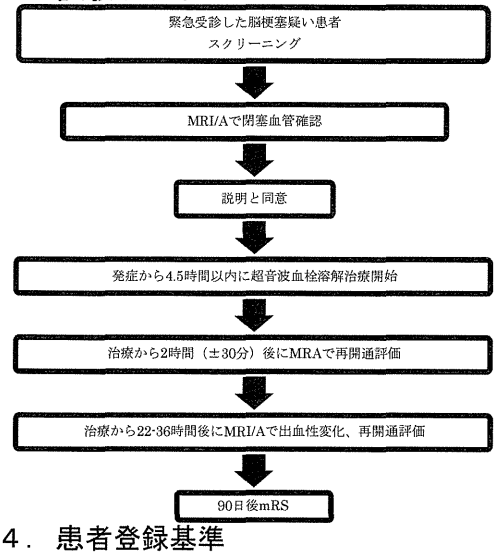
３．試験デザイン



４．患者登録基準

- 年齢20歳以上
- 脳梗塞による神経症候を呈する
- NIHSS 5-25
- 発症前mRS 0-1
- MRAでM1-M2, A1-A2, P1-P2閉塞, (ICA閉塞)
- 発症4.5時間以内に治療可能
- 書面による本人または代諾者の同意
- 超音波側頭骨窓の有無は問わない

５．患者除外基準

- 適正治療指針での適応外
- MRI検査不能の患者
- 試験期間中に頭部・頸部の手術や血管内治療を予定している患者
- 妊婦、授乳中の患者、妊娠している可能性のある患者
- 余命6ヵ月未満と予測される末期の疾患を有する患者
- その他、試験担当医師が不適当と判断する患者

６．主要評価項目

安全性評価項目

- 36時間以内のNIHSS4点以上増悪するCT上の症候性頭蓋内出血
- 90日後の死亡

有効性評価項目

- 治療開始から2時間（±30分）後のMRA上の再開通率（modified Mori Grade 2-3）

７．副次評価項目

- 22-36時間後のMRA上の再開通率（modified Mori Grade 2-3）
- 90日後のmRS 0-1の割合
- 90日後のmRS 0-2の割合
- NIHSSスコアの経時的推移

８．症例数

国内で実施されたJ-ACT II研究では、1年半で58名の対象者を登録している。本研究の対象の多くは、J-ACT II研究で対象であった中大脳動脈閉塞患者である。提供を受けることが可能な装置の台数、研究期間、同意率などを考慮して実施可能な症例数を統計専門家に相談する。

９．安全性評価基準

- 独立安全性評価委員会を設置
- 安全性評価の手順書を別途作成
- 委員会は報告を受けた有害事象、不具合と治験装置との因果関係の妥当性及び治験継続の適否、治験実施計画改訂の要否等について審議および評価し、提言する

１０．ロードマップ案

新規超音波血栓溶解装置概要の確定
2013年10月

- プロトコール大枠の確定
  2013年12月
- プロトコール案作成
  2014年3月
- プロトコール確定
  2015年3月

Ｄ．考察

新規超音波血栓溶解装置の開発状況、虚血性脳卒中の急性期治療の現状およびこれまで行われてきた様々な臨床試験を考慮して、新規装置の治験プロトコール案を作成した。この案をたたき台として、班員、研究協力者および外部の専門家からの意見を収集し2015年3月頃に治験プロトコールを確定する予定である。

F. 研究発表

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2. 学会発表

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3. 黒沼由香, 古賀政利, 徳永敬介, 滝沢歩武, 宮下光太郎, 伊庭裕, 豊田一則. 頸動脈エコーで rt-PA 静注療法を直前に回避し緊急人工血管置換術により経過が良好であった急性大動脈解離を有する脳梗塞の 1 例. 第 32 回日本脳超音波学会総会、徳島、2013 年 6 月
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G. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

厚生労働科学研究費補助金（医療機器開発推進研究事業）
分担研究報告書

MRA/DSAによるrt-PA施行虚血性脳卒中の閉塞血管早期再開通率の検討

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研究要旨
現在開発中の新規超音波血栓溶解装置の臨床導入に向けて、同装置の開発状況、虚血性脳卒中の急性期治療の現状を踏まえて、近い将来予定している治験プロトコール大枠を提案した。治験デザインは、単一治療群、オープンラベル、ヒストリカルデータ対照試験とした。発症4.5時間以内の頭部MRAで脳主幹動脈閉塞を確認した虚血性脳卒中患者を登録する。主な除外基準はアルテプラーゼ（rt-PA）静注療法適正治療指針の適応外である。安全性の主要評価項目は、治療開始から22-36時間の頭部CTで確認されたNIHSS4点以上増悪する症候性頭蓋内出血、発症90病日後の死亡、有効性の主要評価項目は、治療開始から120±30分後のMRA上の再開通（modified Mori Grade 2-3）率とする。現在当施設で収集しているヒストリカルデータなどを対照データとして安全性および有効性の評価を行う。独立安全性評価委員会を設置し安全性のモニターを行う。

A．研究目的

我々は，慈恵会医大グループと共同で低侵襲的低周波超音波装置を用いた急性期血栓溶解療法の臨床試験を計画している．当該試験計画策定に必要な対照データ収集を目的として，急性期虚血性脳卒中に対するrt-PA静注療法例において，超音波照射を併用しない場合の早期再開通率，症候性頭蓋内出血率と3ヵ月後転帰を調べ，データの更新を行った

B．方法

対象は平成17年10月から平成25年4月までの当院rt-PA静注療法施行の384例である．検討項目は，患者背景，脳梗塞病型，MRAもしくは脳血管造影検査（DSA）による血管閉塞部位（内頸動脈（ICA），前大脳動脈（ACA），中大脳動脈（MCA），後大脳動脈（PCA），椎骨脳底動脈（VB）系，閉塞血管なし，評価不能），主幹動脈（ICA，ACA，MCA，PCA）に閉塞があり発症2時間以内にMRAもしくはDSAで再開通の評価をおこなった症例の2時間後，24時間後の再開通の有無を調べた．発症36時間以内のNational Institutes of Health Stroke Scale（NIHSS）4点以上の増悪を伴う頭蓋内出血を症候性頭蓋内出血と定義し，転帰は3ヶ月後の日常生活自立度［modified Rankin Scale（mRS）］で評価し，mRS0-1を転帰良好，mRS0-2を日常生活自立とした．なお，rt-PA静注療法後に閉塞血管に対して経皮経管的脳血栓回収用機器（Merciリトリーバー，PENUMBRAシステム）を使用した症例は，24時間後の再開通の評価と症候性頭蓋内出血，3ヶ月後の転帰の評価からは除外した．また，3ヶ月後の転帰が確認できなかった症例も3ヶ月後のmRSの評価からは除外した．

MRAの再開通の評価にはModified Mori gradeを使用し，Grade2以上の場合に再開通ありとした．DSAの再開通の評価にはThrombolysis in Cerebral Infarction 分類を使用し，Grade2以上の場合に再開通ありとした．

MRAとDSAを併用した評価として，grade0：MRAでmodified Mori grade0, DSAでTICI0，　grade1：MRAでmodified Mori grade1，　DSAでTICI1，

grade 2：MRAでmodified Mori grade2, DSAでTICI2A, grade3：MRAでmodified Mori grade3, DSAでTICI2B, 3という分類を作成し使用した（図1）.

図1 再開通の評価

- MRA：modified Mori grade 0,1,2,3
- DSA: TICI 0,1,2A,2B,3
- MRAとDSAを合わせた評価
  - grade0: MRAでmodified Mori grade 0, DSAでTICI 0
  - grade1: MRAでmodified Mori grade 1, DSAでTICI 1
  - grade2: MRAでmodified Mori grade 2, DSAでTICI 2A
  - grade3: MRAでmodified Mori grade 3, DSAでTICI 2B,3

（倫理面への配慮）
ヒストリカルデータの収集に関する研究は，国立循環器病研究センターの倫理委員会で承認を受けた.

C. 研究結果

患者背景を表1にまとめる．患者は384例，平均年齢は74±13歳であった．男性が63%，既往症は高血圧67%，糖尿病20%，脂質代謝異常35%，心房細動53%であった．臨床病型はラクナ梗塞1%，アテローム血栓性脳梗塞13%，心原性脳塞栓65%，その他の脳梗塞が22%であった．治療前の閉塞血管は内頸動脈（ICA）63例（16%），前大脳動脈5例（1%），中大脳動脈（MCA） M1 120例（31%），M2 61例（16%），後大脳動脈14例（4%），椎骨脳底動脈12例（3%），閉塞血管なし78例（20%），評価不能29例（8%），その他2例（1%）であった．血管内治療が施行されたのは34例であり，閉塞血管はICA15例，M1 12例，M2 1例，椎骨脳底動脈6例であった.

表1 患者背景（n=384）

年齢	74±13歳	閉塞血管	
男性	63%	ICA	16%
高血圧	67%	ACA	1%
糖尿病	20%	MCA	
脂質代謝異常	35%	M1	31%
心房細動	53%	M2	16%
臨床病型		PCA	4%
ラクナ	1%	椎骨脳底動脈	3%
アテローム血栓性	13%	閉塞血管なし	20%
心原性	65%	評価不能	8%
その他	22%	その他	1%

M1，M2，ICA，ACA，PCA閉塞のMRA，DSA，MRAとDSAの併用による再開通の評価を表に示す（表2）.

表2 MCA M1閉塞（n=120）

MRAでの再開通率(modified Mori grade) 例

	0	1	2	3	合計
2時間	19	1	13	5	38
24時間	18	1	12	7	38

DSAでの再開通率(TICI)

	0	1	2A	2B	3	合計
2時間	12	1	0	2	1	16

MRA,DSAでの再開通率(modified Mori grade,TICI)

	0	1	2	3	合計
2時間	24	2	11	6	43
24時間	20	2	11	8	41

※血管内治療が施行された患者は24時間後の評価から除外

MRAとDSAを併用した評価では，M1閉塞の再開通率は2時間以内が40%，24時間以内が46%であり（表2），M2閉塞の再開通率はそれぞれ，71%，71%（表3），ICA閉塞の再開通率はそれぞれ23%，32%であった（表4）.

表3 MCA M2閉塞（n=61）

MRAでの再開通率(modified Mori grade) 例

	0	1	2	3	合計
2時間	4	0	6	4	14
24時間	4	0	6	4	14

DSAでの再開通率(TICI)

	0	1	2A	2B	3	合計
2時間	1	0	0	0	0	1

MRA,DSAでの再開通率(modified Mori grade,TICI)

	0	1	2	3	合計
2時間	4	0	6	4	14
24時間	4	0	6	4	14

※血管内治療が施行された患者は24時間後の評価から除外

表4 ICA閉塞(n=63)

MRAでの再開通率(modified Mori grade) 例

	0	1	2	3	合計
2時間	9	3	3	1	16
24時間	6	4	3	2	15

DSAでの再開通率(TICI)

	0	1	2A	2B	3	合計
2時間	12	0	2	0	0	14

MRA,DSAでの再開通率(modified Mori grade,TICI)

	0	1	2	3	合計
2時間	17	3	5	1	26
24時間	11	4	5	2	22

※血管内治療が施行された患者は24時間後の評価から除外

M1，M2閉塞を合わせたMCA閉塞患者の再開通率はそれぞれ47%，53%，ICA，ACA，MCA，PCA閉塞患者の再開通率はそれぞれ38%，49%（表5），ACA，MCA，PCA閉塞患者の再開通の評価では，それぞれ44%，48%であった（表6）．

表5　ICA,ACA,MCA,PCA (n=263)

MRAでの再開通率(modified Mori grade)　例

	0	1	2	3	合計
2時間	36	5	22	10	73
24時間	32	6	21	13	72

DSAでの再開通率(TICI)

	0	1	2A	2B	3	合計
2時間	25	1	2	2	1	31

MRA,DSAでの再開通率(modified Mori grade,TICI)

	0	1	2	3	合計
2時間	48	7	22	11	88
24時間	39	8	24	16	82

※血管内治療が施行された患者は24時間後の評価から除外

表6　ACA,MCA,PCA (n=200)

MRAでの再開通率(modified Mori grade)　例

	0	1	2	3	合計
2時間	27	2	19	9	57
24時間	26	2	18	11	57

DSAでの再開通率(TICI)

	0	1	2A	2B	3	合計
2時間	13	1	0	2	1	17

MRA,DSAでの再開通率(modified Mori grade,TICI)

	0	1	2	3	合計
2時間	31	4	18	9	62
24時間	27	4	18	11	60

※血管内治療が施行された患者は24時間後の評価から除外

症候性頭蓋内出血は全体では8例（2.3%）であり，M1 閉塞の2.8%，M2閉塞の5.0%，ICA閉塞の4.2%，ICA，ACA，MCA，PCA閉塞患者の3.4%，ACA，MCA，PCA閉塞患者の3.2%であった（図2）．

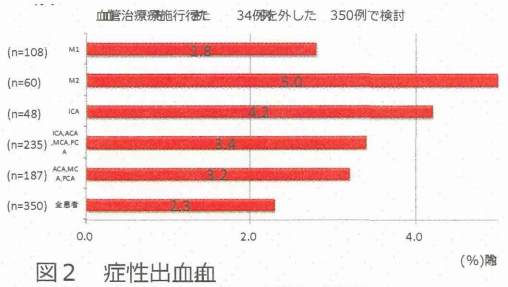
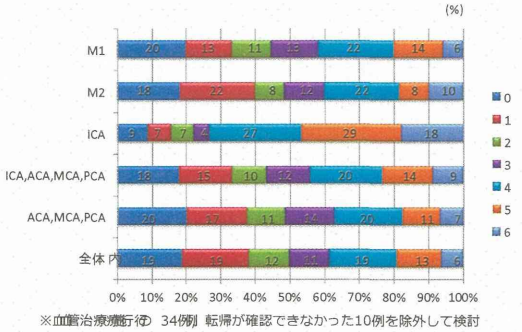


図2　症性出血血
（発症36時間以内，NIHSS4点以上の増悪）

3ヶ月後の日常生活完全自立は，血管内治療を施行された34例と，転帰を確認できなかった10例を除外した340例では，転帰良好（mRS，0-1）は全体で38%，ICA，ACA，MCA，PCA閉塞患者で33%，ACA，MCA，PCA閉塞患者で37%，日常生活自立（mRS，0-2）は全体で50%，ICA，ACA，MCA，PCA閉塞患者で43%，ACA，MCA，PCA閉塞患者で48%であった（図3）．



※血管治療療施行された　34例例　転帰が確認できなかった10例を除外して検討

図3　3ヶ月後mRS

D．考察

現在計画中である超音波血栓溶解療法の対照データ収集を行い，データを更新した．MRA，DSAを用いたM1閉塞の再開通率は，2時間後47%，24時間後50%，M2閉塞の再開通はいずれも71%，ICA閉塞の再開通率は各々23%，32%，MCA（M1，M2）閉塞患者の再開通率は各々47%，53%，ICA，ACA，MCA，PCA閉塞患者の再開通率は38%，49%，ACA，MCA，PCA閉塞患者の再開通率は44%，48%であった．

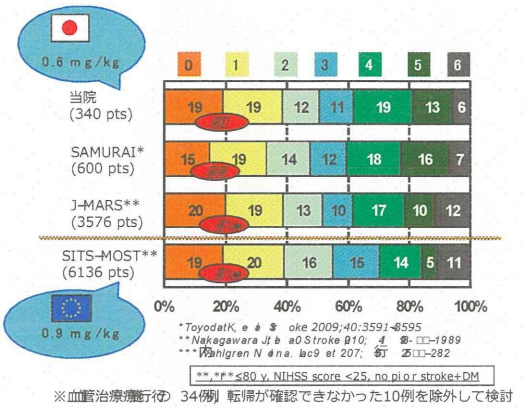
過去にrt-PA投与後に閉塞血管の再開通を評価している研究がいくつか報告されている．

現在までに，rt-PA静注療法後の再開通の評価は，rt-PA投与量は0.6mg/kg，0.9mg/kgの2種類の報告があり，TCD，CTA，MRA，DSAといった異なる評価手段を用いており，評価のタイミングも様々であった．今回我々はMRA，DSAの所見のみを用いて検討を行った．TCDやTCCSを除外した理由は，日本人ではTCDやTCCSにおいて側頭骨窓が不良であり，血流が流れていても頭蓋内血管が描出されない可能性が高いためである

今回の結果のうちM1とM2を合わせた24時間後の再開通率を，本邦から報告されているJ-ACTⅡの再開通率である69%（40例/58例）やKimuraら再開通率80.9%（34例/42例）と比較すると，24時間後の再開通率がやや低い傾向があった．MCA閉塞患者に占めるM1閉塞，M2閉塞の患者数の比率は今回の検討，過去の報告とも2対1であった．J-ACTⅡやKimuraらの報告と今回の我々のMRAとDSAを合わせた再開通率の結果を合わせると，M1，M2閉塞患者の24時間後の再開通率は66%と計算された．

今回は，PCAやACAの再開通率も含めて検討した点が過去の報告と比べ新しい点である．CTのみでrt-PA静注療法を施行する施設も多く，閉塞血管の評価を行わずに新規超音波血栓溶解装置を使用することを想定し，PCAやACA閉塞を含めた検討を行った．

症候性頭蓋内出血は欧州の市販後調査であるSITS-MOSTの1.7%，本邦の市販後調査であるJ-MARS研究の3.5%，10施設の市販後調査であるSAMURAI rt-PA登録研究の 1.3%と同様の結果であった．3ヶ月後の日常生活完全自立も，SITS-MOSTの39%，J-MARSの39%，SAMURAI rt-PA登録研究の33%と同様の結果であった（図4）．



※血管治療施行例 34例 転帰が確認できなかった10例を除外して検討

図4　3ヶ月後mRS

今回，24時間後の再開通の評価と症候性頭蓋内出血，3ヶ月後の転帰の評価において，rt-PA静注療法後に閉塞血管に対して経皮経管的脳血栓回収用機器を使用した症例は除外した．また，3ヶ月後の転帰が確認できなかった症例も3ヶ月後のmRSの評価からは除外した．これは，今回の検討がrt-PA静注療法がもたらす再開通率や転帰のみを評価することが目的であったためであるが，血管内治療を受ける機会が多いICA閉塞やM1起始部閉塞患者はrt-PA静注療法のみでは24時間後も血管が閉塞していた可能性があり，24時間後の再開通率のデータの取扱いには注意が必要であろう．

我々の研究にはいくつかの問題点がある．1つ目は一部後ろ向きの観察研究であること．2つ目MRAやDSAの検査のタイミングが決まっておらず，症例によって検査の施行時間に多少幅があったことがあげられる．

E．結論

急性期脳梗塞に対するrt-PA静注療法時に，MRA，DSAによる血管閉塞や再開通など頭蓋内血管の経時的観察を行い，超音波血栓溶解療法を併用しない場合の閉塞血管再開通頻度や時期を評価し，データの更新を行った．これらのデータを基に，新規超音波血栓溶解装置の治験プロトコールの策定を行う．

F．研究発表

1. 論文発表

なし

2. 学会発表

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G．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

厚生労働科学研究費補助金（医療機器開発推進研究事業）
分担研究報告書

経頭蓋カラードプラ法における探触子頭部固定具の開発

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研究要旨
固定の難しさ故に市販品が存在しない経頭蓋カラードプラ法用の探触子頭部固定具を、有限会社アンリミット・ジャパンと共同で開発した。ヘルメット型の頭部固定装置の試作型1号、2号を改良し、3号を完成させた。患者を対象とした臨床試験では、実用に耐えうる成績を上げている。今後は、臨床での評価を継続し、商品化を目指していく方針である。

A．研究目的

経頭蓋ドプラー (TCD)装置用の探触子頭部固定具は市販されているが、経頭蓋カラードプラ (TCCS)装置用探触子固定具は市販されていない。この探触子はより大型で重く、固定が難しいためと考えられる。今回、有限会社アンリミット・ジャパンと共同で、TCCS装置用の探触子頭部固定具を開発した。

B．　方法

アンリミット・ジャパンと共同で開発した頭部固定具の試作型3号機を、実際に患者に使用し、有用性について評価した。

対象は平成25年7月から平成26年3月までの当院に入院した患者を対象とした。TCCSで側頭骨窓から脳血管の観察が可能な患者で、固定具を使用し頭蓋内血流が安定して観察可能か、脳梗塞の原因となる微小栓子シグナル(microembolic signal: MES)の検出が可能か、奇異性脳塞栓症の原因となる右左シャントの判定が可能か否か、血管同定までの時間と頭部装着感等をTCDの頭部固定具と比較し、それぞれについて検討した。

(倫理面への配慮)

本研究は、侵襲性が極めて低い検査であるが、研究実施前に国立循環器病研究センター倫理委員会の承認を得た。被験者のインフォームド・コンセントを得た上で検査を行った。

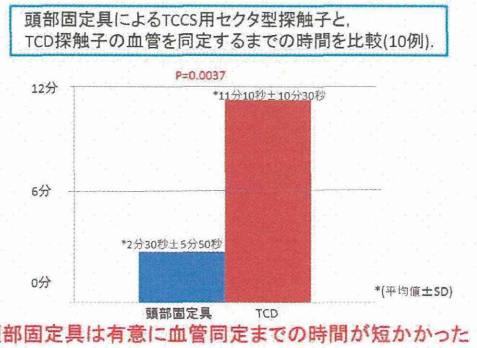
C．　研究結果

対象期間中に10例(男性9例、59.7±21.3歳)の患者に検査を行った。

全ての症例で15～30分間の安定した固定が可能で、右左シャントを含む検査が1人で可能であった。

患者1例で右左シャントの判定が可能であり、9例が「装着感が大変良い」と回答した。

TCCS用探触子頭部固定具と、TCD用探触子頭部固定具で血管を同定するまでの時間を10例で比較した。TCCS用探触子では2分30秒±5分50秒(平均値±SD)、TCD用探触子では11分10秒±10分30秒(p=0.0037)であり、TCCS用探触子頭部固定具は有意に血管同定までの時間が有意に短かった(図)。



頭部固定具は有意に血管同定までの時間が短かかった

D．考察

今回開発したTCCS用探触子頭部固定具は、TCCSで血管を視認しながらその同定ができるため、TCD用探触子頭部固定具に比べ短時間で血管同定が可能であった。頭部装着感や、固定の保持性、安定性も優れていた。今後は症例を蓄積し、MESの検出力がTCDと同等であれば、TCDの代替の検査法として、今後、探触子頭部固定具を用いたTCCSが普及する可能性がある。

また、経食道心エコーで右左シャントを確認するには数人が必要であるが、TCCS用頭部固定具による右左シャントの検査であれば1人で可能であり、検査に割ける人数が少ない場合に有用かもしれない。

今後、MRAや脳血管造影検査で血管閉塞が診断された急性期脳卒中患者に対し、TCCS用探触子頭部固定具により閉塞血管の再開通の評価ができれば、ベッドサイドで簡易にできる検査として有用であると考えられる。

E．結論

TCCS用探触子頭部固定具を開発した。更に臨床応用を重ねたい。今後は、商標の取得、意匠の出願等を行い、商品化を支援したい。

F．健康危険情報

なし

G．研究発表

なし

H．知的財産権の出願・登録状況

なし

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
	なし						

雑誌

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Stroke Incidence and Usage Rate of Thrombolysis in A Japanese Urban City: The Kurashiki Stroke Registry

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Background: To investigate stroke incidence and rate of thrombolytic therapy in an urban city of around 500,000 residents. *Methods:* Patients suffering acute stroke in Kurashiki City (population 474,415) between March 2009 and February 2010 (inclusive) and admitted to 1 of 10 hospitals throughout the city were prospectively enrolled. *Results:* We enrolled patients with first-ever stroke (n = 763; men 415; median age 72 years) and first-ever/recurrent stroke (n = 1009; men 552; median age 73 years). Among first-ever strokes, 68% were cerebral infarctions, 23% were intracerebral hemorrhages, and 8% were subarachnoid hemorrhages. Crude incidences for first-ever stroke per 100,000 residents were 159.8 (95% confidence interval [CI] 148.4-171.1) for all strokes, 108.8 (95% CI 99.4-118.1) for cerebral infarction, and 36.5 (95% CI 31.0-41.9) for intracerebral hemorrhage. After adjustment using the world population model, age-adjusted incidences were 60.7 (95% CI 45.4-75.9) for all strokes, 38.4 (95% CI 26.3-50.5) for cerebral infarction, and 16.1 (95% CI 8.3-24.0) for intracerebral hemorrhage. Among 698 cases with first-ever and recurrent cerebral infarction, thrombolysis was administered for 31 (5%). Of 197 cerebral infarction patients admitted within 3 hours of onset, the thrombolysis rate was 16%. *Conclusion:* In this urban Japanese city, the age-adjusted incidence of first-ever stroke between March 2009 and February 2010 was 60.7 per 100,000 residents, which was relatively low compared with findings for other countries. Thrombolysis was given to approximately 5% of patients with acute ischemic stroke. **Key Words:** Cerebral hemorrhage—cerebral infarct—epidemiology—stroke incidence—thrombolysis.

The socioeconomic burden caused by stroke in both Japan and high-income Western countries is likely to grow as the populations age.[1] With regard to stroke incidence in Japan, we have been able to refer to a couple of ideal studies,[2-4] with the most recent revealing a stroke incidence of approximately 120 per 100,000 adjusted by

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the Japanese standard population model.[4] However, we are uncertain of equivalent data for stroke incidence adjusted by the world standard population model in comparison with findings for other districts. In addition, previous investigations have been conducted in rural districts with small populations (<100,000), and most patients had been diagnosed with stroke based on computed tomography (CT), not by magnetic resonance imaging (MRI).

Since the approval of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) by the Japanese government in 2005, safety and efficacy of IV rt-PA from retrospective and observational surveillance in Japan have appeared similar to those reported by the National Institute of Neurological Disorders rt-PA Stroke Trial,[5,6] but no epidemiologic inspections of IV rt-PA use have been described, such as the usage rate of IV rt-PA per stroke patient in a Japanese urban city of 474,415 residents. In order to plan adequate health care for individuals suffering acute stroke in Japan, we established a prospective stroke register to determine approximate stroke incidence based on MRI and usage rate of IV rt-PA in Kurashiki City, a city in midwestern Japan able to provide a high level of specialized stroke care.

Methods

Kurashiki City, adjacent to Okayama City, is the second largest community (covering 354.7 km^2) in Okayama Prefecture in midwestern Japan. The population of the city has been stable for several years (2009 population 474,415; men 232,244) and has been shown to be representative of a medium-sized Japanese city.[7]

Study Protocol and Stroke Ascertainment

We used Kurashiki Stroke Registry investigators from the Kurashiki City Public Health Center, Kurashiki City Medical Society, 2 comprehensive stroke centers, and 8 primary stroke centers to collect the data. Acute stroke patients who were treated within 7 days of onset at one of these 10 stroke centers were prospectively registered between March 2009 and February 2010. Paramedics in the Kurashiki City emergency medical service transferred possible acute stroke patients to these 10 stroke centers. We had already established an excellent consultation system between stroke centers and outpatient clinics, and consequently acute stroke patients who went to an outpatient clinic, with or without a stroke specialist, were referred to one of these 10 stroke centers.

All data were recorded, including clinical background (gender, age, and cohabitation status), vascular risk factors (history of hypertension, diabetes mellitus, dyslipidemia, and smoking), alcohol consumption, atrial fibrillation, past history of illness (stroke and ischemic heart disease), interval from onset to stroke center, method of admittance (ambulance transference), diagnosis of cerebrovascular disease (cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage), use of IV rt-PA based on previously published criteria,[8] and in-hospital death. The diagnosis of stroke within 7 days of onset was determined on the basis of the neurologic examination. In principle, stroke was defined as a focal neurologic deficit persisting for >24 hours, classified into categories of cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, or other/unknown. Neuroimaging including MRI was performed for all stroke patients. If contraindicated, CT was used. Subjects who died within 24 hours of symptom onset and had evidence of stroke on neuroimaging were also included as stroke cases. After investigators recorded the data on check sheets, these sheets were sent to the central office of the Kurashiki Stroke Registry at the Kurashiki City Public Health Center. The protocol for this investigation was approved by the ethics committee of Kawasaki Medical School.

Statistical Analysis

We calculated the gender- and age-specific rates of first-ever stroke (all subtypes of stroke, cerebral infarction, and intracerebral hemorrhage) per 100,000 residents of Kurashiki City after categorizing all cases into 17 age groups; <10, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and ≥85 years. We also analyzed the first-ever stroke incidence using the age distribution of the Japanese population from the 2005 census (Japanese model population 127,767,000),[9] the European standard population model, and the Segi standard population model (Segi model) using the direct method.[10] Direct method is the adjustment of crude rate to eliminate the effect of differences in population age structures when comparing crude rates for different periods of time, different geographic areas, and/or different population subgroups, as follows:

$$SR = (SUM(ri * Pi))/SUM\ Pi$$

where SR is the age-adjusted rate for the population being studied, ri is the age group–specific rate for age group i in the population being studied, and Pi is the population of age group i in the standard population.

The standard population used for purposes of international comparisons is generally the Segi model. Five-year age groups should normally be used (eg, <10, 10-14, 15-19...80-84, and 85). Because the age distribution was quite different between the Japanese population and the Segi standard model (eg, 15% of >70 years old in Japanese population *v* 4% in the Segi model), age-adjusted incidence by Segi model is extremely lower than crude incidence, especially in a disease occurring in elder residents. The 95% confidence interval (CI) was calculated for all incidence rates.

We compared age-adjusted incidences of all strokes,[1,4,11-24] cerebral infarctions,[1,4,16,24] and intracerebral

hemorrhages[1,4,16,24] between the present and previous reports. We referred to the age-adjusted incidence based on the Segi model and the average incidence according to the incomes of different countries as described in a 2009 systematic review.[1] We also calculated the usage rate of IV rt-PA per all cerebral infarctions and hyperacute cerebral infarction within 3 hours of onset.

Significant trends were examined using the Chi-square and the Mann–Whitney *U* tests. Statistical analyses were performed using PASW statistics software (version 18.0; SPSS, Inc, Chicago, IL). $P < .05$ was considered statistically significant.

Results

Between March 2009 and February 2010, the number of stroke patients hospitalized in the 10 facilities was 1009, including first-ever and recurrent stroke patients (men 552; median age 73 years; 25th-75th percentile; 64-80 years) among 474,415 residents. Of these 1009, there were 763 cases of first-ever stroke (men 415; median age 72 years; 25th-75th percentile; 62-80 years; Table 1). Male patients were significantly younger than female patients (first-ever and recurrent stroke 70 years for men *v* 76 years for women [$P < .001$]; first-ever stroke 69 years for men *v* 75 years for women [$P < .001$]). Diabetes, smoking, and alcohol consumption were more frequently seen in men than women. The 763 cases of first-ever stroke included 516 (68%) cerebral infarctions (287 men) and 173 (23%) intracerebral hemorrhages (103 men). Thrombolysis was performed for 31 (5%) of the 698 first-ever/recurrent cerebral infarction cases, and these 31 comprised 16% of the 197 cases admitted within 3 hours of stroke onset. Among patients with first-ever stroke, 27 patients received thrombolysis (6% of first-ever cerebral infarctions and 19% of cerebral infarctions admitted within 3 hours of onset). The in-hospital case fatality rate was 6%. Admission was by ambulance for 85% of patients with subarachnoid hemorrhage and 72% of those with intracerebral hemorrhage. However, only 41% of cerebral infarction patients used emergency medical transfer by ambulance (Fig 1). Aerial transportation was used in 7 cases (5 cases of intracerebral hemorrhage and 2 cases of cerebral infarction).

Age- and gender-specific rates of first-ever stroke per 100,000 residents, particularly for cerebral infarction, gradually increased with advancing age (Fig 2). In all age groups, the rate of cerebral infarction was higher in men than women. The rate of intracerebral hemorrhage was slightly higher than that of cerebral infarction in residents <50 years old. However, among residents ≥50 years old, the rate of cerebral infarction rapidly increased with age in comparison with intracerebral hemorrhage.

Table 2 shows first-ever stroke incidence (all strokes, cerebral infarctions, and intracerebral hemorrhages per 100,000 residents) according to crude and age-adjusted models. The incidence of all strokes per 100,000 residents was 159.8 (95% CI 148.4-171.2) in the crude model, 151.4 (95% CI 127.3-175.5) in the Japanese model, and 60.7 (95% CI 45.4-75.9) in the Segi model. The incidences of cerebral infarction per 100,000 residents were 108.8 (95% CI 99.4-118.1), 103.3 (95% CI, 83.4-123.2), and 38.4 (95% CI 26.3-50.5), respectively, while those of intracerebral hemorrhage were 36.5 (95% CI 31.0-41.9), 34.5 (95% CI 23.0-46.0), and 16.1 (95% CI 8.3-24.0), respectively. Age-adjusted stroke incidences calculated using the Segi model were markedly lower than crude incidences in our series.

Compared with studies from the last decade, incidence of all stroke adjusted using the Segi model was lower in the present study than in previous studies, apart from the Takashima[4] (rural Japan; Fig 3) and Dijon[11] (France) studies. While incidences of cerebral infarction in Japan (Kurashiki City and Takashima) were lower than in all other regions worldwide, the incidence of intracerebral hemorrhage in Japan took a middle position between high- and low-income countries.

Discussion

Age-adjusted incidence of first-ever stroke in our cohort was 151.4 per 100,000 by the Japanese model and 60.7 per 100,000 by the Segi model. While these data resemble those from Takashima, Japan,[4] our result was relatively lower than findings from previous studies conducted over the last decade.[1,11-24] Two possible explanations may account for this difference. First, because stroke incidence tends to be associated with socioeconomic status or national income,[1] high-income countries may be more likely to implement adequate stroke prevention policies. Indeed, the incidence and mortality rates of cerebral infarction dramatically decreased in Japan for several decades in accordance with proper control of hypertension after World War II.[3,4,25-27] Second, we observed wide disparities in population numbers in each age group between the Japanese model and the Segi model. For instance, patients <40 years old comprised 46% of the population in the Japanese census and 68% in the Segi model,[9,10] and while the Japanese population model listed 15% as >70 years old, the Segi model listed only 4%.[9,10] Stroke incidence in Kurashiki City declined from 151.4 per 100,000 in the Japanese model to 60.7 per 100,000 in the Segi model, a similar tendency to that seen in the register of southern Italy.[14] Finally, more than 95% of stoke patients admitted to general outpatient clinics were constantly referred to 1 of 10 stroke centers in Kurashiki City. Nevertheless, some stroke cases with mild deficit might be excluded from our registration.

Compared with the age-adjusted incidence of cerebral infarction in Figure 3, incidences of intracerebral hemorrhage in both Kurashiki City and Takashima were relatively higher than those in other high-income

Table 1. *Clinical backgrounds of the 1009 stroke patients*

Variables	First-ever and recurrent stroke				First-ever stroke			
	All cases (n = 1009*)	Men (n = 552)	Women (n = 450)	*P* value	All cases (n = 763‡)	Men (n = 415)	Women (n = 341)	*P* value
Age (y), median (IQR)	73 (64-80)	70 (62-77)	76 (67-84)	<.001	72 (62-80)	69 (61-77)	75 (66-84)	<.001
Risk factors (%)								
Hypertension	74	72	76	.088	70	68	73	.121
Diabetes mellitus	27	32	21	<.001	23	28	17	.001
Dyslipidemia	28	26	30	.450	27	25	29	.505
Smoking	26	40	8	<.001	26	42	7	<.001
Alcohol consumption	41	61	15	<.001	42	64	15	<.001
Atrial fibrillation (%)	14	13	15	.545	13	12	14	.595
History (%)								
Ischemic heart disease	12	13	10	.251	11	12	9	.240
Living alone (%)	15	13	18	.053	16	15	19	.223
Onset to door within 3 hours (%)	39	39	39	.905	40	41	38	.740
Transferring by ambulance (%)	52	52	51	.817	54	55	53	.723
Diagnosis (n)								
All strokes, total	1003†	552	449		758§	415	341	
By age group (y)								
<15	1	0	1		1	0	1	
15-19	0	0	0		0	0	0	
20-24	0	0	0		0	0	0	
25-29	3	0	3		2	0	2	
30-34	4	3	1		4	3	1	
35-39	12	7	5		12	7	5	
40-44	9	8	1		8	7	1	
45-49	24	19	5		19	15	4	
50-54	33	21	12		28	17	11	
55-59	70	42	28		57	36	21	
60-64	110	70	40		88	60	28	
65-69	142	100	42		113	80	33	
70-74	150	83	66		103	48	54	
75-79	166	91	75		117	63	54	
80-84	130	67	63		92	47	45	
≥85	149	41	107		114	32	81	
Cerebral infarction (total)	698	395	301		516	287	227	
By age group (y)								
<25	0	0	0		0	0	0	
25-29	3	0	3		2	0	2	
30-34	3	2	1		3	2	1	
35-39	3	3	0		3	3	0	
40-44	1	1	0		1	1	0	
45-49	9	7	2		7	5	2	
50-54	20	13	7		16	10	6	
55-59	41	23	18		31	17	14	
60-64	64	46	18		51	38	13	
65-69	101	73	28		80	59	21	
70-74	118	70	47		77	39	37	
75-79	122	73	49		83	50	33	
80-84	95	54	41		70	39	31	
≥85	118	30	87		92	24	67	
Intracerebral hemorrhage, total	232	131	101		173	103	70	
By age group (y)								
<15	1	0	1		1	0	1	
15-19	0	0	0		0	0	0	
20-24	0	0	0		0	0	0	

(*Continued*)

Table 1. *(Continued)*

Variables	First-ever and recurrent stroke				First-ever stroke			
	All cases (n = 1009*)	Men (n = 552)	Women (n = 450)	*P* value	All cases (n = 763‡)	Men (n = 415)	Women (n = 341)	*P* value
25-29	0	0	0		0	0	0	
30-34	1	1	0		1	1	0	
35-39	4	3	1		4	3	1	
40-44	6	5	1		5	4	1	
45-49	14	11	3		11	9	2	
50-54	7	5	2		6	4	2	
55-59	20	14	6		17	14	3	
60-64	38	21	17		30	19	11	
65-69	31	22	9		24	17	7	
70-74	22	12	10		17	8	9	
75-79	34	16	18		25	11	14	
80-84	29	11	18		16	6	10	
≥85	25	10	15		16	7	9	
Subarachnoid hemorrhage, total	67	21	46		63	20	43	
Other or undetermined categories	6	5	1		6	5	1	
Thrombolysis (n, %)								
Ischemic stroke	31/698 (5)	18/395 (5)	13/301 (5)	.434	27/516 (6)	15/287 (6)	12/227 (6)	.877
Within 3 hours of onset	31/197 (16)	18/112 (17)	13/85 (16)	.552	27/144 (19)	15/80 (19)	12/64 (19)	1.000
Within 2 hours of onset	23/122 (19)	13/67 (20)	10/55 (19)	1.000	19/93 (21)	10/50 (20)	9/43 (21)	1.000
Within 1 hour of onset	5/46 (11)	2/23 (9)	3/23 (13)	1.000	5/39 (13)	2/19 (11)	3/20 (15)	1.000
In-hospital case fatality rate (%)	6	5	9	.031	6	5	9	.072

Abbreviation: IQR, interquartile range.
*In 1009 cases with first-ever and recurrent stroke, 7 cases were of unknown gender.
†Among 1009 cases, 1003 cases had age information. Two cases with cerebral infarction did not have gender information.
‡In 763 cases with first-ever stroke, 7 cases were of unknown gender.
§Among 763 cases, 758 cases had age information. Two cases with cerebral infarction did not have gender information.

countries.[1,4] This finding may be mainly related to ethnic factors, particularly those associated with Asian cohorts.[28] In fact, the rate of intracerebral hemorrhage resembled that of cerebral infarction in Kurashiki City residents <50 years old. We believe that maintaining normal blood pressure in younger residents may be important in preventing intracerebral hemorrhage.

To the best of our knowledge, this is the first Japanese investigation of the IV rt-PA usage rate in a midsize city. The frequency of thrombolytic therapy was 5% for cerebral infarction and 16% for cerebral infarction patients admitted within 3 hours of onset. Compared with previous studies conducted during the last decade,[29-34] our results revealed a higher usage rate of IV rt-PA, particularly for hyperacute stroke patients admitted within 3 hours of onset. The reason may be that Kurashiki City has a well-established medical system for acute stroke care. Regarding stroke advertisements, Japan Stroke

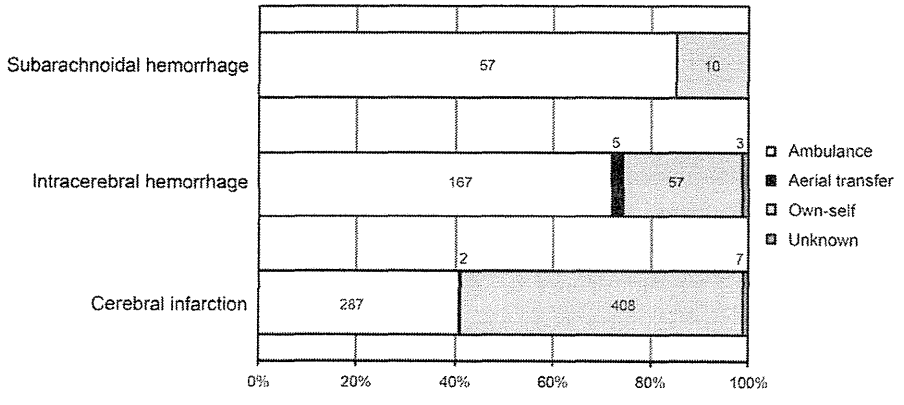

Figure 1. *Proportional frequency of transfer from site of onset to our facilities in terms of stroke subtypes.*

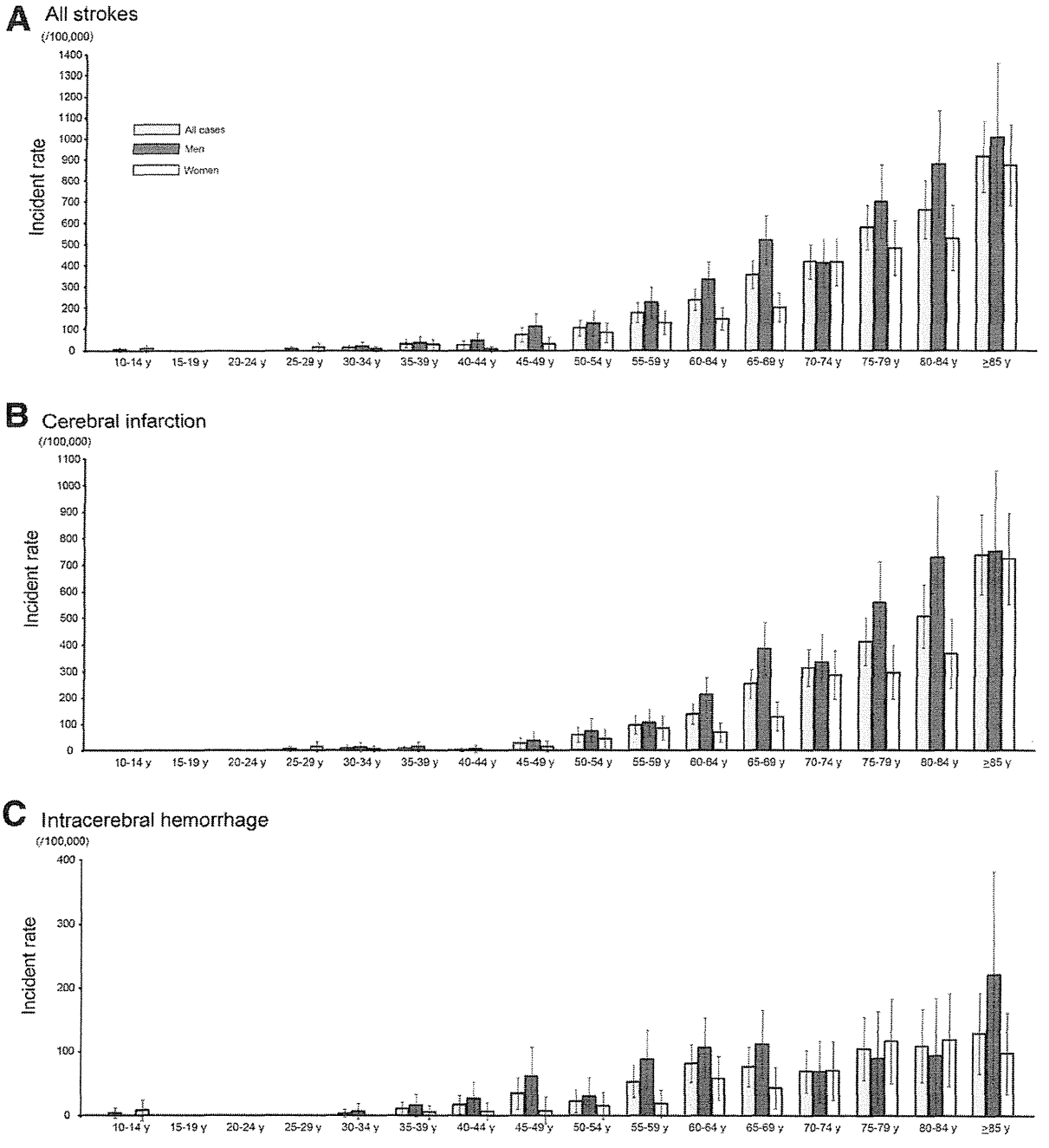

Figure 2. *Age- and sex-specific rates per 100,000 residents for first ever stroke* (A, *all strokes;* B, *cerebral infarction; and* C, *intracerebral hemorrhage).*

Association in Okayama Prefectural branch has undertaken an extensive education campaign on stroke knowledge for Kurashiki City residents using posters, television commercials, and special television programs presented by the public broadcasting station.[35] In the prehospital setting, paramedics always assess the patient with suspected stroke using the Kurashiki Prehospital Stroke Scale.[36] While transferring possible stroke patients, our community provides a direct communication system between paramedics and stroke specialists in 2 comprehensive stroke centers. Consequently, systematic prehospital stroke care seems likely to play an important role in achieving the high-usage rate of IV rt-PA.

The overall in-hospital case fatality rate was 6% for both all strokes and first-ever stroke. These results were not in line with previous reports describing a case fatality rate of 14% in the first 7 days[17] and from 10% to 38% at 28 days after onset.[11,37] Direct comparison of data between the present study and other investigations is not feasible, because the case-fatality rate depends on the

Table 2. *Incidence of first-ever stroke per 100,000 residents*

	All strokes (n = 758)	Cerebral infarction (n = 516)	ICH (n = 173)
Crude model (95% CI)	159.8 (148.4-171.1)	108.8 (99.4-118.1)	36.5 (31.0-41.9)
Japanese population model (95% CI)	151.4 (127.3-175.5)	103.3 (83.4-123.2)	34.5 (23.0-46.0)
Scandinavian population model (95% CI)	91.2 (72.5-109.9)	59.2 (44.2-74.3)	23.0 (13.6-32.4)
Segi population model (95% CI)	60.7 (45.4-75.9)	38.4 (26.3-50.5)	16.1 (8.3-24.0)

Abbreviations: CI, confidence interval; ICH, intracerebral hemorrhage.

initial stroke severity, age, and the observational interval from onset to outcome.[38] However, seen in the most favorable light, short-term mortality in present study seems lower than previously reported.[11,17,37]

Several limitations of the present study must be considered. First, the study only ran over a short period of time (1 year), with no data regarding any secular trends in stroke incidence. We were therefore unable to estimate stroke severity on admission using the National Institute of Health Stroke Scale and long-term outcomes at 3 months after onset. This may have affected our interpretation of the validity of acute stroke care in Kurashiki City. Second, we were unable to compare to our results to some ideal studies investigating Asian ethnic groups, because they restricted the generation of the study population to >40[39] or 25 to 74 years of age.[40]

In conclusion, age-adjusted incidence of first-ever stroke after government approval of thrombolysis was 60.7 per 100,000 residents in Kurashiki City, Japan. Thrombolysis was performed for 5% of cerebral infarction patients and 16% of cerebral infarction patients admitted within 3 hours of onset.

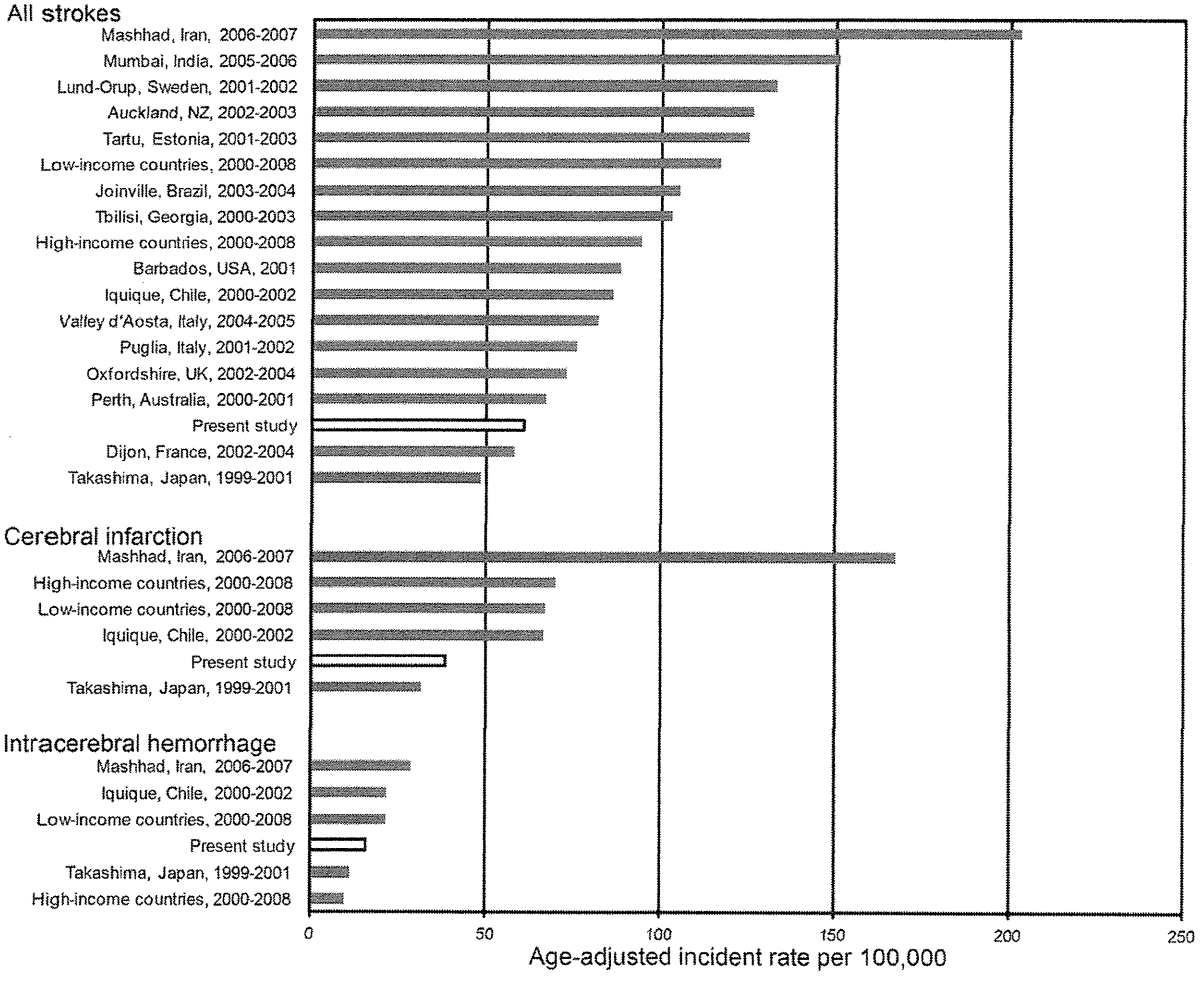

Figure 3. *Age-adjusted incidence of all strokes, cerebral infarction, and intracerebral hemorrhage as estimated by the present and previous studies from 2001 to 2010. All data were adjusted using the Segi standard population model.*

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Early ischaemic diffusion lesion reduction in patients treated with intravenous tissue plasminogen activator: infrequent, but significantly associated with recanalization

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Background and purpose **Recent studies have shown that thrombolysis could decrease or eliminate ischaemic diffusion-weighted imaging lesions. However, the features of such diffusion-weighted imaging lesion reduction are not well known.**

Aims **To clarify, the frequency of and factors associated with lesion reduction were investigated.**

Methods **Patients given intravenous tissue plasminogen activator therapy within three-hours of onset were prospectively enrolled. Magnetic resonance imaging including diffusion-weighted imaging and magnetic resonance angiography was performed four times: on admission, just after intravenous tissue plasminogen activator, 24 h from intravenous tissue plasminogen activator, and seven-days after intravenous tissue plasminogen activator. The diffusion-weighted imaging lesion volume was measured by manual trace using National Institutes of Health imaging software. All patients were divided into three groups according to the early diffusion-weighted imaging lesion volume change from admission to just after intravenous tissue plasminogen activator: the lesion reduction group (>20% decrease); the lesion growth group (>20% increase); and the lesion unchanged group.**

Results **In total, 105 patients [56 males, median age 77 (interquartile range 70–83) years, and National Institutes of Health Stroke Scale score 16 (10–22)] were enrolled. Early diffusion-weighted imaging lesion reduction was observed in seven (7%) patients. The decreased lesion increased subsequently. On multivariate analysis, the glucose level on admission (odds ratio 0·95, 95% confidence interval 0·91 to 0·99, $P = 0·045$) and early recanalization (odds ratio 15·7, 95% confidence interval 1·61 to 153, $P = 0·018$) were independently related to early lesion reduction.**

Conclusion **Early diffusion-weighted imaging lesion reduction was observed in 7% of patients treated with intravenous tissue plasminogen activator. The decreased lesion increased subsequently. Initial glucose level and early recanalization were independently associated with early diffusion-weighted imaging lesion reduction.**

Key words: diffusion-weighted imaging, ischaemic stroke, lesion volume, recanalization, tissue plasminogen activator

Introduction

Diffusion-weighted imaging (DWI) is one of the most sensitive neuroradiological examinations in acute ischaemic stroke, and it can depict an ischaemic lesion clearly as a hyperintense signal (1). DWI hyperintensity was once believed to represent tissue with irreversible damage due to ischaemia (2). Hyperintense signals on DWI increase from initial to follow-up (3–7), and the extent of lesion growth (LG) correlates with clinical outcomes (8–10). However, recent studies revealed that thrombolysis could suppress DWI LG (11–14), and, in addition, DWI hyperintensity could decrease or disappear following intra-arterial (15) or intravenous (IV) (16) thrombolysis.

Aims

Because studies examining such DWI lesion reduction (LR) are few, little is known about the frequency of and factors associated with early LR. Moreover, whether early DWI LR can be a predictor of neurological recovery remains unclear. The aim of this study was to investigate: (1) the frequency of and the factors associated with early DWI LR; and (2) the effect of

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Conflicts of interest: None declared.

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