ解析：$CHADS_2$スコア

（Journal of Neurological Sciences掲載論文）

1-f. サブ解析：スタチン（臨床神経学掲載論文）

2：超急性期脳出血への降圧療法に関する研究

2-a. 多施設共同前向き観察研究の中間解析報告書

3：急性脳主幹動脈閉塞症の実態に関する後ろ向き多施設共同研究

3-a. 研究の主要所見

4：急性期脳出血患者への抗凝固療法再開に関する多施設共同観察研究

4-a. 全国アンケート調査結果

STROKE ACUTE MANAGEMENT WITH URGENT RISK-FACTOR ASSESSMENT AND IMPROVEMENT

SAMURAI

Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA

SAMURAI rt-PA Registry

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ABSTRACT

Objective: To evaluate whether the pretreatment Alberta Stroke Programme Early CT Score (ASPECTS) assessed using diffusion-weighted imaging (DWI) predicts stroke outcomes at 3 months following IV recombinant tissue-type plasminogen activator (rt-PA) therapy.

Methods: Stroke patients treated with rt-PA (0.6 mg/kg alteplase) in 10 stroke centers in Japan were retrospectively studied. ASPECTS was assessed on DWI just prior to rt-PA injection. The primary outcome was a modified Rankin Scale (mRS) score of 0-2 at 3 months. Secondary outcomes included death at 3 months and symptomatic intracerebral hemorrhage (sICH) within 36 hours.

Results: For the 477 patients (316 men, 71 ± 11 years old) enrolled, the median NIH Stroke Scale score was 13 (interquartile range 7-18.5), the median ASPECTS on DWI was 8 (7-10), and sICH was identified in 15 patients (3.1%). At 3 months, 245 (51.4%) had an mRS score of 0-2, and 29 (6.1%) had died. Patients with an mRS score of 0-2 had higher median ASPECTS (9; interquartile range 8-10) than other patients (8; 6-9, $p < 0.001$). Using receiver operating characteristic curves, the optimal cutoff ASPECTS to predict an mRS score of 0-2 was ≥7. On multivariate regression analysis, ASPECTS ≥7 was related to an mRS score of 0-2 (odds ratio 1.85; 95% confidence interval 1.07-3.24), ASPECTS ≤4 was related to death (3.61; 1.23-9.91), and ASPECTS ≤5 was related to sICH (4.74; 1.54-13.64).

Conclusion: ASPECTS on DWI was independently predictive of functional and vital outcomes at 3 months, as well as sICH within 36 hours, following rt-PA therapy for stroke patients. ***Neurology*®** **2010;75:555-561**

GLOSSARY

ASPECTS = Alberta Stroke Programme Early CT Score; **CI** = confidence interval; **DWI** = diffusion-weighted imaging; **EIC** = early ischemic change; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **MRA** = magnetic resonance angiography; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **NINDS** = National Institute of Neurological Disorders and Stroke; **OR** = odds ratio; **PWI** = perfusion-weighted imaging; **ROC** = receiver operating characteristic; **rt-PA** = recombinant tissue-type plasminogen activator; **sICH** = symptomatic intracerebral hemorrhage; **SAMURAI** = Stroke Acute Management with Urgent Risk-factor Assessment and Improvement.

Early ischemic change (EIC) allows the prediction of subsequent infarct locations, and large EIC often results in clinically significant intracerebral hemorrhage (ICH) following thrombolysis.[1-4] Thus, for patients with large EIC on the initial CT, as assessed, for example, using the one-third of cerebral hemisphere rule, IV recombinant tissue-type plasminogen activator (rt-PA) is contraindicated according to several guidelines from the United States, Canada, Europe, and Japan.[5-8] However, visual assessment of the EIC volume depends on the reader's experience and skill, and the intrarater and interrater reliabilities in detecting EIC are not

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Study funding: Supported in part by Grants-in-Aid (H20-Junkanki-Ippan-019 [K.T.]) from the Ministry of Health, Labour and Welfare, Japan.

Disclosure: Author disclosures are provided at the end of the article.

sufficiently high.[9] In addition, strict evaluation of the volume by computerized planimetry takes time to analyze. An alternative approach for grading EIC on CT is a quantitative topographic score, the Alberta Stroke Programme Early CT Score (ASPECTS).[10] For this score, the territory of the MCA is allotted 10 points, and 1 point is subtracted for each area of EIC for each of the defined regions.

Diffusion-weighted MRI (DWI) can quickly detect hyperacute ischemic brain tissue. The contrast between ischemic tissue and normal tissue can be clearer on DWI than on conventional MRI and CT. The scoring of ASPECTS using DWI (DWI-ASPECTS) has been reported to be similar to that using CT.[11] DWI-ASPECTS predicts the risk of symptomatic ICH (sICH) after thrombolysis.[12] However, the evidence for the association between DWI-ASPECTS and chronic outcome after rt-PA therapy has been inconclusive. The aim of the present study was to evaluate whether pretreatment DWI-ASPECTS predicts functional and vital outcomes 3 months after rt-PA therapy.

Table 1 **Baseline characteristics**[a]

	Total (n = 477)	mRS 0-2 (n = 245)	mRS 3-6 (n = 232)
Age, y	71 ± 11	69.0 ± 11.8[b]	73.9 ± 9.5
Male	316 (66.2)	180 (73.5)[b]	136 (58.6)
Hypertension	301 (63.5)	143 (58.6)[c]	158 (68.7)
Diabetes mellitus	89 (18.7)	46 (18.9)	43 (18.5)
Dyslipidemia	102 (21.5)	55 (22.5)	47 (20.4)
Congestive heart failure	30 (6.5)	8 (3.4)[b]	22 (9.8)
Stroke subtype[c]			
Cardioembolism	293 (61.4)	146 (59.6)	147 (63.4)
Atherothrombotic stroke	77 (16.2)	31 (12.8)	46 (19.8)
Lacunar stroke	22 (4.6)	15 (6.9)	7 (3.0)
Other	85 (17.8)	53 (21.7)	32 (13.8)
Arterial occlusion site (n = 457)[b]			
Internal carotid artery	73 (16.0)	8 (3.2)	65 (28.0)
Middle cerebral artery trunk (M1)	135 (29.5)	67 (27.3)	68 (29.3)
Middle cerebral artery branch (M2)	93 (20.4)	55 (22.4)	38 (16.4)
Anterior cerebral artery	7 (1.5)	2 (0.8)	5 (2.2)
Posterior cerebral artery	16 (3.5)	9 (3.7)	7 (3.0)
Vertebrobasilar arteries	21 (4.6)	11 (4.5)	10 (4.3)
Not occluded	99 (21.7)	71 (29.0)	28 (12.1)
Onset to treatment time, min	141 ± 28	140.0 ± 26.9	141.9 ± 29.4
Pretreatment systolic blood pressure, mm Hg	151 ± 20	151.6 ± 18.2	150.1 ± 21.4
Pretreatment diastolic blood pressure, mm Hg	82 ± 15	82.9 ± 13.5	81.7 ± 16.5
Baseline NIH Stroke Scale score	13 (7-18.5)	9 (6-14)[b]	17 (11-20.75)
DWI-ASPECTS	8 (7-10)	9 (8-10)[b]	8 (6-9)

Abbreviations: ASPECTS = Alberta Stroke Programme Early CT Score; DWI = diffusion-weighted imaging; mRS = modified Rankin Scale.
[a] Data are mean ± SD for age, onset to treatment time, and blood pressure, median (interquartile range) for baseline NIH Stroke Scale score and DWI-ASPECTS, and number of patients (%) for others.
[b] $p < 0.01$ vs mRS 3-6 by t test, χ^2 test, or Mann-Whitney U test.
[c] $p < 0.05$.

METHODS Patients were derived from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. The details of this study have been described previously.[13] In brief, this was a retrospective, observational study involving consecutive stroke patients treated with IV rt-PA from October 2005 through July 2008 in 10 stroke centers in Japan. Patient eligibility for alteplase therapy was determined based on the Japanese guideline for IV rt-PA therapy,[8] which followed the inclusion and exclusion criteria used in the National Institute of Neurological Disorders and Stroke (NINDS) study and the Japan Alteplase Clinical Trial.[14,15] According to the Japanese guideline, patients with CT-documented extensive EIC (size is not defined) were not eligible for the treatment. Since the guideline does 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) IV, with 10% given as a bolus within 3 hours of stroke onset, followed by a continuous IV 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, neurologic deficits using the NIH Stroke Scale (NIHSS) score, and stroke subtype according to the TOAST categories,[16] were collected for all patients. Before rt-PA infusion, MRI studies, including DWI and magnetic resonance angiography (MRA), were performed on a 1.5-Tesla machine immediately before or after CT studies, principally within 10 minutes after CT. Administration of rt-PA was began around 10 minutes after CT and MRI. For the DWI sequence, high-b-value images corresponding to diffusion measurements in 3 gradient directions were acquired, in addition to a single, low-b-value image. The high b-value was 1,000 s/mm^2 and the low b-value was 0 s/mm^2 in all stroke centers. At least 2 experienced vascular neurologists in each stroke center evaluated the initial DWI and CT images to calculate quantitative EIC using ASPECTS later as a post hoc analysis. Arterial occlusion was assessed on the initial MRA. ICH was defined as CT evidence of new parenchymal hemorrhage type I or type II within the initial 36 hours[2]; it was also assessed by at least 2 experienced vascular neurologists of each stroke center. Symptomatic ICH was defined as a parenchymal ICH associated with neurologic deterioration corresponding to an increase of ≥4 points from the baseline NIHSS score.

The primary outcome was independence at 3 months, corresponding to a modified Rankin Scale (mRS) score of

0–2. Secondary outcomes were the mRS score of 0–1 at 3 months, death at 3 months, and sICH within the initial 36 hours.

Statistical analysis was performed using the JMP 7.0 statistical software (SAS Institute Inc., Cary, NC). Baseline characteristics were compared between patients with an mRS score of 0–2 and those with an mRS score of 3–6 using χ^2 tests, unpaired t tests, and the Mann-Whitney U test, as appropriate. To obtain the cutoff DWI-ASPECTS for discriminating between patients with and without each outcome, receiver operating characteristic (ROC) curves were constructed. Multivariate analyses were performed to identify predictors for primary and secondary outcomes. For each outcome, a backward selection procedure was performed using $p > 0.10$ of the likelihood ratio test as the exclusion criterion. These analyses were later repeated for patients who did not have culprit infarcts or culprit arterial occlusions in the vertebrobasilar arterial territory, the isolated anterior cerebral artery territory, or the isolated posterior cerebral artery territory. Statistical significance was established at $p < 0.05$.

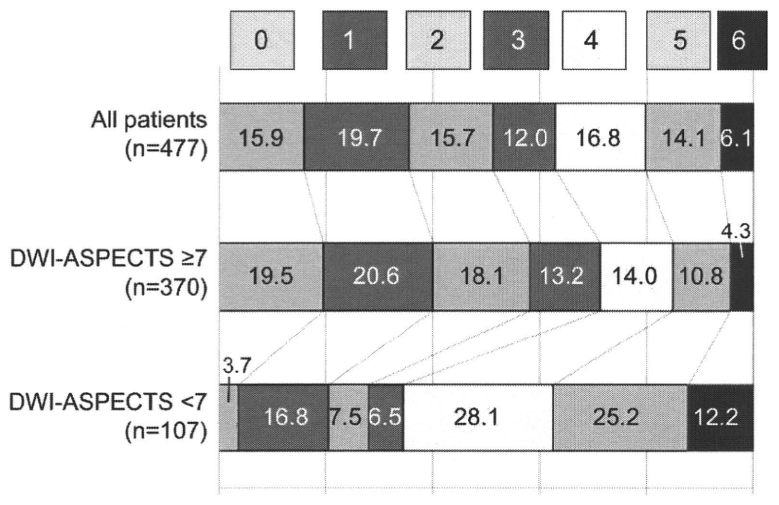
RESULTS A total of 600 consecutive patients were enrolled from the SAMURAI register. Of these, 70 patients could not undergo MRI prior to rt-PA mainly due to contraindications, unsteadiness, or time limitation, and 14 patients had inferior quality DWI images that were unsuitable for evaluating EIC. Of the remaining 516 patients who received pretreatment DWI, 35 were excluded from the analysis because their premorbid mRS score was 3 or more, and 4 were excluded because their 3-month mRS scores were not available. Finally, 477 patients (316 men, 71 ± 11 years old) were studied. The baseline clinical characteristics of these patients are presented in table 1. The median NIHSS score was 13 (interquartile range [IQR] 7–18.5). The median initial DWI-ASPECTS was 8 (IQR 7–10). DWI-ASPECTS was 6 or less in 107 patients (22.4%); of these, 37 patients had ASPECTS on the initial CT of 6 or less. ASPECTS on CT for most of these 37 patients was judged to be 7 or more at the time of the treatment decision, and was revised to be lower on the later reassessment.

Of these 477 patients, 245 (51.4%) were independent (mRS 0–2), and 29 (6.1%) had died by 3 months (figure 1). Within the initial 36 hours, 40 (8.4%) had parenchymal ICH, including 15 (3.1%) with sICH.

Association of DWI-ASPECTS with functional outcome. In table 1, the baseline characteristics are compared between patients with mRS scores of 0–2 and those with mRS scores of 3–6. The median initial DWI-ASPECTS was 9 (IQR 8–10) in patients with mRS scores of 0–2 and 8 (IQR 6–9) in those with mRS scores of 3–6 ($p < 0.001$). Patients with mRS scores of 0–2 were more frequently male ($p < 0.001$), younger ($p < 0.001$), less hypertensive ($p = 0.028$), less commonly had congestive heart failure ($p = 0.007$), and had lower baseline NIHSS scores ($p < 0.001$) than those with mRS scores of 3–6. Stroke subtype ($p = 0.030$) and arterial occlusion site ($p < 0.001$) differed between the groups; the internal carotid artery was relatively often occluded in patients with mRS scores of 3–6. Figure 2A shows the 3-month mRS scores in patients with different DWI-ASPECTS. The percentage of patients with mRS scores of 0–2 was similar among those with DWI-ASPECTS ≥7 and gradually decreased with the reduction in the DWI-ASPECTS when the score was ≤6. The optimal cutoff DWI-ASPECTS to predict patients with mRS scores of 0–2 at 3 months was ≥7, with a sensitivity of 88%, specificity of 33%, and an area under the ROC curve of 0.623 (figure 3). Overall, 215 (58.1%) of 370 patients with DWI-ASPECTS ≥7 and 30 (28.0%) of 107 patients with DWI-ASPECTS ≤6 had mRS scores of 0–2 ($p < 0.001$, figure 1). On multivariate regression analysis using backward selection, DWI-ASPECTS ≥7 was an independent predictor of an mRS score of 0–2 (odds ratio [OR] 1.85, 95% confidence interval [CI] 1.07–3.24; $p = 0.029$), along with younger age, male sex, lower NIHSS score, and absence of internal carotid artery occlusion (table 2).

For the analysis of the secondary outcome on mRS scores of 0–1 at 3 months, 26 patients with the premorbid mRS score of 2 were excluded. For the remaining 451 patients (304 men, 71 ± 11 years old), the optimal cutoff DWI-ASPECTS to predict patients with mRS scores of 0–1 was ≥9, with a sensitivity of 62%, specificity of 56%, and an area under the ROC curve of 0.627. On multivariate

Figure 1 **Modified Rankin Scale score at 3 months**



DWI-ASPECTS = scoring of Alberta Stroke Programme Early CT Score using diffusion-weighted imaging.

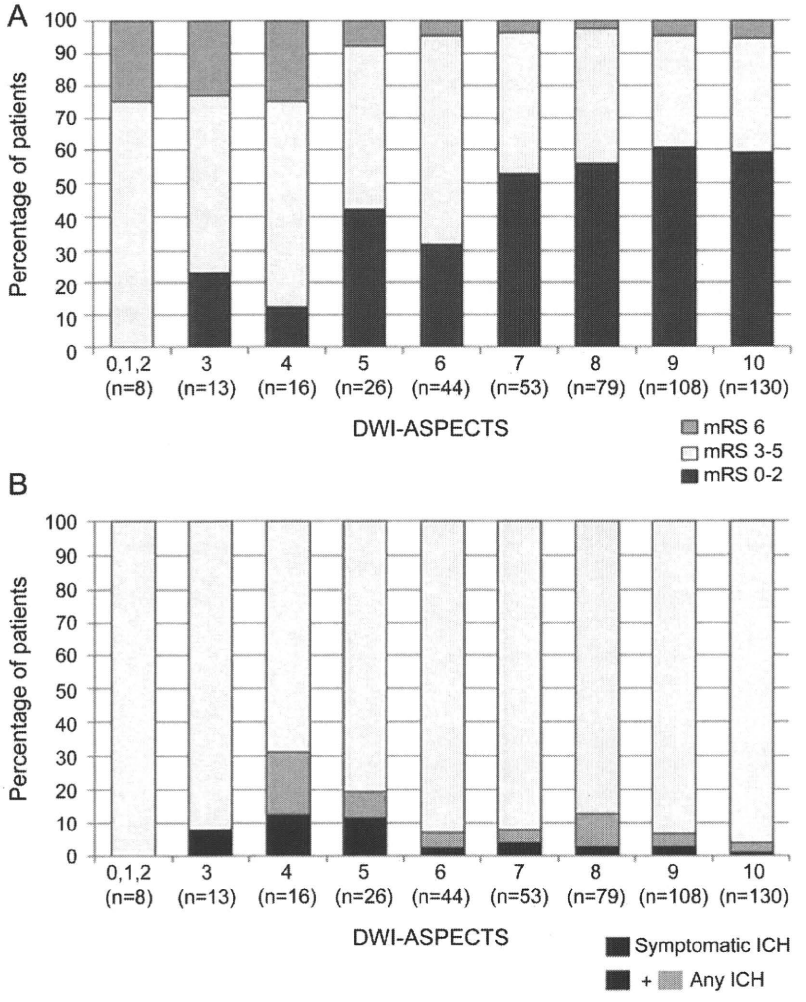
regression analysis, DWI-ASPECTS ≥9 was not an independent predictor of an mRS score of 0–1 (OR 1.40, 95% CI 0.87–2.24; $p = 0.160$).

Association of DWI-ASPECTS with mortality. DWI-ASPECTS was lower in patients who had died by 3 months (median 7, IQR 4–9.5) than in survivors (median 9, IQR 7–10; $p = 0.038$). Among patients with different DWI-ASPECTS, mortality was similar among patients with DWI-ASPECTS ≥7 and exceeded 20% when the score was ≤4 (figure 2A). The optimal cutoff DWI-ASPECTS to predict death at 3 months was ≤5, with a sensitivity of 38%, specificity of 88%, and an area under the ROC curve of 0.613. On multivariate regression analysis, DWI-ASPECTS ≤5 was not related to death at 3 months (OR 1.93, 95% CI 0.68–5.03; $p = 0.206$). When lowering the cutoff by 1 point, based on the findings in figure 2A, DWI-ASPECTS ≤4 was independently related to death (OR 3.61, 95% CI 1.23–9.91; $p = 0.021$) (table 2).

Association of DWI-ASPECTS with ICH. DWI-ASPECTS was lower in patients with sICH (median 7, IQR 5–9) than in those without (median 9, IQR 7–10; $p = 0.011$). The percentage of sICH was 4% or less among patients with DWI-ASPECTS ≥6, and exceeded 10% among patients with DWI-ASPECTS 4 and 5 (figure 2B). The optimal cutoff DWI-ASPECTS for predicting symptomatic ICH was ≤5, with a sensitivity of 40%, specificity of 87%, and an area under the ROC curve of 0.689. On multivariate regression analysis, DWI-ASPECTS ≤5 was an independent predictor of sICH (OR 4.74, 95% CI 1.54–13.64; $p = 0.008$) (table 2).

Analyses excluding patients with vertebrobasilar, anterior cerebral, and posterior cerebral arterial strokes. After excluding 44 patients with ischemia in the vertebrobasilar, anterior cerebral, and posterior cerebral artery systems, 433 patients (287 men, 71 ± 11 years old) were analyzed. The optimal cutoff DWI-ASPECTS to predict patients with mRS scores of 0–2 at 3 months was ≥7, with a sensitivity of 87%, specificity of 37%, and an area under the ROC curve of 0.637. On multivariate regression analysis, DWI-ASPECTS ≥7 was an independent predictor of an mRS score of 0–2 (OR 1.82, 95% CI 1.03–3.24; $p = 0.040$). Similarly, DWI-ASPECTS ≤4 was independently related to death (OR 3.96, 95% CI 1.31–11.19; $p = 0.016$), and DWI-ASPECTS ≤5 was an independent predictor of sICH (OR 4.76, 95% CI 1.52–14.20; $p = 0.009$).

Figure 2 **Modified Rankin Scale score (mRS) at 3 months (A) and parenchymal intracranial hemorrhage (ICH) within the initial 36 hours (B) in patients with each DWI-ASPECTS score**



DWI-ASPECTS = scoring of Alberta Stroke Programme Early CT Score using diffusion-weighted imaging.

DISCUSSION In this study, the associations between DWI-ASPECTS and clinical outcomes at 3 months after IV rt-PA therapy were assessed. The major new finding of this study was that pretreatment DWI-ASPECTS was associated with functional and vital outcomes at 3 months; DWI-ASPECTS ≥7 was predictive of an mRS score of 0–2, and DWI-ASPECTS ≤4 was predictive of death.

Extensive EIC over one-third of the MCA territory on CT has been reported to be predictive of poor functional outcome and symptomatic ICH after thrombolytic therapy.[1-3] ASPECTS ≥8 could exclude most patients with EIC over one-third of the MCA territory on CT,[17] and it had a prognostic value for favorable outcome among acute stroke patients treated with IV rt-PA.[10,18] In contrast, EIC on DWI is the earliest indicator of brain ischemic changes, and it is more sensitive and clearer to delineate the extension of brain ischemia than EIC on CT.[19] A coauthor of this study previously reported

that initial DWI-ASPECTS ≤5 was independently associated with NIHSS score ≥20 at 7 days after rt-PA therapy.[20] In our single-center study, initial DWI-ASPECTS ≥7 was independently associated with an mRS score of 0–1 at 3 months after rt-PA.[21] In this study, DWI-ASPECTS ≥7 was independently predictive of patients with a 3-month mRS score of 0–2.

Barber et al.[11] assessed ASPECTS for stroke patients within 6 hours of onset using both CT and DWI, and they found that DWI-ASPECTS was lower than ASPECTS on CT. The mean ASPECTS difference between the 2 modalities was 0.43. The superior ability of DWI over CT to detect the extension of EIC, as well as the time delay for DWI performance, appeared to cause the difference. Thus, the present cutoff of DWI-ASPECTS ≥7 to predict functional outcome appears to have a close relationship with the cutoff ASPECTS ≥8 on CT as a known prognostic variable for rt-PA-treated patients.[10,18]

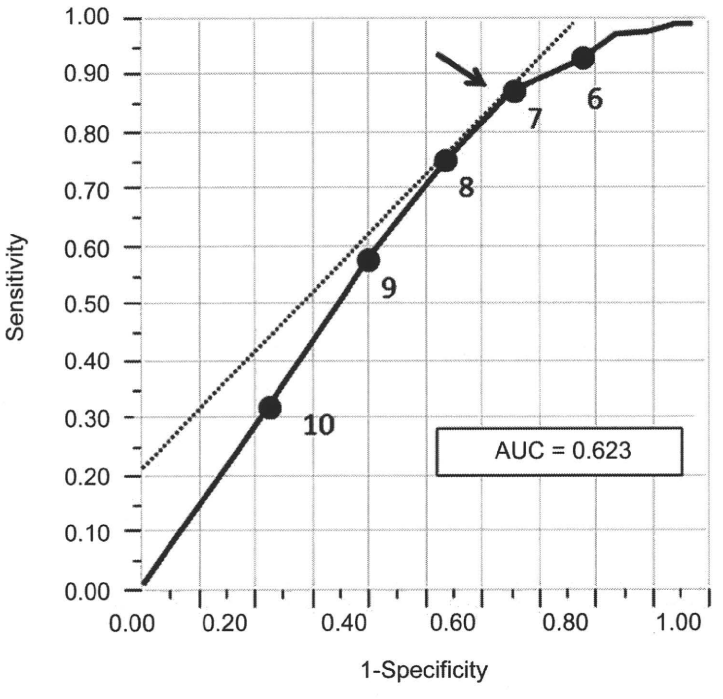
In the NINDS rt-PA Stroke Study, IV rt-PA for patients with baseline ASPECTS on CT <3 increased mortality compared with placebo treatment; 2 of the 5 deaths in the rt-PA therapy group were associated with symptomatic ICH compared with none in the placebo group.[22] DWI-ASPECTS was reported to predict unfavorable short-term outcome (NIHSS score ≥20 at 7 days)[20]; however, to our knowledge, the score has not been previously reported to affect mortality after rt-PA. In figure 2A, the marked increase in mortality is shown below DWI-ASPECTS ≤4, indicating the association of low DWI-ASPECTS and higher mortality rates. However, precise cutpoints were difficult to define. Of the 9 deaths in patients with DWI-ASPECTS ≤4, 3 resulted from symptomatic ICH, 5 from cerebral herniation due to massive stroke, and 1 from severe cardiac failure (data not shown).

Pretreatment DWI volume has recently been recognized as an independent risk for sICH after thrombolysis.[4,23,24] Pretreatment DWI-ASPECTS ≤7 was advocated as a predictor of sICH after IV or intraarterial thrombolysis within 6 hours of onset.[12] In contrast, for our patients receiving IV thrombolysis within 3 hours, pretreatment DWI-ASPECTS ≤5 was an independent predictor of sICH.

MRI is currently not generally the primary imaging modality in acute stroke patients because of the possible time delay, its potentially inferior ability for detecting acute ICH, and its contraindications, which are mainly due to metal implants. Several studies have reported that MRI screening within 3 hours of onset did not delay IV rt-PA therapy or lead to worse outcomes relative to CT screening.[25,26] Regarding hyperacute ICH, MRI was reported to be as reliable as CT, because small amounts of deoxyhemoglobin are detectable within the first hours of ICH on T2*-weighted images.[27,28] Thus, MRI could be used as the modality for emergency imaging of acute stroke patients, whether ischemic or hemorrhagic.[29] In addition, MRI penumbral assessment with the mismatch between DWI and perfusion-weighted imaging (PWI) is promising to improve patient selection and outcome for IV rt-PA therapy.[30,31] Since planimetric PWI-DWI mismatch assessment is time-consuming, ASPECTS can be applied to assess PWI-DWI mismatch.[32]

This study has several limitations. First, DWI-ASPECTS is not useful for evaluating strength and size variations of high-intensity change within each allotted lesion on DWI. Because slight alterations in high intensity on DWI are believed to contain reversible ischemic tissues, DWI-ASPECTS may overestimate the extension of EIC.[33] Second, this was an observational study and patient eligibility for rt-PA was determined according to each patient's situation, though the determination was principally based on the Japanese guidelines.[8] In particular, eligibility of patients having large EIC on DWI depended on each physician's decision, and we did not assess how many patients with low DWI-ASPECTS and relatively high ASPECTS on CT were excluded from the

Figure 3 **Receiver operating characteristic curves of scoring of Alberta Stroke Programme Early CT Score using diffusion-weighted imaging for predicting modified Rankin Scale scores of 0–2**



The arrow indicates the optimal cutoff point. AUC = area under the receiver operating characteristic curve.

Table 2 **Characteristics associated with a modified Rankin Scale score of 0–2 and death at 3 months, and symptomatic intracerebral hemorrhage[a]**

	OR	95% CI	p
mRS 0–2			
Age, per 1-year increase	0.97	0.95–0.99	<0.001
Female	0.59	0.37–0.95	0.031
Hypertension	0.67	0.42–1.05	0.083
Baseline NIHSS, per 1-point increase	0.92	0.89–0.96	<0.001
DWI-ASPECTS ≥7	1.85	1.07–3.24	0.029
ICA occlusion	0.13	0.06–0.28	<0.001
Death			
Congestive heart failure	7.61	2.46–22.35	<0.001
DWI-ASPECTS ≤4	3.61	1.23–9.91	0.021
ICA occlusion	4.45	1.69–11.64	0.003
Symptomatic ICH			
DWI-ASPECTS ≤5	4.74	1.54–13.64	0.008

Abbreviations: ASPECTS = Alberta Stroke Programme Early CT Score; CI = confidence interval; DWI = diffusion-weighted imaging; ICA = internal carotid artery; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio.
[a] Adjusted by characteristics selected by a backward selection procedure.

study. Third, 84 patients lacked MRI information, which may have caused selection bias. Fourth, all of the patients received 0.6 mg/kg alteplase, which is the recommended dose in Japan. Thus, the clinical value of DWI-ASPECTS in patients treated with the generally accepted standard dose of alteplase (0.9 mg/kg) outside of Japan was not ascertained. Fifth, we did not collect data for stroke patients who did not receive thrombolysis. Thus, we could not compare the present results with stroke outcome of patients who were excluded from the therapy because of extensive EIC. Finally, since DWI-ASPECTS for most of the patients was high (the lower 25% value was 7), the median DWI-ASPECTS did not differ much between patients with good outcomes and those without.

Pretreatment MRI with DWI provides valuable information for predicting clinical outcome after IV rt-PA therapy. Although clinical use of rt-PA should not be chosen solely using DWI-ASPECTS because it requires consideration of various underlying conditions, patients with DWI-ASPECTS of 4 or less do not seem to be good candidates for IV rt-PA since most patients with these scores have fatal or dependent outcomes. DWI-ASPECTS of 5 may be another warning sign for choosing rt-PA since more than 10% of patients with this score developed sICH. A confirmation of the present findings using patients treated with the regular dose of alteplase is needed.

DISCLOSURE

Dr. Nezu, Dr. Koga, Dr. Kimura, Dr. Shiokawa, Dr. Nakagawara, Dr. Furui, Dr. Yamagami, Dr. Okada, Dr. Hasegawa, Dr. Kario, Dr. Okuda, Dr. Nishiyama, and Dr. Naganuma report no disclosures. Dr. Minematsu serves on the editorial boards of *Cerebrovascular Diseases*, the *International Journal of Stroke*, and the *Journal of Stroke and Cerebrovascular Diseases* and receives research support from Asteras Pharma Inc., Takeda Pharmaceutical Company Limited, Sanofi-Aventis, Lundbeck Inc., Mitsubishi Tanabe Pharma Corporation, Kyowa Hakko Kirin Pharma, Inc., Hitachi Medical Corporation, MHLM, Japan, Research Grants for Cardiovascular Diseases, Grant-in-Aid, and the Foundation for Biomedical Research and Innovation. Dr. Toyoda receives research support from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan.

Received December 3, 2009. Accepted in final form April 28, 2010.

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わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究
「多施設共同研究 1：rt-PA 患者登録研究」
サブ解析論文：要旨

Early ischemic change on CT versus DWI for stroke patients receiving intravenous rt-PA therapy: SAMURAI rt-PA Registry

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Abstract

Background and Purpose: Alberta Stroke Programme Early CT Score (ASPECTS) is a quantitative topographic score to evaluate early ischemic change (EIC) 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 hyperacute stroke patients and their associations with outcomes after recombinant tissue-type plasminogen activator (rt-PA) therapy based on a multicenter registry.

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

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 6-9] vs. 9 [8-10], $P<0.001$). Higher baseline NIHSS 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 ROC curve for predicting sICH (12 patients) using ASPECTS was 0.673 (95%CI 0.503-0.807) by CT and 0.764 (95%CI 0.635-0.858) by DWI ($p=0.275$). The curve for predicting independence at 3 months (192 patients) was 0.621 (0.564-0.674) by CT and 0.639 (0.580-0.694) by DWI ($p=0.535$).

Conclusion: For hyperacute stroke patients, DWI-ASPECTS scored about 1 point lower than CT-ASPECTS. Both CT-ASPECTS and DWI-ASPECTS were useful predictors of sICH and independence at 3 months after rt-PA.

(*Stroke* 2011, in press)

Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2011;31:123–129
DOI: 10.1159/000321516

Received: March 2, 2010
Accepted: September 15, 2010
Published online: November 17, 2010

Reduced Estimated Glomerular Filtration Rate Is Associated with Stroke Outcome after Intravenous rt-PA: The Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA Registry

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Key Words
Infarction · Intracerebral hemorrhage · Renal dysfunction · rt-PA · SAMURAI

Abstract
Background: The aim of this study was to determine whether renal dysfunction affects the outcome of stroke patients treated with recombinant tissue plasminogen activator (rt-PA). ***Methods:*** A retrospective, multicenter, observational study was conducted to identify the effects of underlying risk factors on intravenous rt-PA therapy using 0.6 mg/kg alteplase in 10 stroke centers in Japan. Consecutive stroke patients with a premorbid modified Rankin Scale (mRS) score ≤3 who received rt-PA were studied. Renal dysfunction was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 on admission. The outcome measures were any intracerebral hemorrhage (ICH) and symptomatic ICH within the initial 36 h; favorable (mRS 0–1) outcome, poor outcome (mRS 4–6) and mortality at 3 months. ***Results:*** Of a total of 578 patients (372 men; 64.4%, 71.4 ± 11.7 years old), renal dysfunction was present in 186 patients (32.2%). These patients were older and more commonly had hypertension, atrial fibrillation, prior ischemic heart disease and prior use of antithrombotic agents than patients without renal dysfunction. ICH (27.4 vs. 16.6%) and symptomatic ICH (8.1 vs. 2.6%) was more common in patients with renal dysfunction than in those without. At 3 months, patients with renal dysfunction had higher median mRS scores than those without (3 vs. 2). After multivariate adjustment for established outcome predictors, renal dysfunction was related to any ICH (odds ratio 1.81, 95% confidence interval 1.16–2.84), symp-

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tomatic ICH (2.64, 1.10–6.56), poor outcome (1.55, 1.01–2.38), and mortality (2.94, 1.38–6.42). ***Conclusions:*** Reduced eGFR was associated with early ICH and 3-month unfavorable outcome in stroke patients receiving intravenous rt-PA.

Introduction

Renal dysfunction is increasingly noted as a risk factor for stroke in the general population [1, 2], as well as in high-risk patients having diabetes mellitus [3], essential hypertension [4], and preexisting atherothrombotic disease [5, 6]. In a large cohort of patients with acute stroke, renal dysfunction was an independent predictor for long-term mortality and poor outcome [7–9].

Though intravenous (IV) thrombolysis is a standard therapy for acute stroke patients, the effect of renal dysfunction on vital and functional outcome measures following therapy is inconclusive. As far as we know, only one study (involving 196 stroke patients) reported that a high admission serum creatinine level was independently predictive of a modified Rankin scale (mRS) score ≥3 at 3 months after IV recombinant tissue plasminogen activator (rt-PA) [10]. This study also reported that an impaired estimated glomerular filtration rate (eGFR), defined as <90 ml/min/1.73 m^2, tended to be associated with symptomatic intracerebral hemorrhage (ICH). Since renal dysfunction appears to be an important predictor for stroke outcome, its significance for rt-PA-treated patients should be ascertained in a larger cohort using a multicenter design.

To identify adequate risk factor control in acute stroke patients treated with thrombolysis, a multicenter study group [Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) Study Group] was formed. Here, we determined the association of renal dysfunction based on admission eGFR with stroke outcome after IV rt-PA using the database of this study group.

Patients and Methods

The SAMURAI rt-PA Registry Trial had a multicenter, hospital-based, retrospective, observational, cohort design [11]. Details of this study have been described previously [11, 12]. In brief, this study involved 600 consecutive patients with acute ischemic stroke receiving IV rt-PA from October 2005 to July 2008. Of these, 22 patients were ineligible for analysis; 17 patients had dependent activity of daily living before onset, corresponding to an mRS score ≥4, and 5 patients had incomplete 3-month mRS score data. Thus, the remaining 578 patients were included in the present study. Each local ethics committee approved the research protocol. Each patient received a single IV alteplase dose of 0.6 mg/kg, with 10% given as a bolus within 3 h of stroke onset, followed by a continuous IV infusion of the remainder over 1 h [13].

From the database of the SAMURAI rt-PA registers, the data listed in table 1 were extracted for this study. Neurological deficits were assessed using the National Institutes of Health Stroke Scale (NIHSS) score just before and 24 h after rt-PA. Ischemic stroke subtype according to the TOAST categories was elucidated based on information of non-contrast computed tomography (CT), diffusion-weighted magnetic resonance imaging (MRI), magnetic resonance angiography, CT angiography, cervical/transcranial ultrasound, transthoracic or transesophageal echocardiography, and 24-hour Holter monitoring in addition to neurological findings [14].

Kidney function was evaluated based on the eGFR using a revised equation for the Japanese population [15]; eGFR (ml/min/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ × 0.739 (for women). To calculate eGFR, admission serum creatinine was used. According to the Kidney Disease Outcomes Quality Initiative guidelines of the National Kidney Foundation [16], renal dysfunction was defined as a reduced eGFR (<60 ml/min/1.73 m^2). The stage of renal dysfunction was classified as follows: stage 3 (eGFR 30–59 ml/min/1.73 m^2), stage 4 (15–29 ml/min/1.73 m^2), and stage 5 (<15 ml/min/1.73 m^2 or dialysis).

The major outcome measures were: any ICH defined as CT or MRI evidence of new ICH within the initial 36 h; symptomatic ICH with neurological deterioration corresponding to an increase of ≥1 point from the baseline NIHSS score (Cochrane/National Institute of Neurological Disorders and Stroke definition); favorable and poor outcome at 3 months, and mortality at 3 months. To assess favorable and poor outcome, definitions in the subanalyses of the National Institute of Neurological Disorders and Stroke rt-PA Trial (an mRS of 0–1 and 4–6, respectively) were used [17–20].

Statistical Analysis

Statistical test results were considered significant if $p < 0.05$. All analyses were performed using JMP statistical software (version 7.0.1; SAS Institute, Cary, N.C., USA). Baseline clinical characteristics and stroke features were compared using Student's unpaired t test for parametric continuous variables, Mann-Whitney's U test for nonparametric variables, and Fisher's exact test and the χ^2 test for categorical variables. To identify independent predictors of ICH within 36 h and stroke outcome at 3 months, multivariate logistic regression analysis was performed. For each outcome, sex, age, and renal dysfunction were initially entered, and the other variables listed in table 1 were chosen by a backward selection procedure using $p > 0.10$ in the likelihood ratio test for exclusion.

Results

A total of 578 patients (372 men, 71.4 ± 11.7 years old) were studied. Of these, 186 (32.2%) patients had renal dysfunction with eGFR <60 ml/min/1.73 m^2; 163 (28.2%)