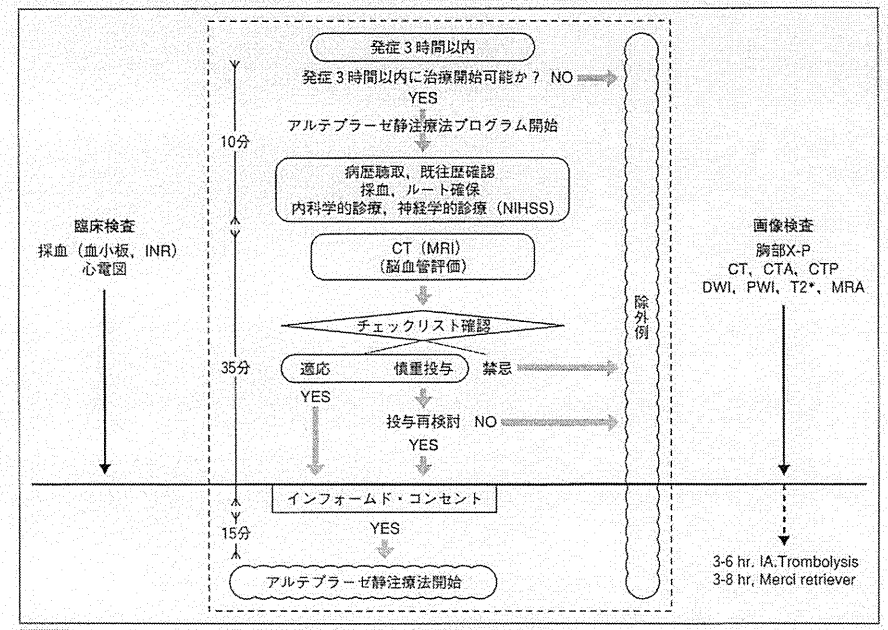

図2 アルテプラーゼ静注療法のアルゴリズムと検査に要する時間

検査に要する時間の律速段階は臨床検査による血小板数などの確認に要する時間であり，画像検査に要する時間とはならない．CTPやPWIなどの虚血性ペナンブラを評価する追加検査は局所線溶療法（IA Thrombolysis）やMerci retrieverの適応判定に用いられる．

（文献3より引用改変）

せることのないように迅速に対応しなければならない．

わが国における急性期脳梗塞に対する0.6mg/kgアルテプラーゼ静注療法は，J-ACTⅡにおいて十分な有効再開通率が確認され，J-MARSにおいて一般臨床における安全性と有効性が確認されたことから，名実ともに確立された治療法である．今後の課題としては，アルテプラーゼ静注療法で血流再開の得られなかった症例に対する各種の血管内治療法の併用の安全性と有効性の確認が必要である．また，アルテプラーゼ静注療法が常に施行できる脳卒中センターを地域ごとに整備し，各センターにおいて適正治療指針に沿った診療体制の確立を目指すとともに，地域医療圏を単位とする脳卒中救急医療連携を構築し，治療適応症例に対して適切に対処することが急務と考えられる．

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脳虚血治療の time window を広げる

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脳虚血治療の time window は，各血流再開療法の有効性と安全性を治療群全体として確実に得るために最適化された「治療適用のための時間枠」である．脳虚血治療の time window を広げるためには，特に閉塞血管の再開通率の向上と症候性頭蓋内出血の抑制が重要である．また，time window が広がるほど，治療の標的である ischemic penumbra（therapeutic window）を画像として見いだすことが重要となる．各種の治療法の組み合わせによる time window の拡大については，血流再開療法の time window が固有の有効再開通率に依存していることを想定した検討が必要である．

Key Words: 脳虚血，ischemic penumbra，血流再開，therapeutic window，time window

Ⅰ．はじめに

発症から3時間以内の急性期脳梗塞に対する rt-PA（Alteplase）の静注による血栓溶解療法の有効性と安全性が明らかにされて以来[12)]，急性期の脳虚血治療としての血流再開療法では，time window による治療選択が一般化しつつある．

現在，一般臨床において適用可能な血流再開療法の time window とその適応対象を整理すると，Alteplase 静注療法は発症から3時間以内のすべての脳梗塞，局所線溶療法（選択的 urokinase 動注療法）[10)]は発症から6時間以内の中大脳動脈閉塞症，Merci Retriever®による血栓回収療法[11)]は発症から8時間以内の脳主幹動脈閉塞症となる．

しかし，脳梗塞の成立には発症からの時間に加えて，脳虚血下での残存脳血流量が関与している[7)]．高度の脳虚血では発症から3時間以内でも脳組織の生存能力（viability），機能的には脳組織の可逆能力（reversibility）を維持することができないのに対して，中等度の脳虚血では発症から6～8時間以内の viability を維持することが可能である．このように，個々の症例から見た血流再開療法の至適 time window は残存脳血流量に依存し，大きくばらつく．一方，各療法に設定された time window 内において脳組織の viability が維持されていても，治療後早期に閉塞血管の再開通が得られなければ，脳梗塞は回避できない．すなわち，time window の設定には各療法に固有の有効再開通率が大きく影響する．

さらに，各療法の time window は，脳虚血下の脳組織の生存能力から決定された時間ではないことにも注意が必要である．これらの time window

は，各療法について有効性と安全性が検証された臨床研究プロトコールの entry criteria として設定された「治療適用のための時間枠」であり，各療法の有効性と安全性を治療群全体として確実に得るために最適化された「治療適用のための時間枠」ということができる．

本稿では，以上のような視点に立って，脳虚血治療の time window をどのように広げることができるか，について解説する．

Ⅱ．Ischemic penumbra と time window

一般に脳塞栓症に伴う脳虚血では，心あるいは大動脈由来の遊離血栓が脳主幹動脈を突然閉塞するため，その末梢灌流領域にただちに神経脱落症候の原因となる脳虚血が生ずる．このような脳虚血域では，残存脳血流量が極度に低下し，脳組織の不可逆的変化が早期から生じる領域（ischemic core）と，その周辺領域に残存脳血流がある程度保たれ，脳機能は停止しているものの脳組織の可逆能力が一定時間維持される領域（ischemic penumbra）とが混在することになる．症候性の脳虚血域における ischemic core と penumbra の割合は，残存脳血流の供給元である側副血行路の発達の程度に依存するとともに，発症からの時間経過とともに ischemic core が拡大するため，ischemic penumbra の存在は閉塞部位が同一でも症例ごとに多様である．

Ischemic penumbra における脳組織の可逆能力は，脳虚血下の残存脳血流量と発症からの時間の２つの因子に依存[7]し，その存在は急性期の血流再開を目的とする治療法の標的となる．

Ischemic penumbra の概念は，もともと 1970 年代に動物実験において見いだされた脳虚血に関する２つの脳血流の閾値（シナプス伝導の障害による脳波の平坦化が生ずる閾値と，細胞膜のイオンポンプが障害され神経細胞死が起こる閾値とが解離している）から定義されたものである[1]．しかし現在では，発症からの時間経過の因子が加味されて理解されている[7]．図１のごとく，ischemic penumbra は，「残存脳血流量と発症からの時間で定義される可逆能力の保たれた領域」＝「血流再開治療法に開かれた窓（therapeutic window[8]）」

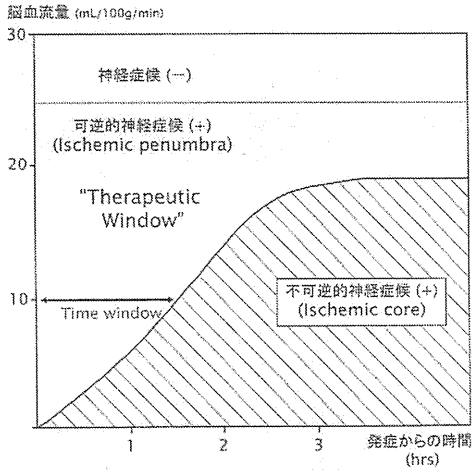

図１　発症からの時間と残存脳血流量から見た ischemic penumbra と ischemic core の関係
（文献７より改変）

Ischemic penumbra は，血流再開療法に開かれた窓（therapeutic window）に相当する．血流再開により脳梗塞が回避され，可逆的神経症候の回復が得られるが，残存脳血流量が低いほど time window（⇔）は短縮する．一方，血流再開がなければ，ischemic core（脳梗塞巣）は発症からの時間と残存脳血流量に依存して出現し，神経症候は回復しない．

として，グラフ上に表すことができる．

基礎的研究によってその存在が確認されたischemic penumbraは，今日，急性脳虚血に対する血流再開治療の標的病態であり，臨床の場ではmultimodal MRIによるdiffusion-perfusion mismatchなどとして，その存在が擬似的に画像化される．Therapeutic windowは，急性脳虚血に対する血流再開治療が適応となる標的（ischemic penumbra）の存在を指し，time windowは急性脳虚血に対する血流再開治療が適用される時間枠を指す．

Ⅲ．血栓溶解療法とtime windowの拡大

Alteplaseの静注による血栓溶解療法では，治療直後の閉塞動脈の再開通率は20～30%[13]と低率にもかかわらず，発症後3時間以内に治療された場合にその有効性が得られている．この事実は，治療後早期（おおむね発症後3～6時間まで）に生じる閉塞動脈の早期再開通が，ischemic penumbraの救済に役立っている可能性を示唆するものである．しかし本治療法では，time windowが発症から3時間以内と狭く適応症例が限られること，症候性頭蓋内出血の発症率が有意に上昇することが問題点である．

Alteplase静注療法のtime windowの拡大については，投与開始時間から見た有効性に関するメタ解析の結果から，発症から4.5時間前後まで拡大できることが想定され（図2）[3]，ECASS 3研究によって，はじめてtime windowが3時間から4.5時間まで拡大された（日本では拡大されていない）[5]．本療法のtime windowをさらに拡大するためには，脳保護治療（低脳温療法や脳保護

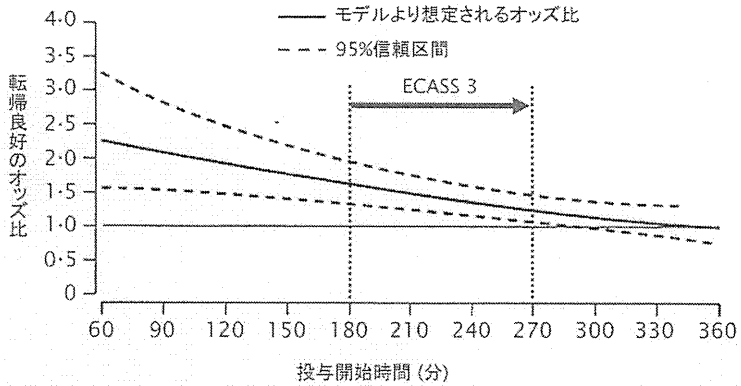

図2　Alteplaseの投与開始時間から見た転帰良好（modified Rankin Scale〔mRS〕：0-1）のオッズ比と95%信頼区間の推定値モデル（文献3より改変）
rt-PA静注法の大規模臨床研究であるATLANTIS，ECASS，and NINDS rt-PA stroke trialsのプールデータを用いた推定値モデルでは，alteplaseの投与が早ければ早いほどその有効性が高いことが示されている（偽薬に対する有効性がオッズ比にて表されている）．

薬の投与）との併用療法によりtherapeutic windowを拡大できるか（図3）[7]，転帰が不良となる症候性頭蓋内出血を減じることができるか，などが課題となる．

一方，rt-PAとしてdesmoteplaseを用いたDIAS研究では，MRIによりdiffusion-perfusion mismatchが認められた症例を対象とした場合，治療のtime windowを発症後3～9時間まで拡大できることが示された[4]．その後の研究で，脳動脈の閉塞部位が明らかなdiffusion-perfusion mismatch出現症例に限って本剤の有効性が示唆された．Desmoteplaseのtime windowの拡大には，神経毒性がなく，フィブリン選択性・特異性が強い薬剤特性からalteplaseとは異なり，症候性頭蓋内出血の出現頻度が低いことも寄与している．

これに対して，局所線溶療法では，閉塞動脈の再開通率が50～70%[2]と高く，発症後6時間以内のtime windowで治療された場合にその有効性が示されている．すなわち，この事実は，閉塞動脈の再開通率が高い血栓溶解療法ほど，早期に高い有効性が得られ，time windowが延長することを示唆している（図4）[3]．また，本治療法では少量の薬剤使用ですむため，薬剤コストの低下と薬剤誘発性の症候性頭蓋内出血の低下も期待できる．

日本では，MELT Japan研究によって，発症から6時間までの中大脳動脈閉塞症に対する選択的urokinase動注療法の有効性が確立している[10]．しかし，本治療法では，Alteplase静注療法が優先され，治療対象が発症後6時間以内の中大脳動脈閉塞症に限られること，手技に要する時間のために残存脳血流が比較的保たれた症例が治療対象となること，カテーテル操作が困難な高齢者が除外されること，などが問題点である．今後は，発症後6時間以内のtime windowを生かして，time windowの短いAlteplase静注療法によって再開通が得られなかった中大脳動脈閉塞症例に対する追加治療として，局所線溶療法を位置付けることを考慮する必要がある．

以上より，血栓溶解療法におけるtime windowの拡大には，再開通率の向上（局所線溶療法の導入），症候性頭蓋内出血の発症率の低減（薬剤特性の改善したrt-PAの使用や脳保護治療の併用），画像による適応症例の選択（diffusion-perfusion

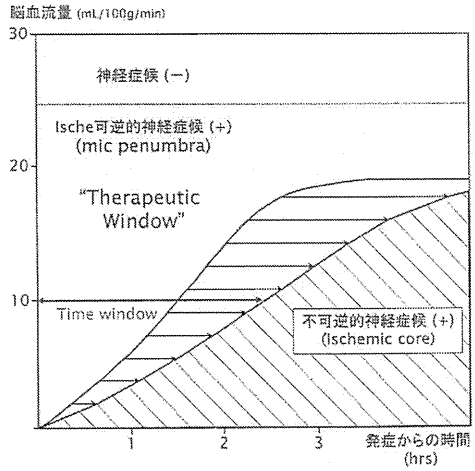

図3　脳虚血に対する急性期の脳保護治療（脳保護薬の投与や低脳温療法）の併用によるtherapeutic windowの拡大（文献7より改変）
急性期脳梗塞に対する脳保護治療の併用により，therapeutic windowの拡大とともに血流再開療法のtime window（⇔）が拡大し，治療適応例の増加とともに転帰の改善が期待される．

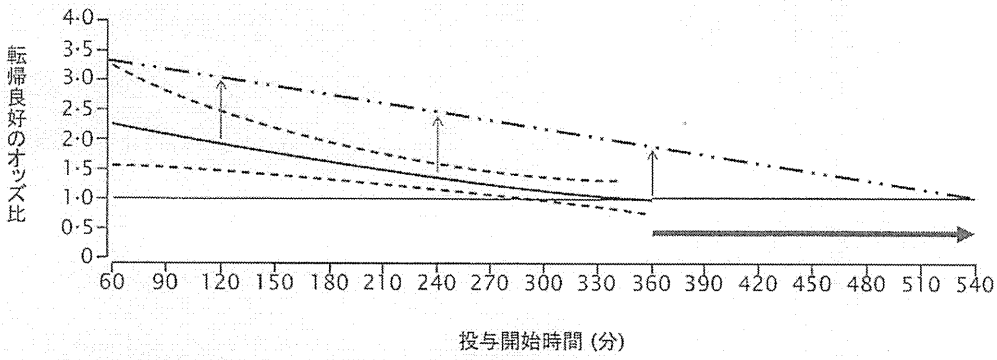

図4　閉塞血管の再開通率が高い血栓溶解療法で推定される投与開始時間から見た転帰良好（mRS: 0-1）のオッズ比（文献3より改変）
閉塞血管の再開通率が高い血栓溶解療法では，Alteplase 静注療法（図2）に比較して，早期に高い有効性（↑）が得られ，time window（→）が延長することが推定される．

mismatch による適応判定）などが寄与すると考えられる．

Ⅳ．血栓回収療法とtime windowの拡大

日本における Alteplase 静注療法の市販後調査[9]や J-ACT 2 の探索的解析[6]によると，その有効性は脳血管の閉塞部位により大きく異なり，内頸動脈閉塞や中大脳動脈近位部閉塞では良好な転帰（mRS 0-1）が得られないことが明らかとなっている（図5）．これらの症例では，Merci Retriever®による血栓回収療法[11]の有効性が期待される．

Merci Retriever®による血栓回収療法の time window は発症から8時間と長く，Alteplase 静注療法が禁忌となる3時間以内の脳主幹動脈閉塞症例や，Alteplase 静注療法後に再開通が得られなかった脳主幹動脈閉塞症例が治療対象となる．本治療法による閉塞血管の再開通率は高く，Alteplase 静注後ではより高い再開通率が得られ，再開通の得られた症例の転帰はきわめて良好である（図6）[11]．

しかし，本治療法では，Alteplase 静注療法が優先されること，脳血管造影カテーテル手技が必要であること，治療の time window が比較的長いことなどから，治療対象症例では，あらかじめ Merci Retriever®のスムーズな導入に向けた対応が必要となる．すなわち，救急搬送された急性期脳梗塞例では，multimodal MRI により脳主幹動脈閉塞の有無および閉塞部位を同定し，diffusion-perfusion mismatch の有無と残存脳血流の程度を評価する．次いで，ただちに脳血管造影室で血管造影カテーテルを導入後に Alteplase 静注療法を開始し，おおむね1時間後に閉塞血管の再開通が得られなければ，Merci Retriever®を導入する．

本治療法の time window は発症から8時間であるとはいえ，残存脳血流がある程度保たれた症

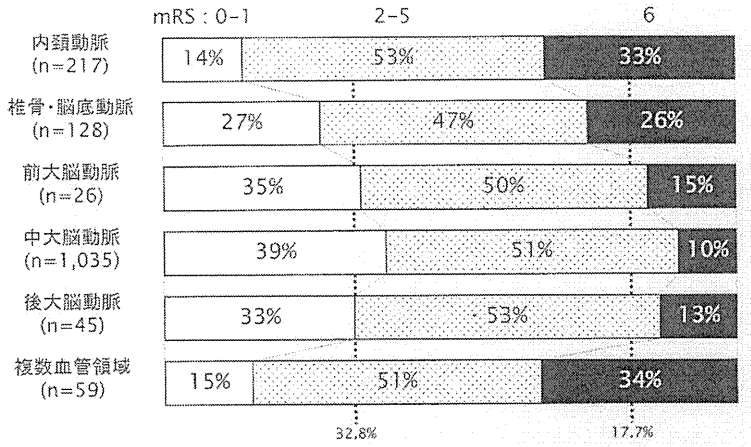

図5　日本の Alteplase 静注療法市販後調査における発症3カ月後の転帰（mRS）：MRI（MRA）による責任血管病変部位別の転帰（文献9より改変）
3カ月後の modified Rankin Scale（mRS）は，内頸動脈と複数血管領域で不良であり，中大脳動脈全体では良好であった．

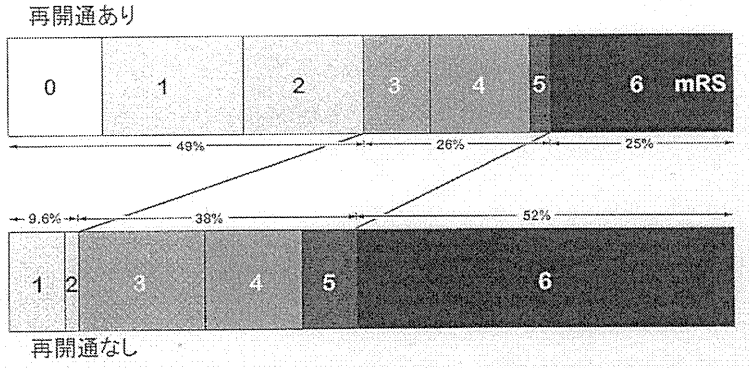

図6　Multi MERCI Trial の最終結果（90日後の mRS）（文献11より改変）
再開通が得られた群の転帰は良好で，49%に良好な転帰（mRS 0-2）が得られたのに対して，再開通が得られなかった群の転帰は不良で，転帰良好（mRS 0-2）は9.6%に止まり，52%が死亡（mRS 6）した．

例では，閉塞血管の再開通により良好な転帰が得られる．逆に，残存脳血流がほとんど保たれていない症例では，閉塞血管の再開通により致命的な出血性脳梗塞を合併する可能性がある．したがって，治療の標的である ischemic penumbra（therapeutic window）をあらかじめ画像として見出すことや脳保護治療の併用が必要と考えられる．

V．おわりに

本稿では，「脳虚血治療の time window を広げる」と題して，血流再開療法の標的病態としての ischemic penumbra と time window との関連，血栓溶解療法や血栓回収療法の time window の拡大に寄与する因子などについて述べた．脳虚血治療の time window を広げるためには，特に閉塞血管の再開通率の向上と症候性頭蓋内出血の抑制が重要である．また，time window が広がるほど，治療の標的である ischemic penumbra（therapeutic window）を画像として見いだすことが重要となる．

各種の治療法の組み合わせによる time window の拡大については，血流再開療法の time window が，固有の有効再開通率に依存していることを想定した検討が必要である．脳虚血治療の time window は，各療法の有効性と安全性を治療群全体として確実に得るために最適化された「治療適用のための時間枠」であり，その拡大についてはよくデザインされた臨床研究によって検証されなければならない．

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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%)

Table 1. Baseline clinical characteristics

Baseline characteristics	Renal dysfunction (eGFR <60 ml/min/1.73 m²) (n = 186)	No renal dysfunction (eGFR ≥60 ml/min/1.73 m²) (n = 392)	p value
Male patients	113 (60.8)	259 (66.1)	0.227
Age, years	76.0 ± 9.8	69.2 ± 12.0	<0.001
Body mass index	22.7 ± 3.2	23.0 ± 3.4	0.397
Hypertension	137 (73.7)	219 (55.9)	<0.001
Diabetes mellitus	37 (19.9)	70 (17.9)	0.568
Dyslipidemia	35 (18.8)	89 (22.7)	0.329
Atrial fibrillation	97 (52.2)	148 (37.8)	0.001
Liver disease	8 (4.3)	9 (2.3)	0.194
Prior ischemic heart disease	37 (19.9)	37 (9.4)	<0.001
Prior ischemic stroke	39 (21.0)	62 (15.8)	0.129
Prior use of antithrombotic agents	92 (49.5)	125 (31.9)	<0.001
Systolic blood pressure, mm Hg	150 ± 20	151 ± 20	0.613
Diastolic blood pressure, mm Hg	80 ± 16	83 ± 15	0.077
Stroke subtype			
Large-artery atherosclerosis	24 (12.9)	65 (16.6)	0.141
Cardioembolism	128 (68.8)	236 (60.2)	
Lacune	5 (2.7)	23 (5.9)	
Other	29 (15.6)	68 (17.4)	
Internal carotid artery occlusion	29 (15.6)	59 (15.2)	0.902
Blood glucose, mmol/l	7.68 ± 2.77	7.61 ± 2.61	0.787
Hemoglobin A1c, %	5.8 ± 1.0	5.8 ± 1.1	0.995
Total cholesterol, mmol/l	4.68 ± 1.07	5.01 ± 1.01	<0.001
Triglyceride, mmol/l	1.30 ± 0.72	1.32 ± 0.95	0.809
HDL cholesterol, mmol/l	1.27 ± 0.36	1.38 ± 0.40	0.003
LDL cholesterol, mmol/l	2.83 ± 0.88	3.01 ± 0.87	0.043
Time to treatment onset, min	145 (121–167)	146 (122–166)	0.991
Admission NIHSS score	13 (7–19)	12 (7.25–18)	0.423

Numbers of patients (%) are shown except otherwise indicated; data are means ± SD or medians (IQR).

patients belonged to stage 3, 15 (2.6%) to stage 4, and 8 (1.4%) to stage 5. Four patients with stage 5 were on maintenance hemodialysis.

The patients with renal dysfunction were older ($p < 0.001$) and more commonly had hypertension ($p < 0.001$), atrial fibrillation ($p = 0.001$), prior ischemic heart disease ($p < 0.001$), and prior use of antithrombotic agents ($p < 0.001$) than patients without renal dysfunction (table 1). Serum total cholesterol ($p < 0.001$), HDL cholesterol ($p = 0.003$), and LDL cholesterol ($p = 0.043$) levels were lower in patients with renal dysfunction than in those without. NIHSS scores were not significantly different between patients with renal dysfunction and those without immediately before [median (interquartile range, IQR); 13 (7–19) vs. 12 (7.25–18), $p = 0.423$] and 24 h after IV rt-PA [9 (3–18) vs. 7 (3–15), $p = 0.070$; fig. 1a].

Any ICH [51 (27.4%) vs. 65 patients (16.6%), $p = 0.004$] as well as symptomatic ICH within 36 h from IV rt-PA therapy [15 (8.1%) vs. 10 patients (2.6%), $p = 0.004$], was more common in the patients with renal dysfunction than in those without. After multivariate logistic regression analysis, renal dysfunction was significantly related to both any ICH (odds ratio, OR, 1.81, 95% confidence interval, CI, 1.16–2.84, $p = 0.009$) and symptomatic ICH (2.64, 1.10–6.56, $p = 0.031$; table 2). When the value of eGFR (a continuous variable) was used instead of eGFR <60 ml/min/1.73 m² (a categorical variable) as an indicator of renal dysfunction, it was related to any ICH (OR 0.89, 95% CI 0.80–0.99 per 10-ml/min/1.73 m² increase, $p = 0.029$) but not symptomatic ICH (0.89, 0.73–1.08, $p = 0.231$).

At 3 months, the patients with renal dysfunction had higher mRS scores than those without [median (IQR); 3

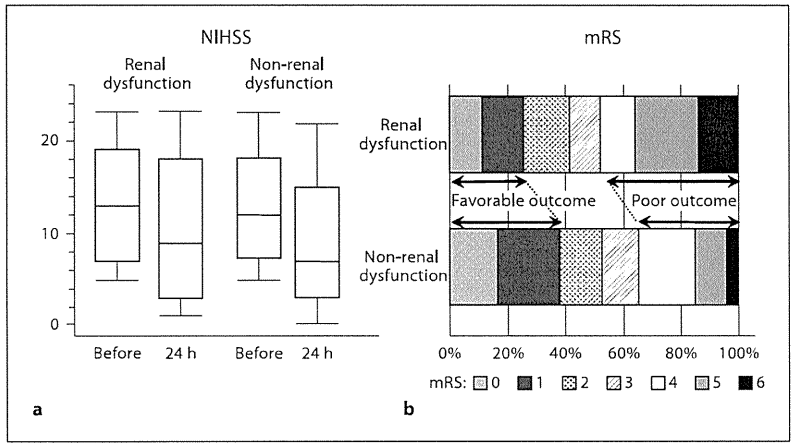

Fig. 1. Neurological deficits and outcome of patients with and without renal dysfunction. NIHSS score just before and 24 h after IV rt-PA therapy (**a**) and mRS score at 3 months (**b**) in patients with and without renal dysfunction. **a** Horizontal lines in boxes = Median NIHSS score; boxes = IQR; whiskers = upper and lower 90% ranges.

Table 2. Characteristics associated with ICH within 36 h

Characteristics	Any ICH			Symptomatic ICH		
	OR	95% CI	p value	OR	95% CI	p value
Male	1.12	0.71–1.78	0.638	1.99	0.74–6.32	0.201
Age (per year)	0.99	0.97–1.01	0.423	1.00	0.96–1.04	0.868
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	1.81	1.16–2.84	0.009	2.64	1.10–6.56	0.031
Atrial fibrillation	1.93	1.24–3.01	0.004	–	–	–
Liver disease	1.53	0.40–4.79	0.488	–	–	–
Prior use of antithrombotic agents	–	–	–	4.31	1.72–12.06	0.003
Blood glucose (per mmol/l)	1.06	0.98–1.14	0.153	1.11	0.96–1.26	0.126
Triglyceride (per mmol/l)	–	–	–	1.00	0.99–1.01	0.174
Admission NIHSS score (per point)	1.03	0.99–1.06	0.069	–	–	–

– = The variable was not included after the backward selection procedure.

Table 3. Characteristics associated with outcome at 3 months

Characteristics	Favorable outcome (mRS 0–1)			Poor outcome (mRS 4–6)			Death		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Male	1.14	0.74–1.76	0.545	0.84	0.55–1.29	0.430	0.68	0.32–1.48	0.331
Age (per year)	0.97	0.96–0.99	0.005	1.04	1.02–1.06	<0.001	1.01	0.97–1.05	0.718
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	0.70	0.44–1.09	0.114	1.55	1.01–2.38	0.046	2.94	1.38–6.42	0.006
Prior ischemic heart disease	–	–	–	–	–	–	4.33	1.84–10.05	<0.001
Internal carotid artery occlusion	0.24	0.10–0.51	<0.001	6.07	3.38–11.39	<0.001	4.32	2.00–9.36	<0.001
Blood glucose (per mmol/l)	0.91	0.84–0.99	0.024	1.08	1.01–1.17	0.033	1.17	1.04–1.31	0.007
Admission NIHSS score (per point)	0.91	0.88–0.94	<0.001	1.11	1.08–1.15	<0.001	1.09	1.04–1.15	<0.001

– = The variable was not included after the backward selection procedure. For favorable outcome analysis, patients with premorbid mRS score 2–3 were excluded.

(1–5) vs. 2 (1–4), $p < 0.001$; fig. 1b]. Twenty-five patients (13.4%) with renal dysfunction had died; of these, 5 died of stroke, 6 of heart disease (4 heart failure, 1 myocardial infarction, and 1 infectious endocarditis), 6 of severe infection (3 sepsis and 3 pneumonia), and 8 of unknown causes. In contrast, 15 patients (3.8%, $p < 0.001$) without renal dysfunction had died; of these, 9 died of stroke, 2 of pneumonia, and 4 of unknown causes. Similarly, favorable outcome was less common [48 (25.8%) vs. 149 patients (38.0%), $p = 0.004$], and poor outcome was more common [89 (47.9%) vs. 136 patients (34.7%), $p = 0.003$] in patients with renal dysfunction than in those without. After multivariate logistic regression analysis, renal dysfunction was significantly related to poor outcome (OR 1.55, 95% CI 1.01–2.38, $p = 0.046$) and mortality (OR 2.94, 95% CI 1.38–6.42, $p = 0.006$), although it was not related to favorable outcome (OR 0.70, 95% CI 0.44–1.09, $p = 0.114$; table 3). When the value of eGFR was used instead, it was significantly related to mortality (OR 0.81, 95% CI 0.67–0.96 per 10-ml/min/1.73 m^2 increase, $p = 0.020$), but not to favorable outcome (OR 1.09, 95% CI 0.99–1.20, $p = 0.081$) or poor outcome (OR 0.95, 95% CI 0.86–1.04, $p = 0.268$).

Discussion

In this observational study, we determined the influence of renal dysfunction on early ICH and the long-term outcome of ischemic stroke patients receiving IV rt-PA therapy. The major finding was that renal dysfunction, defined as reduced eGFR (<60 ml/min/1.73 m^2), which was calculated using the admission creatinine level, was related to any ICH and symptomatic ICH within 36 h, as well as poor outcome (mRS 4–6) and death at 3 months, although it was not related to favorable outcome (mRS 0–1).

According to the result of the largest postmarketing surveillance on rt-PA, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study [21], advanced age, body weight, atrial fibrillation, high systolic blood pressure, hyperglycemia, admission NIHSS score, and current infarction on baseline imaging scans were associated with symptomatic ICH. In addition, advanced age, male sex, use of antiplatelet agents other than aspirin, congestive heart failure, higher diastolic blood pressure, hyperglycemia, higher NIHSS score, current infarction, and premorbid dependency were related to death at 3 months. Similar results have been reported in several other studies [22–26]. However, these studies did not assess renal dysfunction as a potential factor affecting stroke outcome. The present study is unique in that renal dysfunction was included as a potential factor and was proven to be associated with patient outcome after rt-PA.

Alteplase is metabolized by the liver, and liver function affects the half-life of alteplase [27]. In this study, liver disease was not associated with stroke outcome. In contrast, renal dysfunction might not prolong the half-life of alteplase. For example, the plasma concentration-time profile of alteplase was not altered after bilateral nephrectomy in rat models [28].

Renal dysfunction is a bystander of stroke, since it is associated with traditional vascular risk factors, including aging, hypertension, diabetes mellitus, dyslipidemia, and smoking [29]. In addition, renal dysfunction is now known to be an independent predictor for stroke [1, 2, 5, 30, 31], partly via nontraditional vascular risk factors, e.g. inflammatory factors, and homocysteinemia. However, the effect of these nontraditional risk factors on stroke outcome has not been clarified, in particular after rt-PA. In patients with acute stroke not receiving IV rt-PA, albuminuria was independently associated with hemorrhagic transformation [32]. Since ICH is a major cause of poor outcome for thrombolysed patients, renal dysfunction may affect chronic outcome after rt-PA via increasing ICH risk. Moreover, renal dysfunction might impair endothelial release of t-PA [33], and increase plasminogen activator inhibitor-1 activity [34] and plasma levels of lipoprotein(a) [35]; these abnormalities might obstruct the reperfusion phenomenon and worsen stroke outcome after IV rt-PA.

An interesting finding regarding the patients who died was that indirect death other than stroke was common as the cause of death for patients with renal dysfunction, though direct stroke death accounted for most of the causes of death for patients without renal dysfunction. This finding suggests that patients with renal dysfunction often had heart problems and susceptibility to infection, developed dependency and died due to non-stroke complications.

Certain limitations need to be considered prior to interpretation of the present results. First, patients who did not receive IV rt-PA were not included in this study. Thus, the influence of renal dysfunction on stroke outcome could not be compared between patients who were treated with rt-PA and those who were not. Second, renal dysfunction was correlated with older age, hypertension, atrial fibrillation, prior ischemic heart disease, and prior use of antithrombotic agents, and this multicolineality may inflate the variances of the parameter estimates. Thus, the present association of renal dysfunction with outcome measures after multivariate analyses may be

overestimated to some extent. Third, eGFR was not measured prior to stroke onset, and therefore eGFR may have been affected by stroke. Fourth, eGFR was calculated using admission creatinine levels, which may have been impaired by acute stroke effects. Repeated assessment in the chronic stroke stage is needed to ascertain that the present patients with reduced eGFR have chronic kidney disease. Fifth, urinary albumin was not measured. Generally, urinary albumin increases during acute ischemic stroke [36]. Finally, the present results based on low-dose rt-PA therapy (0.6 mg/kg) may not be applicable to the regular dose therapy (0.9 mg/kg).

In conclusion, reduced eGFR based on the admission creatinine level was predictive of an unfavorable outcome after IV rt-PA in acute stroke patients. In patients with renal dysfunction, additional therapeutic strategies to improve the efficacy of rt-PA are needed.

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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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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

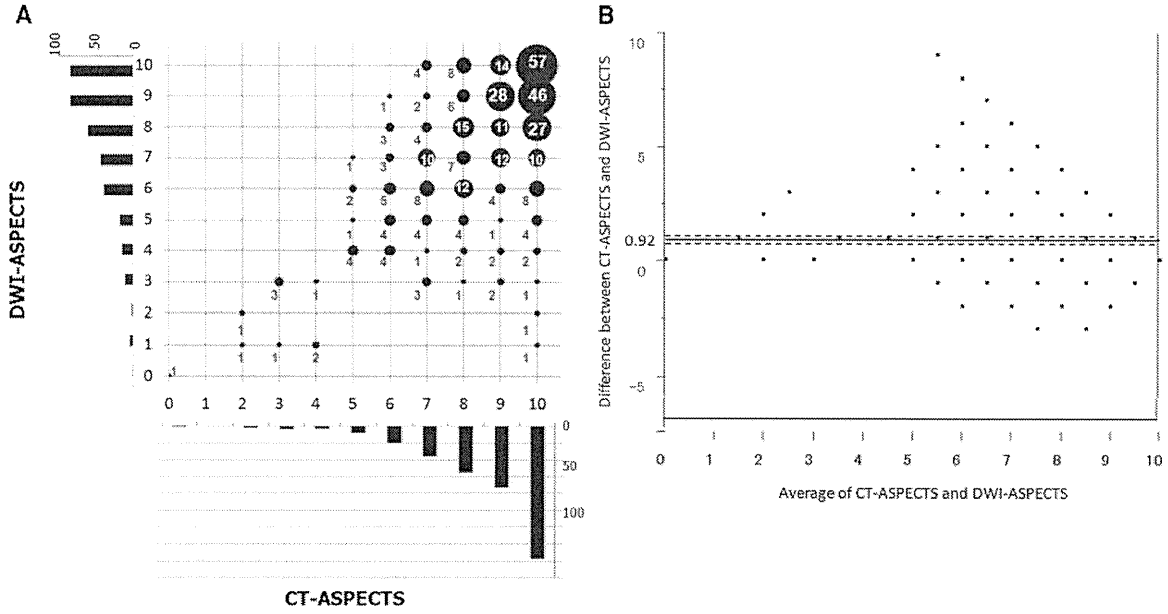

Figure 1. Number of patients assessed using CT-ASPECTS and DWI-ASPECTS (**A**). Bland and Altman plot of CT-ASPECTS and DWI-ASPECTS. The mean difference between CT-ASPECTS and DWI-ASPECTS was +0.92. The horizontal line showed the mean difference in scores and the dotted lines showed the 95% CI (**B**). 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