も多く，その場合は仰臥位のまま下肢を30°程度挙上させる．また，Mingazzini徴候をチェックする．仰臥位で股関節を90°ぐらい屈曲してもらい，両下腿をベッドと水平になる状態で維持してもらい，片側が下がるかどうかを検査する．

脳梗塞は病型診断を行うことが重要である

脳梗塞は，原因によってラクナ梗塞，アテローム血栓性脳梗塞，心原性脳塞栓症，その他の脳梗塞の臨床カテゴリーに分類される．各病型で病態が異なるため，治療方針を立てるにあたって病型診断を進めることが重要である．脳梗塞の病型診断のための検査として，頭部CT，MRI検査による脳梗塞巣の同定，頸動脈および経頭蓋超音波検査，MR angiography，CT angiography，必要な場合はさらに脳血管造影検査による脳血管の評価，胸部X線，心電図，経胸壁および経食道心エコー図検査による心臓および大動脈弓部の評価，血液検査などが必要である．

急性大動脈解離合併例にはrt-PA静注療法は禁忌(表1)

急性大動脈解離が原因で局所脳虚血症状を呈することがある．上行大動脈の解離が腕頭動脈～右総頸動脈へと進展して，左片麻痺を呈する場合が多い．来院時の血圧が低値であったり，一旦意識障害が出現した後に回復した例などは特に急性大動脈解離の合併を疑う必要がある．わが国でrt-PA静注療法が承認されて約1年半が経過した段階で，胸部大動脈解離の合併に気付かずrt-PA静注療法を受けた脳梗塞患者10例が，投与後に容態が急変し死亡に至ったことが報告された．病歴(直前の胸痛，背部痛)や身体所見(血圧低下，末梢動脈拍動の減弱もしくは左右差，大動脈弁逆流性雑音)，検査所見(胸部X線写真での上縦隔拡大)などから大動脈解離を強く疑う場合は，rt-PA静注療法を始める前に胸部CT検査や頸部血管エコー検査によって解離の存在を除外する必要がある．画像診断の結果から大動脈解離が考えられれば，本治療を行うべきではない．ただし，大動脈解離には，典型的な病歴や所見を呈さず，厳しい時間制約のなかでの診断が困難な場合も多い[1]．

若年者で，一側の頸部痛・頭痛を呈しつつ，延髄外側症候群を示唆する所見を有する場合は脳動脈解離を疑え

若年発症の脳卒中の原因として多いものの一つに脳動脈解離がある．脳動脈解離は脳梗塞やくも膜下出血を生じ得る．わが国では頭蓋内椎骨動脈解離が多いことから，一側の頸部痛・頭痛や延髄背外側の脳梗塞を発症してWallenberg症候群を呈する症例が多い．Wallenberg症候群の典型的な症状は，嚥下障害，めまい，病巣側のHorner症候群，上下肢失調，顔面の温痛覚低下および対側半身の温痛覚低下である．

一過性脳虚血発作(TIA)は早期診断・治療がきわめて重要，決して軽視してはいけない

一過性脳虚血発作(transient ischemic attack：TIA)は，脳梗塞の前触れ発作として以前からよく知られているが，治療しなくても短時間で症状が消失してしまうため，「軽症の脳卒中」として後回しにされがちである．しかし，最近の研究により，従来考えられていた以上にTIA発症後短期間に完成型脳梗塞を発症するリスクが高い(治療しなければ90日以内に15～

表2　ABCD^{2}スコア（文献4より作成）

	基準	点数
Age（年齢）	年齢60歳以上	1
Blood pressure（血圧）	収縮期血圧140 mmHg以上かつ/または 拡張期血圧90 mmHg以上	1
Clinical features （臨床症候）	片側脱力 脱力を伴わない言語障害	2 1
Duration（持続時間）	60分以上 10～59分	2 1
Diabetes（糖尿病）	あり	1

20%が脳梗塞を発症し，そのうちの約半数は発症後2日以内に起こる）ことが明らかになってきた．さらに，TIA後早期に診断・治療を行えば，脳卒中発症リスクが約8割も低減できることが欧州より相次いで報告された[2,3]．これらの研究成果から，TIAの早期診断・治療の重要性が叫ばれるようになり，急性期のTIAを脳梗塞と区別せずに包括して急性脳血管症候群（acute cerebrovascular syndrome：ACVS）と呼び，救急疾患の対象として脳卒中を水際で予防しようというコンセプトが急速に浸透してきている．

最近，TIA後の脳卒中発症リスクを予測するスコアとして，ABCD^{2}スコアが広く用いられている（**表2**）[4]．これは7点満点で脳卒中の発症リスクを評価するものであり，その点数が高いほど脳卒中発症リスクは高いとされている（TIA発症後2日以内の脳卒中発症リスク：0～3点1.0%，4～5点4.1%，6～7点8.1%）．

失神をTIAと診断するべからず

日常診療において，失神発作がTIAと診断されることが少なくない．TIAは，脳局所の一過性虚血により一過性の脳局所神経症候を生じるものである．一方，失神発作は，脳全体の一過性脳血流低下による突然の意識および姿勢保持の喪失後，速やかにかつ完全に回復がみられるもので脳局所神経症候は伴わない．失神の原因で多いものは，血管迷走神経反射などの神経調節性や不整脈などの心原性によるものである．

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ABCD²＜4の一過性脳虚血発作（TIA）患者は，ABCD²≧4のTIA患者と同様の90日以内の脳卒中リスクをもつ

Amarenco P, Labreuche J, Lavallée PC
Patients with transient ischemic attack with ABCD²＜4 can have similar 90-day stroke risk as patients with transient ischemic attack with ABCD²≥4.
Stroke 43：863-865，2012

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背景

ABCD²スコアは，プレホスピタルのツールとして一過性脳虚血発作（transient ischemic attack：TIA）患者をトリアージするために提案されている[1]．2008年7月にNational Institute for Health and Clinical Excellenceは，ABCD²スコア4点以上の患者は医療機関への最初の連絡から24時間以内に原因となっている疾患について直ちに評価し，ABCD²スコア4点未満の患者は翌週以内に評価することを推奨した[2]．これは，ABCD²スコア4点未満の患者では，90日以内の脳卒中リスクがABCD²スコア4点以上の患者よりかなり低いという事実に基づいている[1]．TIAクリニックはこのルールを履行しており，その結果を報告した[3]．

しかし，本論文の著者らは，SOS-TIAコホートにおいて，ABCD²スコアが4点未満のTIA患者の5人に1人が，迅速な医学的判断が必要である重要な所見（症候性の同側頸動脈狭窄，高度の頭蓋内狭窄，心房細動もしくはその他の心原性塞栓源）を有していたことを報告した[4]．彼らは，SOS-TIAコホートにおいて，迅速な医学的判断が必要である重要な臨床所見について層別化された，ABCD²スコア4点未満と4点以上でみた90日以内の脳卒中リスクについてこの論文で報告している．

対象と方法

1．コホート

患者は，2003年1月から連続的にSOS-TIA registryに登録された．詳細な対象と方法についてはすでに報告されている[4][5]．今回の報告では3ヵ月後の追跡とともに2008年12月までのコホートをアップデートした．一次エンドポイントは症状発症から90日目の脳卒中であった．

2．データ解析

患者は，3つのサブグループに分けられた；すなわち，①ABCD²スコア4点以上の患者，②ABCD²スコア4点未満で緊急治療基準〔50%以上の症候性頸部内頸動脈狭窄，50%以上の症候性頭蓋内動脈狭窄，もしくはASCO分類グレード1によって定義された主要な心原性塞栓源[6]（僧帽弁狭窄，人工弁，4週間以内の心筋梗塞，左室の壁在血栓，左心室瘤，spontaneous echo contrastあるいは左房内血栓の有無は問わない発作性心房細動もしくは心房粗動の既往，sick sinus

syndrome，拡張型心筋症，駆出率＜35%，心内膜炎，intracardiac mass，卵円孔開存＋*in situ* thrombosis，卵円孔開存＋肺塞栓併発もしくは脳梗塞に先行する深部静脈血栓症）〕のない患者，③ABCD²スコア4点未満で緊急治療基準のある患者である．脳卒中リスクは90日間に脳卒中イベントのあった患者の率とし，Fisher's exact test を用いてサブグループ間で比較した．有意差がみられたので，ABCD²スコア4点以上の患者群を reference として，post hoc pairwise comparison を行った．統計学的検討は2-tailed α level が0.05で行われた．データは SAS software package Version 9.1 によって解析された．

結　果

2003年1月から2008年12月までの間に TIA クリニックを受診した2,398例の患者のうち，1,713例は definite もしくは possible TIA で，ABCD²スコアの完全な情報があった．そのうち，1,679例は90日目の追跡情報があり，本解析に含められた．

平均年齢（SD）は64（16）歳で52%は男性であった．高血圧（高血圧の治療歴もしくは来院時血圧140／90mmHg 以上）は68%，脂質異常症（脂質異常症の治療歴もしくは来院時 LDL-コレステロール160mg/dL 以上）は41%，糖尿病（治療歴）は11%，現在の喫煙は21%にみられた．701例（42%）は ABCD²スコア4点以上，377例（22%）は，50%以上の症候性頸部内頸動脈狭窄（157例），50%以上の症候性頭蓋内動脈狭窄（85例），もしくは主要な心原性塞栓源（169例）の存在と定義された緊急治療の基準の少なくともひとつを有していた．緊急治療の基準は，ABCD²スコア4点未満の患者の18%（180例），ABCD²スコア4点以上の患者の28%（197例）に認められた．

90日以内に34例が脳卒中を発症し，そのうち3例が致死的であった．TIA クリニック受診後90日以内に4例の非脳卒中死もあった（全例 ABCD²スコア4点以上であった）．サブグループ別でみれば，90日以内の脳卒中発症率（イベント数/患者数）は，ABCD²スコア4点以上の患者群で3.4%（24/701），ABCD²スコア4点未満で緊急治療基準あり群で3.9%（7/180），ABCD²スコア4点未満で緊急治療基準なし群で0.4%（3/798）であった（図1；p for between-group comparison＜0.0001）．ABCD²スコア4点以上群を reference として用いたとき，90日以内の脳卒中発症率は ABCD²スコア4点未満で緊急治療基準なし群で有意に低かった（p＜0.0001）が，ABCD²スコア4点未満で緊急治療基準あり群では同じであった（p＝0.82）．ABCD²スコア4点以上群の90日以内の脳卒中発症率をみると，緊急治療基準のある患者では4.6%（9/197），緊急治療基準のない患者では3%（15/504）であった．非脳卒中死4例を90日以内のアウトカムに含めた場

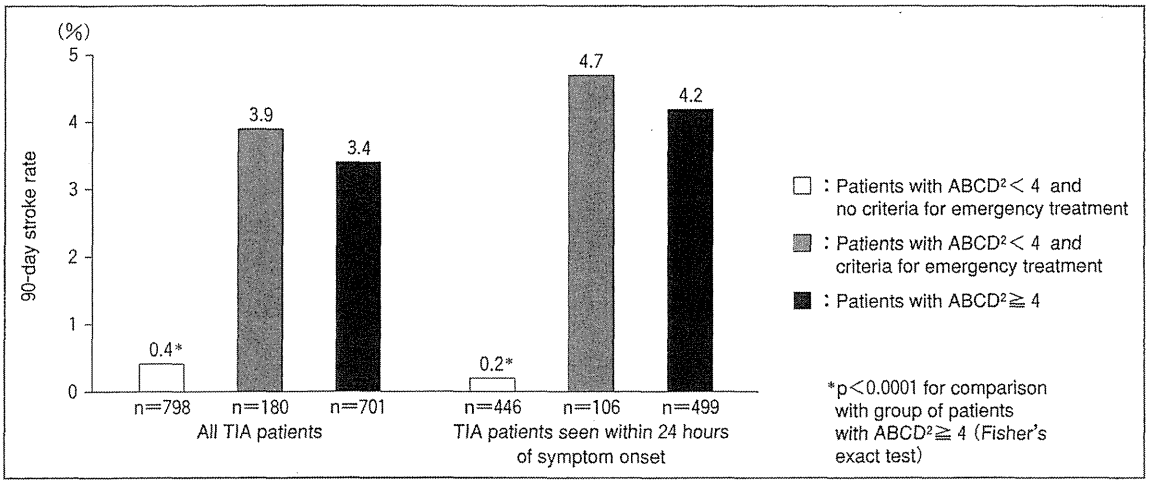

図1　サブグループ別の90日以内の脳卒中発症率

合，ABCD²スコア4点以上の患者における90日以内の脳卒中発症率は4.0%で，ABCD²スコア4点未満で緊急治療基準のある患者の90日以内の脳卒中発症率とは違いのないままであった（p=1.00）．症状発症24時間以内に受診した患者のみでの解析でも同様の結果が得られた（図1）．

考　察

本論文の著者らは，ABCD²スコア4点未満のTIA患者のうち50%以上の症候性頸部内頸動脈狭窄，50%以上の症候性頭蓋内動脈狭窄，もしくはASCO分類グレード1によって定義された主要な心原性塞栓源を有する患者（ABCD²スコア4点未満の患者の5人に1人）は，ABCD²スコア4点以上のTIA患者と同様の90日以内の脳卒中リスクをもつことを認めた．したがって，これらの患者においては徹底的な検査を遅れることなく行わなければならない．彼らは，ABCD²スコア4点未満の患者に関して翌週以内に評価することを推奨しないためにNational Institute for Health and Clinical Excellenceの基準は改訂されるべきであると考えている．

ABCD²スコアの2つの異なる使用法がある．一つは，緊急検査（TIA発症もしくは最初の医療機関への連絡から数時間以内）が不可能な国や地域における，リスクを予測するための検査の代替とみなしたプレホスピタルのトリアージツールとしての使用である．しかし，TIAクリニックが利用できる場合は，迅速検査の実際の所見に基づいたトリアージが優先されるべきである．

24時間以上病院で経過観察されるべき例を決定するためのトリアージツールとして，徹底的な初期検査後にABCD²スコアを使うこともある．おそらくこれがABCD²スコアのより安全な利用法である．可能であれば，ABCD²スコアにかかわらずすべてのTIA患者は，迅速な医学的判断が必要な全患者を検出するために，医療機関への最初の連絡から24時間以内にできるだけ早く評価され，また，残りの患者のうちABCD²スコア4点以上の患者は，24時間以上病院で経過観察されるべきであろう．

解　説

現在，海外では，TIA後の脳卒中発症リスクを予測するスコアとして，ABCD²スコアが広く用いられている[1]．これは，A(age)：60歳以上は1点，B（Blood pressure）：収縮期血圧140mmHg以上and/or拡張期血圧90mmHg以上は1点，C（Clinical features）：片側脱力は2点，脱力を伴わない言語障害は1点，D（Duration）：症状持続時間が60分以上は2点，10～59分は1点，およびD（Diabetes）：糖尿病があれば1点の7点満点で脳卒中の発症リスクを評価するものである．TIA発症後2日以内の脳卒中リスクは，ABCD²スコアが0～3点では1.0%，4～5点では4.1%，6～7点では8.1%で，その点数が高いほど脳卒中発症リスクは高くなる．ABCD²スコアに加えて，MRIの拡散強調画像（DWI）所見の有無，大血管の動脈硬化病変の有無を評価することにより，TIA後の早期脳卒中発症リスクの予測精度をより高めることができるとの報告もある[7]．

ABCD²スコアは，もともと一般開業医でも（検査を行う前に）使える脳卒中リスク予測スコアとして提案されたものであり，ABCD²-Iスコア[8]などの画像検査所見を加えたスコアは，もちろん画像検査などが可能な専門病院で用いられるスコアである．発症後間もないTIA例については，ABCD²スコアにかかわらず，できるだけ早く検査を行って機序を同定し，治療を開始することが重要であると考える．

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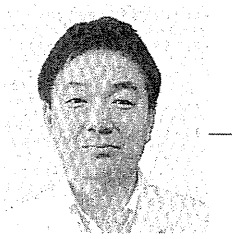
特集 プライマリケア医こそ知っておくべき 一過性脳虚血発作(TIA)治療の最新動向



3．一過性脳虚血発作(TIA)の発症機序と症候

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はじめに

一過性脳虚血発作(transient ischemic attack, TIA)は脳梗塞の前触れ発作として以前からよく知られていたが，最近の研究により，従来考えられていた以上に短期間に脳梗塞を発症するリスクが高い(TIA発症後90日以内に15～20%，うち約半数が2日以内)ことが明らかになってきた[1]．さらに，TIA後早期に診断・治療を行えば，脳卒中発症リスクが劇的に改善することが欧州より相次いで報告され[2,3]，TIA発症後の早期診断・治療の重要性が認識されるようになった．『脳卒中治療ガイドライン2009』では，「TIAを疑えば，可及的速やかに発症機序を確定し，脳梗塞発症予防のための治療を直ちに開始しなくてはならない」(グレードA：行うよう強く勧められる)と記載されている[4]．すなわち，TIAは脳梗塞同様，速やかに発症機序を診断したうえで病態に応じた治療方針の決定が求められている．本稿では，TIAの発症機序と症候について解説する．

発症機序

TIAの発症機序は脳梗塞とおおむね同じであるが，症候が一過性で終わるTIAと持続する脳梗塞では，発症機序の頻度が多少異なると考えられる．TOAST分類[5]に準じてTIAを分類した過去の報告[6-9]によれば，各病型の頻度は，アテローム血栓性(large artery atherosclerosis) 8～23%，心原性(cardioembolism) 15～31%，ラクナ(small vessel occlusion) 18～31%，その他の原因2～6%，原因不明17～43%と報告されている(表1)．以下に，各病型の特徴を述べる．

1．アテローム血栓性TIA

アテローム血栓性TIAは，頸部や頭蓋内主幹動脈のアテローム硬化性病変を基盤として生じるTIAである．動脈原性塞栓(artery-to-artery embolism)や血行力学的機序(hemodynamic mechanism)により発症し，従来TIAの病態の中心と考えられてきた．動脈原性塞栓では，内頸動脈起始部や頭蓋内主幹動脈などに形成されたアテローム硬化性病変に由来する血栓が遊離して，微小塞栓子として末梢の血管を一時的に閉塞することによりTIAを発症する．血行力学的機序では，アテローム硬化による高度狭窄または閉塞があり，何らかの原因でその動脈の灌流領域の灌流圧が低下した場合にTIAを発症する．一般的には，起立時，排尿・排便時，運動時，食後など，末梢血管が拡張し血圧が低下しやすい状況で発症しやすい．代表的な症候として，内頸動脈高度狭窄または閉塞がある際にみられるlimb-shakingがある．Limb-shakingは「一側の上肢や下肢(主に上肢)の短時間で粗雑な不規則に震える不随意運動」で，急に立ち上がったりしたときに病変の対側上下肢に出現する．一見するとてんかん発作と間違われることがある．症状は5分以内に消失することが多い．

欧米の報告では，主幹動脈病変を有するTIAはその後の脳梗塞発症リスクが高いと報告されており，MR angiographyや頸部血管エコー検査などで早期に主幹動脈病変の有無を確認することが重要である．経頭蓋超音波ドプラを用いて微小塞栓シグナル(microem-

表1　TOAST分類に準じたTIAの発症機序別頻度

報告者	報告年	症例数	発症機序による分類				
			アテローム血栓性	心原性	ラクナ	その他	不　明
Sempere AP, et al	1998	103	8%	31%	29%	6%	26%
Weimar C, et al	2002	1,429	15%	15%	25%	2%	43%
Purroy F, et al	2007	388	23%	22%	18%	4%	33%
尾原知行ほか	2011	105	19%	27%	31%	6%	17%

（文献6～9より引用改変）

bolic signal：MES）が検出されれば，TIAの発症機序として動脈原性塞栓が最も強く想定される．

2．心原性TIA

心原性TIAは，脳梗塞と同様，心房細動，人工弁，心筋症，急性心筋梗塞などの心疾患を背景に，心臓内に形成された血栓が，脳血管へ塞栓症を起こすことにより発症する．TIAの症候として，失語，失行，同名半盲，無視などの皮質症状や意識障害を呈する例が多い．

心房細動は心原性TIAの原因として最も頻度が高い．発作性心房細動の診断のためには，ホルター心電図検査などを積極的に行っていく必要がある．原因不明のTIA例では，右左シャント陽性（多くは卵円孔開存）例が多く，右左シャントがTIAの原因としてまれではないとする本邦からの報告もある[10]．

3．ラクナTIA

ラクナTIAは，ラクナ梗塞の責任血管である穿通枝のlipohyalinosisやmicroatheromaが原因となって生じると考えられる．顔面，上肢，下肢のうち，2つ以上を含む半身の運動障害あるいは感覚障害を呈する．失語，失行，同名半盲，無視などの皮質症状や意識障害は認めない．画像にて穿通枝領域に虚血病巣を認める場合には確定診断となるが，TIAでは虚血病巣を認めない例も多く，TIAの症候としてラクナ症候群を呈し，主幹動脈の狭窄性病変や塞栓源心疾患を認めない場合も，暫定的にラクナTIAと診断される．

TIA後の脳梗塞発症の機序として，欧米ではアテローム血栓性が多いと報告されているが，本邦ではラクナTIAも脳梗塞に進展しやすい[9,11]．また，穿通枝領域のTIAには，発作を短期間に繰り返し，治療を行っても半数以上が脳梗塞へと進展するcapsular warning syndrome[12]と称される病態もあり，特にラクナ梗塞の多いわが国においては，軽視できない病態である[13]．

4．その他の原因，原因不明

脳梗塞同様に，大動脈プラークからの塞栓，動脈解離，もやもや病，血液凝固異常などがTIAの原因となり得る．また，主幹動脈が物理的に圧迫され血流が遮断されることによりTIAを発症する場合がある．特に椎骨動脈は解剖学上物理的な圧迫を受けやすく，頸部回旋時に環軸椎で圧迫されることにより症状が出現するbow hunter症候群や，前斜角筋により圧迫されるPowers症候群が有名である．TIAの場合，精査を行っても原因が特定できない症例も少なくない．

表2　TIAの局所神経症候（NINDS Classification of CVD-Ⅲ）

左頸動脈系の症候
- 運動障害（構音障害，筋力低下，麻痺，右上下肢・顔面のclumsiness）
- 左眼の視力喪失（一過性黒内障），まれに右同名半盲
- 感覚症状（右上肢・下肢・顔面の感覚脱失やパレステジアを含むしびれ）
- 失語症（言語障害）

右頸動脈系の症候
- 左頸動脈系の場合と反対側に同様な症状を呈する．
- 失語症は，優位大脳半球が右の場合のみ生じる．

椎骨脳底動脈系の症候
- 運動障害（上肢・下肢・顔面の左右どちらか一側あるいは両側の筋力低下，麻痺，clumsiness）
- 感覚症状（左右どちらか一側あるいは両側の感覚脱失，しびれ感，パレステジア）
- 左右どちらか一側あるいは両側の視野障害
- 姿勢調節障害，回転性めまい，平衡障害，複視，嚥下障害，構音障害

（これらは単独では，TIAとはみなされない）

（文献14より引用改変）

症　候

TIAの症候は，脳または網膜の局所虚血により生じる短時間の神経機能障害である．基本的には，脳血管の支配領域における脳虚血障害に基づく局所神経症候であり（表2）[14]，頸動脈系，椎骨動脈系，およびそれらの穿通枝領域に大別される[15]．片麻痺，半身の感覚

表3　TIAとしては考えがたい症候(NINDS Classification of CVD-Ⅲ)

TIAとしては非典型的な症候
a．椎骨動脈系の症状を伴わない意識障害
b．強直性あるいは間代性痙攣
c．症状が身体の複数の部位に広がっていく場合
d．閃輝性暗点
単独ではTIAとみなされない症候
a．身体の他の部位に広がっていく(行進性の)感覚障害
b．回転性めまいのみ
c．浮動性めまい(めまい感)のみ
d．嚥下障害のみ
e．構音障害のみ
f．複視のみ
g．尿あるいは便の失禁
h．意識レベルの低下に伴う視力障害
i．片頭痛に伴う神経症状
j．confusion(錯乱)のみ
k．健忘のみ
l．転倒発作(drop attack)のみ

(文献14より引用改変)

障害，言語障害，単眼の視力消失などの症状が一過性(多くは数分～数十分)に出現するのが典型的である．TIAを繰り返す場合，その神経症候は一定せずに異なることもある．急性期脳梗塞とTIAに関する全国調査(Japan Multicenter Stroke Investigator's Collaboration, J-MUSIC)では，TIAの症候として運動麻痺が最も多く(64.7%)，次いで構音障害(36.4%)，感覚障害(23.8%)の順であった[16]．

1990年に発表されたNINDS(National Institute of Neurological Disorders and Stroke)のCVD-Ⅲ分類では，非典型的症候や単独の出現ではTIAとみなされない神経症候が挙げられている(表3)[14]．しかし，この基準が提案されたのは主にCTでの評価による時代であり，現在では，これに当てはまる症候であっても病初期のMRIで梗塞巣が検出される症例はまれではない[15]．DWIが陽性であった479例のうち24時間以内に神経症候の消失した39例中，NINDSの分類により単独ではTIAとみなされない神経症候を呈したものが9例(23%)あり，その内訳は，構音障害のみが6例(15%)で最多であり，感覚障害のみ2例(5%)，めまいのみ1例(2%)であった[17]．Oxford Vascular Studyのデータによると，椎骨脳底動脈系の脳梗塞275例中45例(16.4%)で，回転性めまいのみ，複視のみ，全身性の脱力などの一過性神経発作(transient neurological attack：TNA)が先行していたと報告されている[18]．これらの結果から，MRI検査が普及した現在においては，表3の基準を見直す必要があると思われる．

おわりに

TIAの症候は脳梗塞の症候と同じであるが，一過性であるTIAの場合，来院時にはほぼ症状が消失していて，詳細な病歴，既往歴，合併症の聴取のみが診断の決め手になることが多く，日常臨床においてその診断は難しい．また，脳梗塞の場合，梗塞巣の部位，サイズ，数などが発症機序を特定する1つの判断材料になることが多いが，TIAの場合，その多く(組織傷害の有無に基づく定義を用いた場合はすべて)で梗塞巣を認めないため，発症機序が特定できないことも少なくない．しかし，できる限り精査を行い，最善の脳卒中予防策を講じることが重要である．

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Review

Epidemiology and Registry Studies of Stroke in Japan

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Stroke is the most prevalent cardiovascular disease in Japan. This review introduces two epidemiologic studies and four registry studies of stroke in Japan. The Hisayama Study was begun as a population-based prospective cohort study of cerebrovascular and cardiovascular diseases in 1961 in the town of Hisayama. Most of the deceased subjects of the study underwent autopsy examinations from the beginning of the study. Changes in stroke trends in the last 50 years were clarified by comparison of data from different study cohorts registered every 13 to 14 years. The Suita Study was based on a random sampling of Japanese urban residents. Several reports from this study showed the significance of pre-hypertension, as well as hypertension, as a risk factor for stroke by itself and in combination with other underlying characteristics. In addition, the Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC), the Japan Standard Stroke Registry Study, the Fukuoka Stroke Registry, and the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry are explained as registry studies involving Japanese stroke patients.

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Introduction

Stroke is the most prevalent cardiovascular disease and the most prevalent neurological disease in Asia.[1] Many countries in East Asia and Southeast Asia have higher mortality rates from stroke than from ischemic heart disease, the opposite of Western countries.[1] The prevalence of intracerebral hemorrhage (ICH) and intracranial arterial sclerosis is another unique feature of Asian patients.[2,3] Among Asian countries, Japan was the first to become an aging society; the others, in particular Korea, have been rapidly approaching one. Thus, the epidemiologic characteristics of stroke in Japan seem to be good examples for other countries.

In this review, epidemiological studies and patients' registry studies of stroke in Japan are briefly introduced.

The Hisayama Study

The Hisayama Study was begun as a population-based prospective cohort study of cerebrovascular and cardiovascular diseases in 1961 in the town of Hisayama, a suburban community adjacent to the Fukuoka metropolitan area, Kyushu, in western Japan. Four study cohorts were established from Hisayama residents ≥ 40 years of age in 1961, 1974, 1988, and 2002 after screening examinations. One of the strengths of this study is that most of the deceased subjectsof the study underwent autopsy examinations from the beginning of the study (80% between 1962 and 1994),[4] and thus, the morphological features of the brains examined by autopsy or brain imaging are available for most of the stroke cases in each cohort. The study was initiated to respond to the doubts of Western researchers in the pre-

CT era that the very high mortality from ICH in Japan might be due to overdiagnosis of ICH. The autopsy results in the consecutive residents proved that the prevalence of ICH was not so high as was believed by Japanese physicians but also showed that ICH was still more common than ischemic stroke as a cause of death in Japan.[5]

Of the many studies on stroke and other neurological diseases including dementia, those on stroke incidence and mortality are briefly introduced here. After 12-year follow-up for each of the first three study cohorts, the age-adjusted incidences of total stroke were 1,210 per 100,000 person-years for men and 598 for women in the first cohort (1961); they declined steeply in both sexes from the first to the second cohort (1974) and then declined relatively moderately in both sexes from the second to the third cohort (1988, Figure 1).[6] Changes in the incidence among cohorts differed greatly between ischemic stroke and ICH. The incidence of ischemic stroke declined by 37% for men from the first to the second cohort, while the incidence of ICH declined by 61% for men. In contrast, the age-adjusted incidences of coronary heart disease were 340 per 100,000 person-years for men and 113 per 100,000 person-years for women in the first cohort, and they increased for both sexes in the newer cohorts, although they were much smaller than the stroke incidences in all of the cohorts. The different tendencies in the changes in incidence between stroke and coronary heart disease seem to be partly due to changes in prevalence of cardiovascular risk factors among the three cohorts: severe hypertension and current smoking became significantly less frequent, while glucose intolerance, dyslipidemia, and obesity became more frequent. Stroke mortality declined continuously as a result of changes in stroke incidence and significant improvements in acute stroke management; the age-adjusted stroke mortalities among the three cohorts were 634 (the first cohort: 1961), 232 (the second cohort: 1974), and 138 (the third cohort: 1988) per 100,000 person-years, respectively, for men and 286, 162, and 102 per 100,000 person-years, respectively, for women.

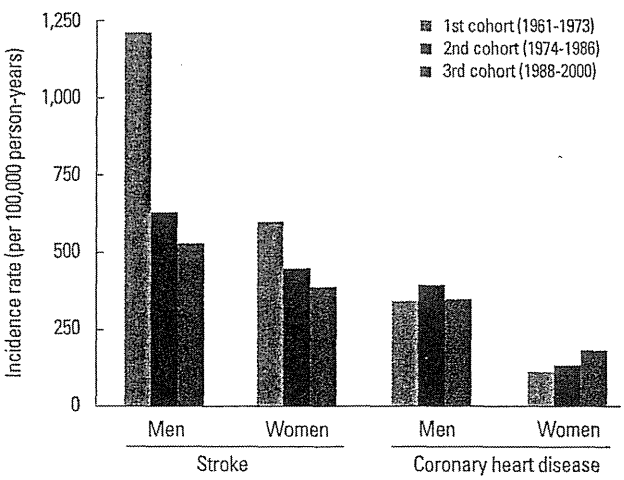

Figure 1. Age-specific incidences of stroke and coronary heart disease among the 3 cohorts of the Hisayama Study, with 12-year follow-up in each cohort.[6]

Among the ischemic stroke subtypes, the age-adjusted incidence of lacunar infarction declined significantly from the first to the third cohort for both sexes (5.68 per 100,000 person-years in the first cohort and 1.59 per 100,000 person-years in the third cohort for men during the 13-year follow-up), whereas the incidences of atherothrombotic and cardioembolic infarctions did not change during this period.[7] As a result, the proportion of ischemic stroke subtypes differed greatly among the 3 cohorts; two-thirds of the male patients had lacunar infarction in the first cohort, compared to two-fifths in the third cohort. The high incidence in the first cohort and recent decline of lacunar infarction were similar to those for ICH, suggesting that intracranial small artery disease has been prevalent in the Japanese population and that the effect of recent developments in preventive therapy, especially antihypertensive therapy, are protective from development of the small artery disease.

Of the 410 patients in the first cohort who developed first ever stroke during 32-year follow-up, 108 (26%) experienced recurrent stroke within 10 years after the index stroke.[8] The cumulative recurrence rates at 1, 5, and 10 years were: 10.0%, 34.1%, and 49.7% after ischemic stroke; 25.6%, 34.9%, and 55.6% after ICH; and 32.5%, 55.0%, and 70.0% after subarachnoid hemorrhage (SAH), respectively.

Of the 333 patients in the first cohort who developed first-ever stroke during 26-year follow-up, 268 (80.5%) died within 10 years after the index stroke, of whom 239 (89.2%) underwent autopsy examinations.[9] The risk of death was greatest in the first year (men 40.3%; women 43.7%). The 30-day case fatality rate was substantially greater in patients with ICH (63.3%) or SAH (58.6%) than in patients with ischemic stroke (9.0%). The risk of dying after the index stroke was twelve times higher during the first year and two times higher during the overall 26-year period as compared to the risk for stroke-free controls. The most common cause of death was the index stroke in the first year, and the impact of recurrent stroke increased gradually thereafter.

The Hisayama Study is one ofthe first sophisticated epidemiological study and one of the most successful epidemiological study of cerebrovascular and cardiovascular diseases in the world. Several unique characteristics of Asian stroke patients were ascertained by this study. The Hisayama Study is still developing by expanding the target diseases into common nonvascular diseases and by adding genomic information for the analysis.

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The Suita Study

Following the Hisayama Study, several epidemiological projects on cerebrovascular and cardiovascular diseases were started in Japan. Most of the study cohorts involved rural or suburban residents, since they are likely to continue to live in the area. The Suita Study was unique in that urban residents were registered.

Suita city, which contains the National Cerebral and Cardiovascular Center where the author works, is located adjacent to Osaka city, which is the second largest metropolitan area in Japan. The Suita Study was based on a random sampling of 12,200 Japanese urban residents. At baseline, participants between the ages of 30 and 79 years were randomly selected from the municipality's population registry and stratified into groups by sex and age in 10-year increments in 1989. Of these, 6,485 people underwent regular health checkups between 1989 and 1994. During an average 11.7-year (64,391 person-years) follow-up period, 213 strokes, consisting of 141 ischemic stroke, 32 ICH, 22 SAH, and 18unclassified strokes, and 133 myocardial infarctions were documented.[10,11] Thus, the incidence of stroke did not differ much as compared to that of myocardial infarction in contrast to the high stroke incidence in the Hisayama Study (especially in its first cohort; the age-adjusted incidence of total stroke for menbeing 1,210 per 100,000 person-years and that of coronary heart disease being 340 per 100,000 person-years), although adjustments for age and other conditions are needed for accurate comparison between the studies. These findings suggest that the data from the Suita Study were influenced by the Western lifestyle, particularly diet.

Among the many publications from the Suita Study, those on the association between blood pressure (BP) levels and stroke incidence are briefly introduced here. The association between high-normal BP and cerebrovascular and cardiovascular disease had not been well studied in the Asian population. The percent ages of the participants with optimal, normal, and high-normal BP and hypertension Stage 1 and Stage ≥2, according to the ESH-ESC 2007 criteria, were 31%, 20%, 18%, 20%, and 11% for men and 42%, 17%, 16%, 16%, and 9% for women, respectively.[9] Compared with the optimal BP group, the multivariate hazard ratios (HRs) (95% confidence intervals [CIs]) of stroke for normal and high-normal BP and hypertension Stage 1 and Stage ≥2 were 2.12 (1.04 to 4.30), 2.43 (1.21 to 4.86), 2.62 (1.35 to 5.09), and 4.38 (2.24 to 8.56) in men and 1.05 (0.49 to 2.24), 1.29 (0.63 to 2.67), 1.21 (0.61 to 2.45), and 2.20 (1.07 to 4.50) in women, respectively; the risk of myocardial infarction for each BP category was similar to that of stroke. Population-attributable fractions of high-normal BP and hypertension for combined stroke and myocardial infarction were 12.2% and 35.3% in men and 7.1% and 23.4% in women, respectively (Figure 2). These findings indicate the significance of pre-hypertension as a vascular risk factor and the necessity for pre-hypertensive patients to attempt to control BP through lifestyle modifications.

The combined impacts of BP categories and other risk factors were also thoroughly investigated in the Suita Study. A study on glucose abnormalities and that on chronic kidney disease (CKD) are summarized.[11,12] The percentages of subjects with normoglycemia, impaired fasting glucose, and diabetes mellitus, defined according to the 2003 American Diabetes Association recommendations, were 59%, 35%, and 6% for men and 75%, 21%, and 4% for women, respectively.[12] Compared with normoglycemic subjects, the multivariate HRs (95% CIs) for stroke were 1.11 (0.81-1.52) in individuals with impaired fasting glucose and 2.08 (1.29-3.35) in individuals with diabetes mellitus. Compared with normoglycemic and optimal BP subjects, increased risks of combined stroke and coronary heart disease were observed in the normoglycemic subjects with high-normal BP or hypertension, in impaired fasting glucose subjects with normal or higher BP, and in diabetic subjects regardless of BP category (P-value for interaction = 0.046). The percentages of CKD subjects, defined as an estimated glomerular filtration rate

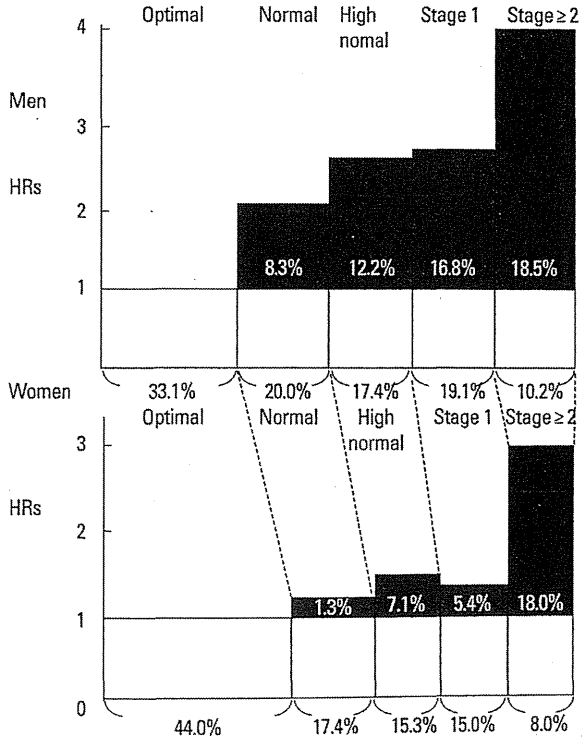

Figure 2. The HRs and positive fractions attributable to exposure to each blood pressure category at baseline for cardiovascular disease (including stroke): the Suita Study. The gray area displays the excessive incidence of CVD due to normal and high-normal blood pressures and hypertension stages 1 and ≥2 (From reference 10 with permission).

(GFR) <60 mL/min/1.73 m^2, using the Modification of Diet in Renal Disease equation modified by the Japanese coefficient (0.881), were 8.9% for men and 11.3% for women.[10] Compared with the GFR ≥90 mL/min/1.73 m^2 group, the HRs (95% CIs) for stroke were 1.9 (1.3 to 3.0) in the GFR 50 to 59 mL/min/1.73 m^2 group and 2.2 (1.2 to 4.1) in the GFR <50 mL/min/1.73 m^2 group. Compared with the optimal BP subjects without CKD, the normal BP, high-normal BP, and hypertensive subjects without CKD showed increased risks of stroke. However, the impact of each BP category on stroke (P for interaction: 0.03 in men, 0.90 in women) was more evident in men with CKD. These results show that pre-hypertension can be a stronger vascular risk factor when combined with other traditional and newer risk factors than when it is the sole risk factor.

As is known, extracranial carotid atherosclerotic lesions are less frequent in the Asian population than in the Western population. The prevalence of asymptomatic extracranial carotid artery lesions and its relationship to cardiovascular risk factors were determined using ultrasound in the Suita residents.[13] Significant sex differences were shown in the prevalence of atherosclerotic lesions in the extracranial carotid artery; 4.4% of all the subjects, 7.9% of the men, and 1.3% of the women aged 50 to 79 years had atherosclerosis accompanied by area stenosis >50%, and these values increased to 6.5%, 11.1%, and 2.1% for the subjects aged 60 to 79 years, respectively (Figure 3). In addition, accumulation of established major coronary risk factors (i.e., hypertension, smoking, and hypercholesterolemia) affected carotid atherogenesis in both sexes.[14]

Registry studies on stroke

In this chapter, major registry studies on ischemic stroke in Japan are introduced (Table 1).

The Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC) was a nationwide, multicenter, prospective, hospital-based registration study from May 1999 through April 2000, when intravenous recombinant tissue plasminogen activator (rt-PA) was not yet approved for clinical use. A total of 156 hospitals participated in the study, and 16,922 patients (70.6±11.5 years old) with acute ischemic stroke (94%) and transient ischemic attack (TIA, 6%) who were hospitalized within 7 days of onset were registered. As was common in the Asian population, lacunar stroke was the leading subtype (38.8%), followed by atherothrombotic (33.3%) and cardioembolic stroke (21.8%).

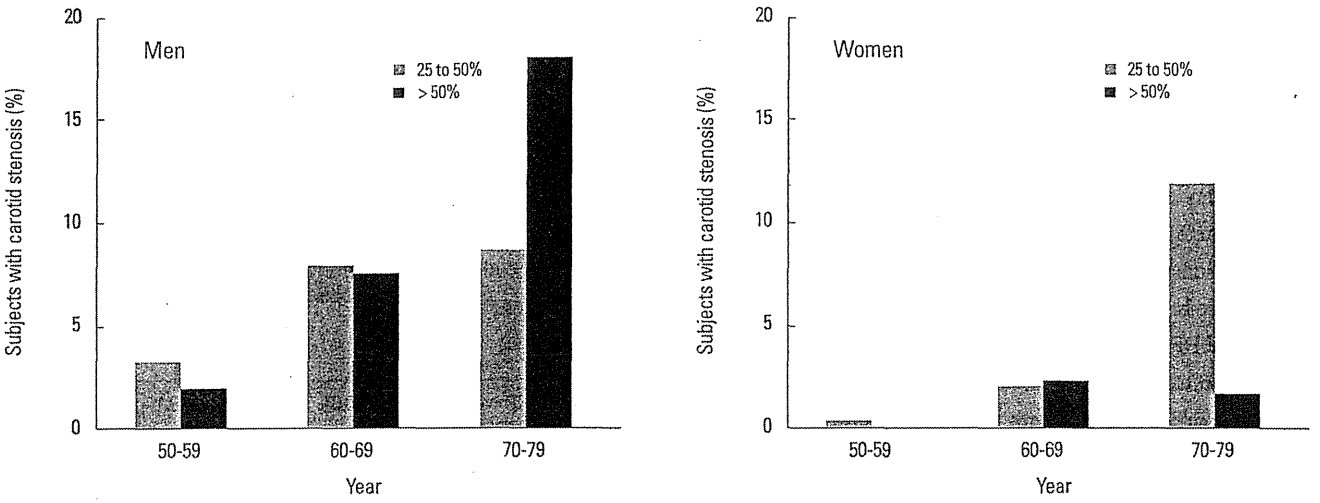

Figure 3. Percentage of subjects with asymptomatic carotid artery stenosis: the Suita Study.[13]

Table 1. Registry studies on Japanese stroke patients

Study	Years	Patients	Patient number	Institutes
Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC)	1999-2000	Ischemic stroke and transient ischemic attack (TIA), ≤7 days	16,922	156 hospitals over Japan
Japan Standard Stroke Registry Study (JSSRS)	2000-ongoing	Stroke and TIA, ≤7 days	Ongoing (47,782 by Nov 2007)	162 hospitals over Japan
Fukuoka Stroke Registry (FSR)	Retrospective: 1999-2007 Prospective: 2007-ongoing	Stroke, ≤7 days	Retrospective: 5,547 Prospective: Ongoing (4,315 by Feb 2011)	7 hospitals in the Fukuokametropolitan area
Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry	2005-2008	Ischemic stroke receiving intravenous rt-PA	600	10 hospitals over Japan

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The median National Institutes of Health stroke scale (NIHSS) score on admission was 5 (interquartile range 2 to 11), and 60.8% of the patients had a modified Rankin Scale (mRS)score of 0-2 at discharge, while 6.9% died during acute hospitalization.[15] In the follow-up study of survivors, the 1-year cumulative mortality was 6.8%, which was relatively low compared to that from Western countries.[16] The cause of death included cerebrovascular disease in 24.1%, pneumonia in 22.6%, heart disease in 18.1%, and cancer in 11.0%.

The Japan Standard Stroke Registry Study (JSSRS) is an ongoing multicenter stroke registration study based on a computerized database from 162 Japanese institutes. From January 2000 through November 2007, a total of 47,782 patients with acute stroke and TIA who were hospitalized within 7 days after onset was registered. Many subanalyses of the registry data have been reported in Japanese books published every two to four years. As the major findings, 75.4% of stroke patients had ischemic stroke, 17.8% had ICH, and the remaining 6.8% had SAH. As subtypes of ischemic stroke, 33.9% had atherothrombotic, 31.9% had lacunar, and 27.0% had cardioembolic stroke. It is interesting that the leading stroke subtype changed from lacunar stroke in J-MUSIC (1999-2000) to atherothrombotic stroke in JSSRS (2000-2007), although the participating hospitals and designs of the two studies were not identical. Effects of sex and age on stroke subtypes, underlying risk factors, initial conditions at onset, and outcomes of ischemic stroke patients were reported in English.[17] Briefly, women were older than men at stroke onset (75.0 ± 11.7 years versus 69.3 ± 11.4 years), and women more frequently had cardioembolic events (odds ratio [OR] 1.090, 95% CI 1.036 to 1.146) after age-adjustment. Onset-to-arrival time was longer ($\beta = 0.0554$, $P = 0.026$), the initial NIHSS score was higher ($\beta = 0.1565$, $P < 0.001$), and duration of hospitalization was longer ($\beta = 0.0355$, $P = 0.010$) in women than in men after multivariate adjustment. At hospital discharge, women less commonly had an mRS score of 0-1 (OR 0.802, 95% CI 0.741 to 0.868) and more commonly had an mRS score of 4-6 (OR 1.410, 95% CI 1.293 to 1.537) than men. Thus, women developed more severe strokes than men in Japan.

The Fukuoka Stroke Registry (FSR) is an ongoing, multicenter, hospital-based registry in which acute stroke patients were enrolled from seven stroke centers in the Fukuoka metropolitan area. The FSR has the strengths that the database extensively collected underlying patients' information, image data principally using MRI/MRA, long-term follow-up of vital and functional conditions for years, and serological and genome genetic analyses for most participants. The associations of several risk factors, including pre-stroke glycemic control[18] and admission proteinuria[19] with clinical outcomes of ischemic stroke patients were published in the last couple of years. As a unique risk factor of ischemic stroke in Japanese, and probably in Korean people, a windblown sand dust originating from mineral soil in the deserts of China and Mongolia was significantly associated with the incidence of atherothrombotic brain infarction after adjusting for expected confounders, including meteorologic variables and other air pollutants in this cohort.[20]

Finally, let us consider the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry.[21] This registry included 600 consecutive patients (377 men, 72 ± 12 years old) with ischemic stroke and TIA who received intravenous rt-PA therapy in ten Japanese stroke centers that were balanced regionally between October 2005 (when intravenous alteplase therapy was approved in Japan) and July 2008. Symptomatic ICH within 36 hours with ≥ 1-point increase from the baseline NIHSS score developed in 3.8% of patients (95% CI 2.6 to 5.7%). At 3 months, 33.2% (95% CI 29.5 to 37.0%) of patients had an mRS score of 0-1, and the mortality was 7.2% (95% CI 5.4 to 9.5%). Analysis of 399 patients with a premorbid mRS score ≤ 1 who met the approved European indications(≤ 80 years old, an initial NIHSS score ≤ 24, etc.) showed that 40.6% (95% CI 35.9 to 45.5%) had a 3-month mRS score of 0-1. These percentages were similar to those in Western postmarketing surveys using 0.9 mg/kg alteplase. Several published subanalyses clarified the associations of risk factors and initial stroke features with thrombolysis outcomes.

The publications that were discussed in this review dealt with only a small part of each study, and the studies that were introduced represent only a small part of Japanese epidemiologic and registry studies. The author hopes that the readers of this journal will find the similarities (or differences) in stroke epidemiology between Japanese people and those in other countries of great interest.

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Neurol Med Chir (Tokyo) 53, 526～530, 2013

Special Theme Topic:
Stroke During Pregnancy or Delivery

Antithrombotic Therapy for Pregnant Women

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Abstract

Coagulability increases during pregnancy, and thromboembolism can easily occur. Venous thromboembolism is a cause of death in pregnant women, but arterial thrombosis such as ischemic stroke in pregnancy is also not uncommon. In pharmacotherapy for thromboembolism in pregnant women, fetal toxicity and teratogenicity must be carefully considered. As anticoagulants in pregnant women, unfractionated heparin and low-molecular-weight heparin are recommended, but warfarin is not recommended since it has a low molecular weight and crosses the placenta. Various types of new oral anticoagulant drugs have been available in Japan since 2011. However, the Japanese package inserts for these anticoagulants advise quite cautious administration in pregnant women. The guidelines on pregnant women include less information about antiplatelet drugs than anticoagulant drugs. Aspirin may cause teratogenicity and fetal toxicity, and perinatal mortality is increased. However, when low doses of aspirin are administered as antiplatelet therapy, the US Food and Drug Administration has assigned pregnancy category C, and treatment is relatively safe. Neurosurgeons and neurologists commonly encounter pregnant women with thromboembolism, such as ischemic stroke. Up-to-date information and correct selection of drugs are necessary in consultation with specialists in perinatal care.

Key words: acute stroke, anticoagulation, antiplatelet therapy, thromboembolism, venous thrombosis

Introduction

Coagulability increases during pregnancy, and thromboembolism can easily occur, primarily of the venous system. Venous thromboembolism is a cause of death in pregnant women, but arterial thrombosis such as ischemic stroke in pregnancy is also not uncommon. In pharmacotherapy for thromboembolism in pregnant women, fetal toxicity and teratogenicity must be carefully considered. However, since pregnant women are usually excluded from pharmaceutical clinical trials for ethical reasons, information on toxicity and teratogenicity in pregnancy is limited. This study presents an overview of the current status and problems with antithrombotic therapy in pregnant women, based on the "Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS 2010)"[3] by the Japanese Circulation Society (JCS) Joint Working Group (fiscal year 2009); and the "Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009)"[4] by the same group (fiscal year 2008).

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Pregnancy and Thromboembolism

Plasma fibrinogen, von Willebrand factor, and factors V, VII, VIII, IX, X, and XII are increased and activated in late pregnancy, thus increasing the risk of thromboembolism. Therefore, thromboembolism is clearly a danger in pregnant women at high risk for embolism, such as those with valvular heart disease, but thromboembolism such as cerebral sinus venous thrombosis may also occur in pregnant women without such risk factors. In addition, the effects of estrogen and elastase during pregnancy may cause evident structural changes in blood vessel walls, leading to increased fragility. For example,

patients with Marfan's syndrome tend to develop aortic dissection. The structure of cerebral and cervical blood vessel walls may also be affected. Moreover, compression of the inferior vena cava due to uterine enlargement may lead to deep vein thrombosis (DVT). Therefore, pregnancy is a risk factor for thromboembolism, particularly venous thrombosis.

Nevertheless, the safety of antithrombotic drugs as treatment, as mentioned above, has not been well established. Fetal toxicity and teratogenicity are major concerns of drug administration in pregnancy, and are affected by placental transfer of drugs and the stage of pregnancy (Table 1).

Anticoagulant Drugs in Pregnant Women

The JCS Joint Working Group provides the following recommendations for anticoagulant therapy in pregnancy.

Class I: In pregnant women with a prior history of DVT but no other risk factors, follow-up observation until delivery and warfarin administration for 4–6 weeks postpartum is recommended.

Class IIb:

1. In pregnant women with a prior history of DVT and other risk factors (e.g., congenital or acquired blood dyscrasias), prophylactic administration of low-molecular-weight heparin or moderate dose-adjusted unfractionated heparin starting during pregnancy and warfarin administration for 4–6 weeks postpartum are recommended.
2. In all patients with a prior history of DVT, use of elastic stockings pre- and postpartum is recommended.
3. In patients requiring long-term warfarin therapy who wish to become pregnant, planned pregnancy with a switch from warfarin to dose-adjusted heparin, or promptly switching from warfarin to dose-adjusted heparin when pregnancy is confirmed at an early stage by frequent pregnancy testing is recommended.

Therefore, unfractionated heparin or low-molecular-weight heparin is recommended in pregnant women; whereas warfarin is not recommended. Table 2 summarizes the effects of anticoagulant drugs in patients during pregnancy and breastfeeding.[3] Table 3 shows the US Food and Drug Administration (FDA) pregnancy categories for these drugs.[1]

Unfractionated heparin and low-molecular-weight heparin do not cross the placenta because of their high molecular weight and do not cause harm to the fetus. However, in Japan, the use of low-molecular-weight heparin for thromboembolism prophylaxis in patients with a history of valvular heart disease or DVT is not covered by health insur-

Table 1 Pregnancy stage, teratogenicity, and fetal toxicity

Pregnancy stage	Teratogenicity and fetal toxicity
Fertilization to day 27	no effect stage: malformations do not occur (no fertilization, no implantation, or miscarriage)
Days 28 to 50	absolutely sensitive stage: important fetal organ formation, highest risk of teratogenicity
Days 51 to 112	relatively sensitive stage: genitalia and palate formation not yet complete, teratogenicity such as cleft palate
Day 113 to delivery	potentially sensitive stage: risk of teratogenicity is rare, attention must be paid to fetal toxicity

Table 2 Effects of anticoagulant drugs in patients during pregnancy and breastfeeding

Drug	Classification	FDA category	Characteristics/adverse reactions	Teratogenicity	Breastfeeding during use	Package insert	
						Pregnancy	Breastfeeding
Warfarin	coumarin derivative	D	teratogenicity, fetal hemorrhagic complications	yes	allowed	contra-indication	contra-indication
Heparin	unfractionated heparin	C	bone demineralization with long-term administration (fractures in mothers), higher incidence of thrombosis than with warfarin, risk of heparin-induced thrombocytopenia	no	allowed	contra-indication	
Enoxaparin	low-molecular-weight heparin	B	reports of heparin-induced thrombocytopenia, not indicated for thrombus prophylaxis in cardiovascular disease	no	allowed	relative contra-indication	relative contra-indication
Dalteparin	low-molecular-weight heparin	B	reports of heparin-induced thrombocytopenia, not indicated for thrombus prophylaxis in cardiovascular disease	no	allowed	contra-indication	contra-indication

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Table 3 US Food and Drug Administration (FDA) pregnancy categories

The FDA-assigned pregnancy categories as used in the Drug Formulary are as follows:

Category A
Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B
Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D
There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X
Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

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ance. Consequently, unfractionated heparin is generally administered. Noteworthy adverse reactions with heparin include hemorrhage, which is a common complication with all antithrombotic drugs, and heparin-induced thrombocytopenia. Another important adverse reaction in pregnant women is possible fractures due to bone demineralization caused by long-term administration of heparin. In addition, because of increased heparin-binding proteins, increased circulating plasma volume, increased clotting factors, and problems with renal clearance, the need for heparin during pregnancy is greater than in non-pregnancy. Since January 2012, home heparin self-injection in pregnant women after mechanical heart valve replacement or those with a history of DVT has been covered by health insurance.

Warfarin, the leading oral anticoagulant drug, has a low molecular weight and does cross the placenta. Therefore, warfarin administration during the absolutely and relatively sensitive stages (days 28 to 112) can cause abnormalities in fetal osteogenesis and chondrogenesis, as well as central nervous system malformations such as microencephaly. These teratogenic effects are considered dose-dependent. In addition, because enzyme systems and vitamin K-dependent clotting factors are undeveloped in the fetus, the effects of warfarin are more easily manifest

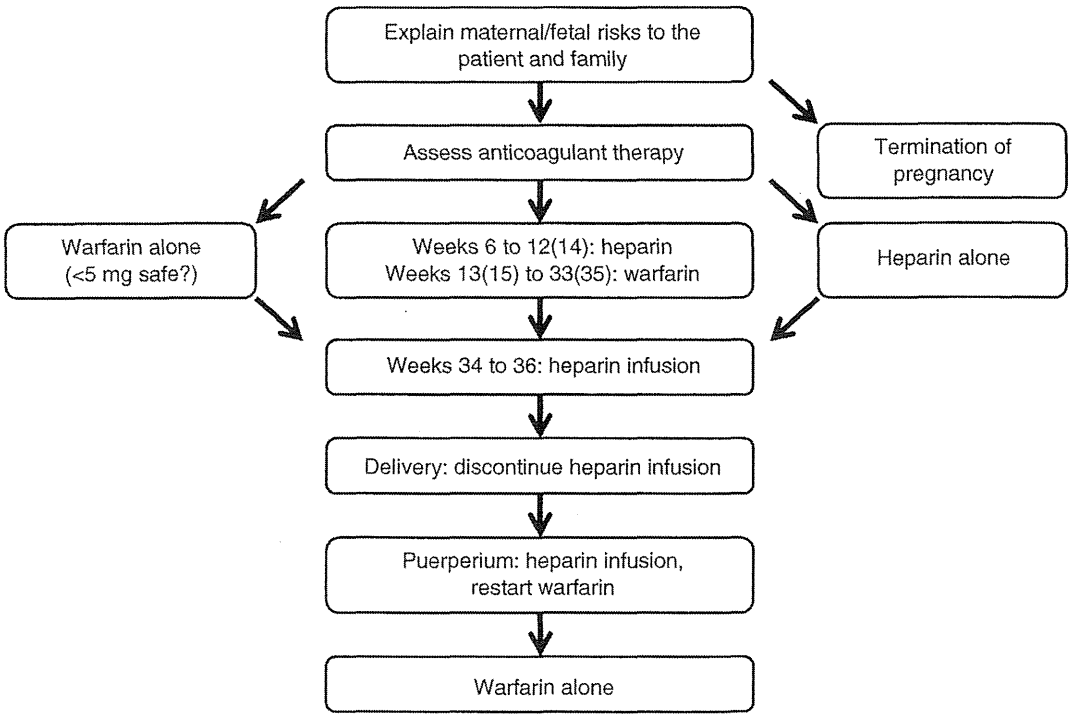

Fig. 1 Anticoagulant therapy in pregnant women with mechanical heart valve replacement. Modified with permission from the *Circulation Journal* (76: 240–260, 2012), ©2012, the Japanese Circulation Society.[3]

in the fetus than in mothers. Therefore, to prevent teratogenicity in the absolutely and relatively sensitive stages, and to prevent complications such as fetal intracranial hemorrhage in the later period of pregnancy due to decreased clotting factors, warfarin administration is not recommended in pregnant women.

Figure 1 shows anticoagulant therapy in pregnant women after mechanical heart valve replacement,[3] consisting of warfarin and heparin administration from week 14 to about week 33 of pregnancy. The rationale based on guidelines is that the prophylactic effects of heparin on thrombus are uncertain.[1,4] Moreover, the rationale for a daily dose of warfarin ≤ 5 mg is based on the dose-dependence of warfarin teratogenicity. However, an oral warfarin dose of 5 mg is considered quite high in Japanese patients, so warfarin should be carefully administered while monitoring the prothrombin time (international normalized ratio). The guidelines from the American Heart Association/American Stroke Association[2] recommend that the following options may be considered for pregnant women with ischemic stroke or transient ischemic attack and high-risk thromboembolic conditions such as hypercoagulable state or mechanical heart valves: adjusted dose unfractionated heparin throughout pregnancy, for example, a subcutaneous dose every 12 hours with monitoring of activated partial thromboplastin time; adjusted-dose low-molecular-weight heparin with monitoring of anti-factor Xa throughout pregnancy; or unfractionated heparin or low-molecular-weight heparin until week 13, followed by warfarin until the middle of the third trimester and reinstatement of unfractionated heparin or low-molecular-weight heparin until delivery (Class IIb, Level of Evidence C). Because home heparin self-injection is now covered by health insurance, the number of patients using heparin is thought to be increasing.

Various types of new oral anticoagulant drugs have been available in Japan since 2011, and these can be clinically used in patients with non-valvular atrial fibrillation and those undergoing lower limb orthopedic surgery. These new agents include the direct thrombin inhibitor dabigatran and the activated factor X inhibitors edoxaban, rivaroxaban, and apixaban. In large-scale clinical trials, these new oral anticoagulants have reduced hemorrhagic complications to the same or greater extent than warfarin, and in particular, the incidence of intracranial hemorrhage compared to warfarin is markedly decreased.[5] In addition, argatroban, an intravenous direct thrombin inhibitor, is now widely used as an alternative to heparin for treatment of the acute phase of cerebral infarction and in heparin-induced thrombocytopenia. However, the Japanese package inserts for these anticoagulants advise quite cautious administration in pregnant women. In other words, dabigatran, edoxaban, and apixaban should only be used when the benefits outweigh the risks, and rivaroxaban should not be given to pregnant women. Argatroban has been assigned pregnancy category B by the FDA, but the Japanese package inserts specify that argatroban should not be administered to pregnant women.

Antiplatelet Drugs in Pregnant Women

Venous thrombosis occurs more often than arterial thrombosis in pregnant women, and the guidelines include less information about antiplatelet drugs than anticoagulant drugs. Table 4 summarizes the effects of antiplatelet drugs in patients during pregnancy and breastfeeding.[3] Aspirin, the leading antiplatelet drug, may cause teratogenicity and fetal toxicity such as premature closure of the ductus arteriosus, and perinatal mortality is increased. But when low doses of aspirin are administered as antiplatelet therapy, the FDA has assigned pregnancy category C, and treatment is relatively safe. However, the drug package insert says "contraindicated (regardless of dose) in pregnant women within 12 weeks of the expected date of delivery (pregnancy week 28 or later)." Therefore, a full explanation and

Table 4 Effects of antiplatelet drugs in patients during pregnancy and breastfeeding

Drug	FDA category	Characteristics/adverse reactions	Teratogenicity	Breastfeeding during use	Package insert	
					Pregnancy	Breastfeeding
Aspirin (low dose)	C	considered relatively safe, do not use in pregnancy week 28 or later regardless of dose	no	potential toxicity	relative contraindication	contraindication
Dipyridamole	B	hypotension, worsening of angina pectoris	no	probably allowed	relative contraindication	contraindication
Ticlopidine	B	hemorrhage, liver dysfunction	no	potential toxicity	relative contraindication	contraindication

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