2 CAST (Chinese Acute Stroke Trial)[2]

目的: 脳梗塞急性期におけるアスピリン 160 mg/日の経口投与の効果が検討された.

対象: 発症 48 時間以内の急性期脳梗塞 21,206 例がエントリーされた.

治療: アスピリン 160 mg/日またはプラセボが 4 週間投与された. 一次評価項目は, 4 週間以内の全ての死亡と, 退院時の死亡または要介助の割合である.

結果: 4 週間以内の死亡率は, アスピリン群で 3.3%と, プラセボ群の 3.9%に比べ有意 (2 p=0.04) に低かった. 4 週間後の死亡または非致死性脳卒中の頻度が, アスピリン群で 5.3%, プラセボ群で 5.9%と有意差 (2 p=0.03) を認め, 12%の相対危険度の低下を示した. 退院時の死亡または要介助状態の割合が, アスピリン群で 30.5%, プラセボ群で 31.6%と, アスピリン群でまさる傾向が示された. 一方, 出血性合併症 (脳出血および輸血を要する頭蓋以外の出血) はアスピリン群で多くみられたが有意差はなかった

結論: 発症 48 時間以内のアスピリン 160 mg/日の投与は有効である.

3 IST, CAST の統合解析[3]および Cochrane Review[4]

IST, CAST を併せた検討では, 治療期間内の脳梗塞再発, 死亡, 新たな脳卒中または死亡は, アスピリン群で有意に抑制されていた (図 1). また, アスピリンの有用性が, 年齢, 性別, 意識レベル, CT 所見, 血圧, 脳卒中分類, ヘパリン併用の有無などの違いにかかわらず認められた. 心房細動を有する例では有意差は認められなかった.

Cochrane Review では, 脳梗塞急性期おける抗血小板療法の効果について, 9 試験 41,399 例のデータを用いてメタアナリシスが行われた[4]. IST, CAST の 2 試験が全データの 98%を占めていた. 抗血小板療法により, 死亡または要介助の割合が有意に減少し, 1,000 人あたり, 生存または自立の患者が 13 人増加するとしている. また, 抗血小板療

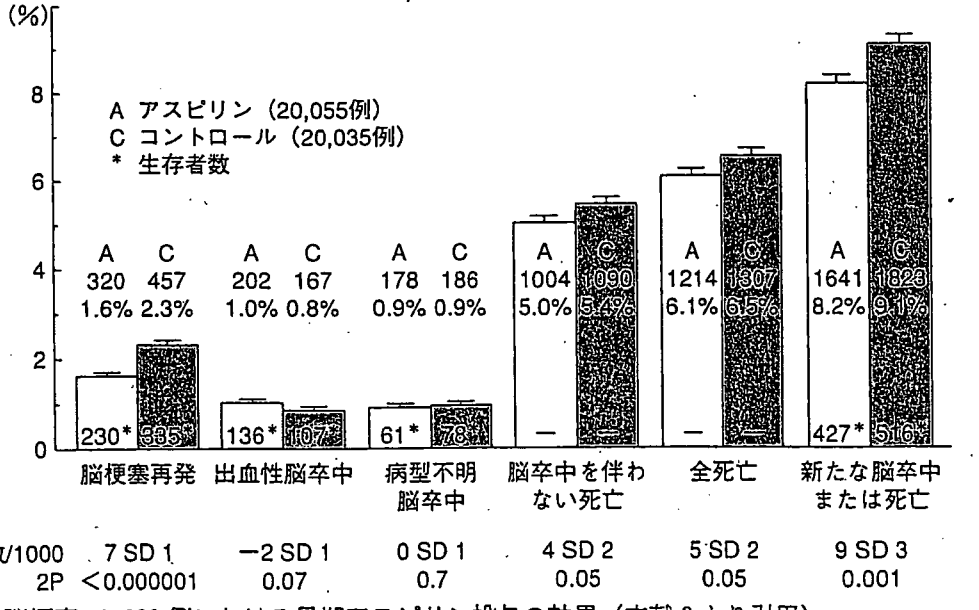

図 1 脳梗塞 40,000 例における早期アスピリン投与の効果 (文献 3 より引用)

法により，完全回復の割合が有意に増加し，1,000人あたり10人の完全回復患者が増加するとしている．脳出血は抗血小板療法により1,000人あたり2人増加するが，脳梗塞は1,000人あたり7人減少する．結論として，アスピリン160～300 mg/日の投与は，発症48時間以内の脳梗塞患者の早期再発を抑制し，長期予後も改善するとしている．

4) オザグレルナトリウム第III相試験[5]

目的：急性期脳血栓症におけるオザグレルナトリウムの効果を検討する．

対象：発症5日以内の脳血栓症283例が登録された．

治療：オザグレルナトリウム160 mg/日（140例），またはプラセボ（143例）を14日間点滴投与した．

結果：28日後の改善度は，オザグレル群が有意（$p<0.01$）に優れていた．改善以上を示した割合はオザグレル群62.3%，プラセボ群37.2%であった．とくに運動障害の改善が特徴的で，28日後に運動障害が改善以上を示した割合は，オザグレル群55.4%，プラセボ群31.7%と，オザグレル群で有意（$p<0.01$）に多かった（図2）．副作用は，オザグレル群で5.1%，プラセボ群で6.4%と差がなく，出血性副作用は，プラセボ群で1例に胃出血がみられたのみであった．

結論：発症5日以内の脳血栓症のオザグレルナトリウムの点滴投与は有効である．

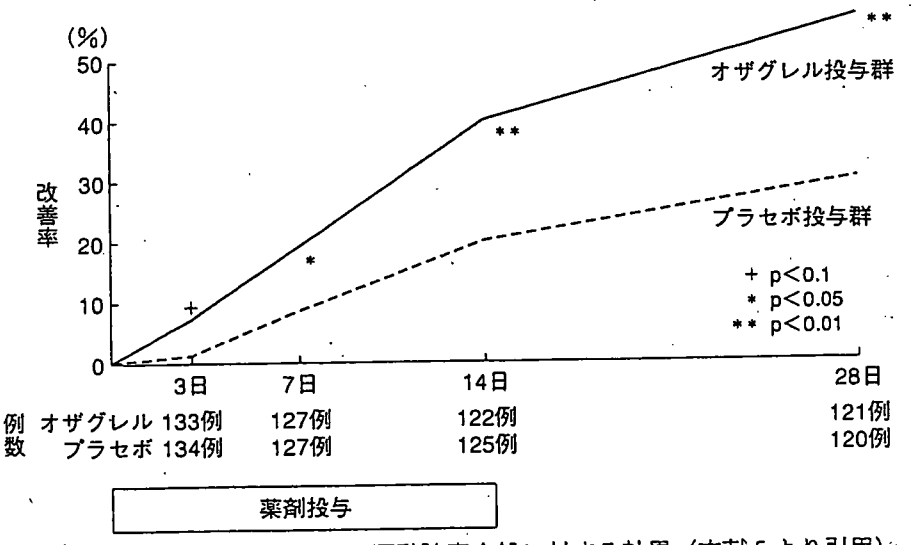

図2 オザグレルナトリウムの運動障害全般に対する効果（文献5より引用）

4 根拠となった臨床研究の問題点と限界

IST，CAST，Cochrane Reviewの結果は，アスピリンの急性期脳梗塞における有効性を示すものではあるが，効果としてはそれほど大きいものではない．また，ISTのサブ解析では，心房細動合併例では効果が認められていない．心房細動合併例の多くは，心原性脳塞栓症と考えられ，これらの例ではアスピリン投与の適応はないと考えられる．今後は，病型別の検討やアスピリン不応症の診断と対応など，より個別化されたエビデンスが必要である．

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また，オザグレルの臨床試験は，わが国においてのみ行われた試験で，外国では評価されておらず，発売もされていない．また，本試験における臨床症候の重症度は，主治医が主観的に判断したものであり，客観性に欠けることが指摘されている．二重盲検であるから結果に問題があるわけではないが，ストロークスケールや，重症度，日常生活動作スケールなどにより客観的に評価された国際規模の試験がぜひとも望まれるところである．

5 本邦の患者に適応する際の注意点

日本人は，欧米人にくらべ脳出血が多いとされ，抗血小板薬による出血性合併症も多い可能性が指摘されている．したがって，外国でのデータをそのままわが国に当てはめることは無理がある．出血性脳卒中をはじめとした出血性合併症は，アスピリン投与により増加することが考えられ，出血合併例の予測が今後の課題といえる．また，アスピリン不応症をどのように診断するかも今後検討される必要がある．

6 コメント

2004年3月に脳卒中に関連した日本の5学会（日本脳卒中学会，日本脳神経外科学会，日本神経学会，日本神経治療学会，日本リハビリテーション医学会）により脳卒中合同ガイドライン委員会が組織され，わが国で初めての脳卒中治療ガイドライン[6]が発表された．その中で，脳梗塞急性期の抗血小板療法がとりあげられ，上記のアスピリン，オザグレルナトリウムにおけるエビデンスをふまえ，表1のごとく記載されているが，どちらを選択するか，あるいは両者でもよいのか，その辺りの記載はない．

アスピリンは，血小板のcycloxygenase（COX）を阻害することにより強力な血小板凝集作用をもったthromboxane A_2（TXA_2）の合成を阻害して血小板凝集抑制作用を発揮する．しかし一方で，内皮細胞のCOXも阻害して，血小板凝集抑制作用をもったプロスタサイクリンの合成も阻害し，いわゆるアスピリンジレンマが問題となる．オザグレルナトリウムは，TXA_2のみを直接阻害するため，アスピリンジレンマを解決する薬剤であり，理論的には優れているといえる．しかし，アスピリンと直接比較した試験はなく，また，少量アスピリンとオザグレルナトリウムの併用療法の効果も期待され，今後は是非ともこれらの検討が望まれる．

実際の臨床の場では，オザグレルナトリウムは，脳血栓症のなかでも穿通枝領域の梗塞に効果があるとされ，すなわちラクナ梗塞において選択されることが多い．アテローム血栓性脳梗

表1 脳卒中治療ガイドライン．脳梗塞急性期の抗血小板療法（文献6より引用）

推奨
●オザグレルナトリウム160 mg/日の点滴投与は，急性期（発症5日以内）の脳血栓症（心原性脳塞栓症を除く脳梗塞）患者の治療法として推奨される（グレードB）
●アスピリン160～300 mg/日の経口投与は，発症早期（48時間以内）の脳梗塞患者の治療法として推奨される（グレードA）．

グレードA：行うよう強く勧められる
グレードB：行うよう勧められる

塞においては，アスピリンと，抗トロンビン薬であるアルガトロバンの併用が選択されることが多い．上記のガイドラインでは，抗血小板療法の他に，血栓溶解療法，抗凝固療法などが別個に記載されているが，実際の臨床の場では，上記のようにこれらを組み合わせて治療を行うことも少なくない．今後は，どのような治療の組み合わせによりどのようなメリット，デメリットがあるのかについても検討して行く必要がある．

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<山脇健盛>

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＜シンポジウムII＞

抗血小板薬並びに抗凝固薬の標準化に関する遺伝子解析研究

宮田　敏行[1)]　宮下光太郎[2)]　宮田　茂樹[3)]
嘉田　晃子[1)]　長束　一行[2)]
[1)]国立循環器病センター研究所病因部，[2)]同　内科脳血管部門，[3)]同　輸血管理室

Key words：血小板，アスピリン，ワルファリン，VKORC1，抗血小板薬の適正使用
(脳卒中 29：721—725，2007)

はじめに

ワルファリンは世界で最も広く用いられている経口抗凝固薬である．本薬剤による各種血栓症ないし塞栓症の再発予防効果が確立している一方，治療域が狭いのでコントロールが難しいことが指摘されている．ワルファリンの投与量の個人差は，体重や食事などの環境因子に加え，遺伝因子も影響するといわれていたが，最近2つの遺伝子，*CYP2C9* と *VKORC1* の遺伝子多型がかかわることが明らかとなってきた．これらの遺伝子多型に加えて，年齢や性・体重などの要因を加味すると，投与量の個人差の50%以上が説明されるとの報告が見られる．抗凝固作用を保ちつつ出血等のイベントを軽減するため，これらの遺伝子情報をうまく使うことが，今後重要になると考えられる．アスピリンは非心原性脳梗塞や心筋梗塞の予防に対する有効性が明確な抗血小板薬である．ワルファリンはその効果をPT-INRで判定し投与量を調節して用いられるが，アスピリンについては血小板凝集能測定により投与量を調整する場合もあるものの，多くの臨床の現場では体重や患者の状態にかかわらず一定量で治療がなされることが多い．適切な評価系を用いてアスピリンの効果を判定し，患者個人に適した投与を行うことができれば，さらに確実な治療効果を得られると考えられる．実際，アスピリン効果に個人差があり，血小板機能抑制が十分でない患者群をアスピリンレジスタンスと定義し，この患者群で血栓塞栓症の再発が高率に認められるとの報告が近年増加している．私たちは，二次予防としてアスピリン投与を受けている患者を対象に，アスピリンレジスタンスに対する最適な評価法(COX-1や血小板機能測定など)とリスク因子(投与法や併用薬など)を明確化するために，多施設共同前向き観察研究ProGEAR研究（後述）を実施している．

本稿では，近年注目を集めているファーマコゲノミクスのなかでも，遺伝子情報と臨床が最も近いと考えられている抗凝固薬ワルファリンに関して，自験例を取り上げ紹介したい．また，抗血小板薬アスピリンの安全安心な使用を目指した遺伝子研究を含んだ多施設共同前向き研究を紹介する．

ワルファリンがかかわるビタミンKサイクル

ビタミンKのKは，スカンジナビア語の血液凝固を意味するblood koagulationに由来する．1943年のノーベル生理医学賞は，デンマークのHenrik Dam博士と米国のEdward Doisy博士の血液凝固不全を起こすビタミン欠乏症の研究に贈られたが，これがビタミンKであった．ビタミンK欠乏症は致死的な出血を起こすが，本症状はビタミンK投与により回復する．

ビタミンKサイクルを図1に示す．還元型ビタミンKはγ-グルタミルカルボキシラーゼ(GGCX)の活性に必須である．GGCXは，凝固因子であるプロトロンビン，VII因子，X因子，IX因子，凝固制御因子であるプロテインC，プロテインSをカルボキシル化し，これらの因子を成熟型へと変換する酵素である．即ち，GGCXは還元型ビタミンKと酸素を使い，これらの因子のN末端ドメインにあるGlu残基の側鎖にCO_2を付加し，Gla（γ-カルボキシルグルタミン酸）残基とビタミンK2，3エポキシドを生成する反応を触媒する．こうしてGla化された凝固因子はカルシウムイオンを結合し，血小板膜などの反応の場に濃縮され，凝固反応を進めるとともに，プロテインC，Sは凝固の制御を行う．この反応で生成したビタミンKエポキシドは，再利用のため還元型へと変換されるが，この反応を触媒する酵素が2004年にクローニングされたビタミンKエポキシド還元酵素（VKOR）である[1)2)]．ワルファリンはVKORのアンタゴニストであり，VKOR

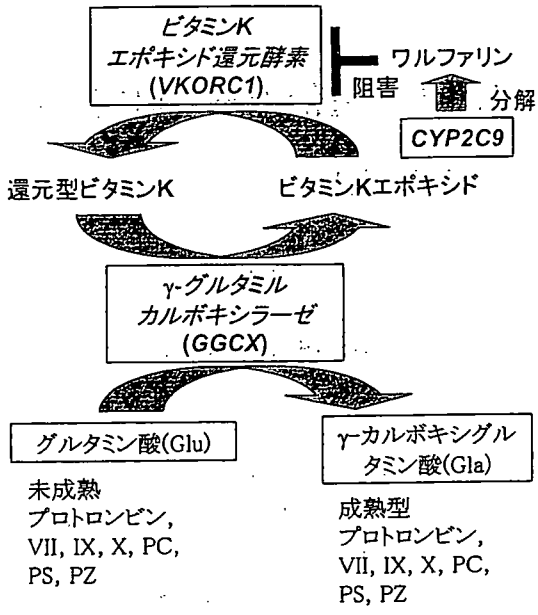

図1　ビタミンKサイクル
ビタミンK依存性γグルタミルカルボキシラーゼ（GGCX）は，還元型ビタミン，二酸化炭素，分子状酸素を用いて，ビタミンK依存性凝固因子のGlaドメイン内のグルタミン酸（Glu）残基をGla（γカルボキシグルタミン酸）残基に変換し，それに伴ってビタミンK2，3エポキシドを生成する．このエポキシドは，ビタミンKエポキシド還元酵素（VKORC1）の作用により還元型ビタミンKへと変換され，再度反応に利用される．ワルファリンはビタミンKのアンタゴニストであり，VKORC1の阻害薬である．ワルファリンはビタミンKサイクルを止めることにより，ビタミンK依存性凝固因子の成熟化を抑制し，凝固能を抑制する．

活性を阻害することによりビタミンKサイクルを止め，凝固因子の成熟型への変換を抑制することにより抗凝固能を発揮する．

VKORはクローニングされた当時，蛋白質複合体の1成分と考えられ，サブユニット1との名称にもとづいてVKORC1と命名された．しかし，その後の詳細な酵素学的研究により，本酵素単独でVKOR活性を示すことが明確に示された[3]．*VKORC1*遺伝子は3つのエクソンでコードされた163残基から成る3回膜貫通領域をもつ小胞体膜に局在する比較的小さな蛋白質である．分子のC末端には，小胞体残留シグナル（K××K××）配列をもつ．活性中心は第3膜貫通ドメインにあるC_{132}とC_{135}と考えられている．ビタミンKは疎水性物質なので，活性中心が膜内に埋め込まれているのは，理にかなっていると考えられる．

先天性*VKORC1*遺伝子欠損症は，2つの疾患，即ち先天性ビタミンK依存性凝固因子欠損症タイプ2と先天性ワルファリン抵抗性を起こす．前者は稀な出血性疾患として報告されている．ちなみにタイプ1は先天性*GGCX*欠損症である．後者は，ワルファリン服薬にもかかわらず凝固能が抑制されない患者として同定されるので，凝固コントロールのため，多量のワルファリンが必要となる．*VKORC1*のV66M変異のヘテロ接合体患者では，一日に25mg以上のワルファリンを必要とするが，血中ワルファリン濃度は5.7mg/*l*以上で治療域（0.7～2.3mg/*l*）より高かった．この変異をもつ家系員のビタミンK依存性凝固因子活性は正常であり，血清中にPIVKA-II（Gla残基の形成が不十分なプロトロンビン）は検出されなかった[4]．また，L128R変異を有するヘテロ接合体患者は，一日に45mgのワルファリンまで抵抗を示し，Phenprocoumon（long-acting ビタミンKアンタゴニスト）服用で，INRが1.0にもかかわらず血清中の濃度は85mg/*l*（通常，1～6mg/*l*）と極めて高値を示した．この患者は低分子量ヘパリンを用いて10年間イベント無しでコントロールを行えている[5]．

ワルファリン量の個人差にかかわる候補遺伝子

2004年にワルファリンの標的酵素*VKORC1*がクローニングされたことを契機に，本酵素の遺伝子多型を用いたワルファリン量の個人差に関する研究が世界中で同時に進められた．私達もワルファリンの維持量の個人差の遺伝的背景を探る目的で，*VKORC1*，*GGCX*，カルメニン（*CALU*）を候補遺伝子として研究を進めた[6][7]．*CALU*は小胞体内腔蛋白質で，γカルボキシル化を抑制する機能が報告されている．まず，これらの遺伝子の蛋白質コード領域を日本人96人のDNAでシークエンスを行い，遺伝子多型（変異）を収集し，これらの多型とワルファリン量との関連を検討した．その結果，それぞれの遺伝子に，12個，31個，25個の多型を同定した．ミスセンス変異は*VKORC1*にH68R変異（1名），*GGCX*にR325Q変異（43名がヘテロ体，8名がホモ体），*CALU*にR4Q変異（32名がヘテロ体，4名が変異ホモ体）が同定された[6]．

ワルファリン量の個人差にかかわる遺伝子多型

多型のあいだの連鎖不平衡やアレル頻度を考慮し，9多型を選んで国立循環器病センター内科脳血管部門へ入院した脳卒中患者より収集した93試料のタイピ

表1　ワルファリン投与量と関連が認められた遺伝子多型

gene	SNP	genotype	n	mean ± SD (mg/day)	P
VKORC1	− 1639 G > A *	AA	79	2.83 ± 1.00	
		GA	14	3.70 ± 1.11	0.004
		GG	0	—	
VKORC1	1173 C > T *	TT	79	2.83 ± 1.00	
		CT	14	3.70 ± 1.11	0.004
		CC	0	—	
VKORC1	3730 G > A *	GG	79	2.84 ± 1.00	
		GA	14	3.68 ± 1.12	0.006
		AA	0	—	
GGCX	8016 G > A	GG	48	3.25 ± 1.19	
	(R325Q)	GA	39	2.63 ± 0.77	0.022
		AA	6	2.79 ± 1.07	
CYP2C9	42613 A > C	AA	83	3.06 ± 1.05	
	(CYP2C9 * 3)	AC	9	2.17 ± 0.84	0.015
	(I359L)	CC	0	—	

国立循環器病センターの脳梗塞患者93名を対象とした．P値はone-way ANOVAで計算した．＊ *VKORC1* の3つの遺伝子多型は連鎖不平衡していた．*VKORC1*-1639Aアレルの保有者は肝 *VKORC1* mRNA発現が低いと報告されている．*GGCX* R325Q変異の機能に関する報告はない．CYP2C9 I359L変異はCYP2C9＊3と呼ばれ，S-ワルファリンの7位の水酸化に対するKmは極めて高いと報告されている．

ングを試行した[7]．これらの患者は脳梗塞の再発予防のため，ワルファリンによりINRが1.6〜2.6にコントロールされている．これまでの研究から，ワルファリンの代謝分解を行う *CYP2C9* の遺伝子変異がワルファリン量の個人差にかかわることが明らかにされているが，日本人は *CYP2C9* の活性低下を伴う遺伝子変異の頻度が低い，という結果であり，日本人は欧米人に比して少ないワルファリンでコントロールできるという臨床上の経験則を説明できなかった．

VKORC1，*GGCX*，*CALU* の遺伝型とワルファリン量との関連の結果を表1に示す[7]．3つの遺伝子の5つの遺伝子多型がワルファリン投与量と関連を示した．*VKORC1* の3つの多型は連鎖不平衡しており，−1639Aアレル保有者の肝 *VKORC1* mRNA量はGアレル保有者に比べて低いことが示されている[8]．このことは，Aアレル保有者はVKOR活性が低いと考えられ，少量のワルファリンでコントロール可能であることを示唆している．実際，表1のデータはAアレル保有者は低用量でコントロールされていた．AA型の保有者はワルファリン2.83 ± 1.00mg/日（平均 ± SD）でコントロールされているが，ヘテロ接合体であるGA型保有者は約0.9mg/日多いワルファリンでコントロールされていた．また，*CYP2C9*＊3（I359L）の変異型 *CYP2C9* はワルファリン分解活性が低いといわれているが，変異型ヘテロ接合体保有者は野生型保有者に比べ，0.9mg/日少ないワルファリンでコントロールされており，これまでの諸家の知見とよく一致した．一方，*GGCX* はR329Q変異が関連を示したものの，他のグループからは本変異の関連は報告がない．次いで多変量解析を行いワルファリン量に影響を与える因子を調べたところ，年齢は1.7%，性別は8.1%，体重は7.8%，*VKORC1* 多型5.9%，*GGCX* 多型4.6%，*CYP2C9* 多型5.2%，それぞれ影響を与えると計算された．

ワルファリン投与量の個人差を説明する研究が各国で行われて発表されている．それらをまとめたのが図2である[9]．遺伝因子として *VKORC1* と *CYP2C9* が挙げられ，諸家の報告を見ると *VKORC1* の遺伝子多型の方がワルファリン投与量への影響が大きい様である．しかし，遺伝要因に年齢・性別・体重などを考慮しても，個人差の約半分が説明できずに残っている．今後，

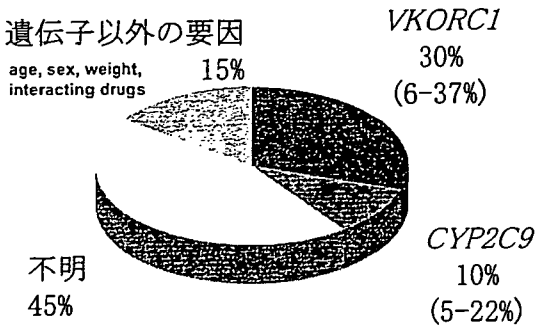

図2　ワルファリン投与量の個人差にかかわる遺伝因子と環境因子の寄与度
各国で行われた研究[9]をもとに，遺伝因子（VKORC1, CYP2C9）と遺伝子以外の要因（年齢，性別，体重，併用薬など）の寄与を推測した（括弧内は最小値－最大値）．これらを考慮しても約45%のワルファリン量の個人差は説明できない．

ワルファリンの処方に際して，どのように遺伝子多型情報を取り入れるかが重要になろう．

アスピリンレジスタンス

心血管系疾患の2次予防としての低用量アスピリンの有効性は広く認められている．しかし，アスピリン服薬にもかかわらず2年間で12.9%の患者にイベント再発が認められるといわれている[10]．最近，アスピリンの抗血小板効果には個人差が認められるとの報告がなされ，それをもとにアスピリンレジスタンスという疾患概念が生まれてきた．アスピリンの効果を血小板凝集能やトロンボキサン代謝産物量などでモニターし，イベント再発との関連を調べた研究では血小板凝集が十分には抑えられていない患者の再発率が高く，アスピリンレジスタンスを示す患者の予後は悪いとの報告がなされている[11][12]．アスピリンをより安全・安心に用いるため，アスピリンの効果を何らかの手法でモニタリングすることが望まれるが，現時点では確立された評価方法はない．そこで，アスピリンレジスタンスの実態を解明し，適切な評価方法や明確な診断基準の確立を目指して，多施設共同前向きコホート観察研究（The Study on Profile and Genetic factors of Aspirin Resistance：ProGEAR Study）を全国23施設の協力のもとに進めている（www.clinicaltrials.gov, ClinicalTrials.gov Identifier：NCT00250380）．この研究は，脳梗塞/TIAおよび急性冠症候群の二次予防としてアスピリンの投与を受けている長期服薬患者600症例の登録を目標に，3種類の血小板機能検査，2種類のCOX-1機能測定を行い，登録後2年間の血栓塞栓症の発症を追跡する研究である．同時に，その遺伝子背景をCOX-1, COX-2遺伝子を中心として解析する予定である．本邦でのアスピリン抵抗性の実態ならびにその背景因子について明らかにできるものと期待している．

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Abstract

Genetic aspects on the effects of anticoagulant and antiplatelet drugs

Toshiyuki Miyata, Ph.D.[1], Kotaro Miyashita, M.D.[2], Shigeki Miyata, M.D.[3], Akiko Kada, M.P.H[1] and Kazuyuki Nagatsuka, M.D.[2]
[1]Research Institute, National Cardiovascular Center
[2]Cerebrovascular Division, Department of Medicine, National Cardiovascular Center
[3]Division of Transfusion Medicine, National Cardiovascular Center

Warfarin is the most widely prescribed oral anticoagulant, but there is greater than 10-fold interindividual variability in the dose required to attain a therapeutic response. Pharmacogenetic analysis of two genes, the warfarin metabolic enzyme *CYP2C9* and warfarin target enzyme, vitamin K epoxide reductase complex 1 *VKORC1*, confirmed their influence on warfarin maintenance dose. The contribution to inter-individual variation in warfarin dose in our patients on stable anticoagulation with a target International Normalized Ratio of 1.6–2.6 was 5.9% for *VKORC1* -1639G>A and 5.2% for *CYP2C9* 42613A>C. Recent studies have shown that VKORC1 haplotype and CYP2C9 genotypes predicted about 40% of the individual variations of warfarin dose. Including non-genetic factors such as age, sex, weight and drug interactions with genotype information predicted more than 50% of warfarin dosing variability.

Aspirin reduces the risk of cardiovascular events in patients with atherosclerotic diseases. However, its effectiveness is limited because a significant portion of the patients with arterial thrombosis who are treated with aspirin has a recurrent event. This is designated as aspirin resistance. To understand aspirin resistance and to develop the effective monitoring system of aspirin effectiveness, we are conducting the Study on Profile and Genetic factors of Aspirin Resistance: ProGEAR Study.

(Jpn J Stroke 29: 721—725, 2007)

Key words: platelet, aspirin, warfarin, VKORC1, antiplatelet therapy

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Antithrombotic Therapy and Predilection for Cerebellar Hemorrhage

Kazunori Toyoda[a] Yasushi Okada[a] Setsuro Ibayashi[d] Tooru Inoue[b]
Kotaro Yasumori[c] Daisuke Fukui[a] Takeshi Uwatoko[a] Noriko Makihara[a]
Kazuo Minematsu[e]

Departments of [a]Cerebrovascular Disease, [b]Neurosurgery and [c]Neuroradiology, Cerebrovascular Center and Clinical Research Institute, National Hospital Organization Kyushu Medical Center, and [d]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, and [e]Cerebrovascular Division, Department of Medicine, National Cardiovascular Center, Suita, Japan

Key Words
Intracerebral hemorrhage · Stroke · Anticoagulants · Warfarin · Antiplatelet therapy · Diabetes mellitus

Abstract
Background: With the recent increase in the use of antithrombotic therapy, intracerebral hemorrhage (ICH) has been found to be a common complication. We determined whether the use of oral antithrombotic therapy and the patients' preexisting comorbidities were predictive of cerebellar hemorrhage (CH; previously reported to be associated with anticoagulants) as compared to other ICH, and whether antithrombotic therapy affected the clinical severity of CH. ***Methods:*** A study of 327 consecutive patients hospitalized in our institute within 3 days after the onset of ICH, including 38 patients with a CH. ***Results:*** CH accounted for 12% of all ICH, 75% of which occurred in patients on warfarin therapy with an international normalized ratio (INR) for prothrombin time >2.5 ($p < 0.0001$), and 33% of which occurred in patients on ticlopidine therapy ($p = 0.017$). Warfarin therapy with an INR >2.5 and high blood glucose on admission were independently predictive of CH as compared to other ICH. In addition, previous ischemic stroke ($p = 0.002$) and heart diseases ($p = 0.018$) were more prevalent in patients with CH than in those with other ICH. The number of major arteriosclerotic comorbidities and risk factors was also independently predictive of CH risk. ***Conclusions:*** We confirmed that warfarin therapy with an INR >2.5 is associated with CH. Patients with CH frequently had arteriosclerotic comorbidities requiring antithrombotic therapy that can complicate their acute management.

Introduction

The use of oral antithrombotic agents, namely oral anticoagulant and antiplatelet drugs, is widespread for the prevention of various arteriosclerotic events, including stroke and certain cardiovascular diseases [1, 2]. Of the various antithrombotic agents, warfarin increases the risk and worsens the outcomes of intracerebral hemorrhage (ICH) [3, 4]. The contribution of antiplatelet therapy to the risk of ICH is still controversial [5, 6]. Recently, we have reported that in patients with ICH, prior oral antiplatelet therapy is independently predictive of clinical deterioration, including the hematoma growth, during the first 2 days [7]. Prior antiplatelet therapy is also predictive of 30-day and 3-month mortality after ICH [8,

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Kazunori Toyoda, MD
Cerebrovascular Division, Department of Medicine
National Cardiovascular Center, 5-7-1 Fujishirodai, Suita
Osaka 565-8565 (Japan)
Tel. +81 6 6833 5012, Fax +81 6 6872 7486, E-Mail toyoda@hsp.ncvc.go.jp

9]. Thus, ICH is an important complication of both oral anticoagulant and antiplatelet therapies.

Overall, cerebellar hemorrhage (CH) accounts for approximately 10% of all ICH [10, 11], and hypertension is the leading risk factor for CH. Anticoagulant therapy has traditionally been considered as another important etiological factor [10], given the data reported in previously published articles [12, 13]. In several studies, there was a high percentage of CH (14–38%) among patients on oral anticoagulant therapy developing ICH [13–15], while in other studies the percentage was lower (1–6%) [16–18]. The precise contribution of antiplatelet therapy to the occurrence of CH has not yet been determined. Given the current prevalence of arteriosclerotic diseases and the consequent use of antithrombotics, it is necessary to focus our attention on the relationship between CH and the pre-existing use of anticoagulants and antiplatelets.

The first aim of this study was to determine the underlying risk factors and comorbidities, including the use of oral antithrombotic therapy, which were associated with an increased risk of CH as compared to other ICH. The second aim of this study was to determine the effect of antithrombotic therapy on the clinical severity of CH.

Methods

We studied 327 consecutive Japanese patients, 197 men and 130 women aged 33–92 years, with nontraumatic ICH who were hospitalized within 3 days after stroke onset in our cerebrovascular center between January 1999 and February 2005. Patients were identified using the prospectively recorded database for all the inpatients in our institute. Patients with ICH due to aneurysmal rupture, vascular malformations and with hemorrhagic transformation after brain infarction, as well as those who hemorrhaged primarily into the ventricles, were excluded. Patients on thrombolysis or intravenous antithrombotics including heparin, those who were pregnant and pediatric patients were also excluded.

In all patients, ICH was verified on CT scan immediately following admission to our center. The location, number and volume of the hematomas, the presence of ventricular bleeding, and the time interval from ICH onset to CT scanning were documented. ICH volume was determined using the ABC/2 method by neuroradiologists blinded to the patients' clinical histories [19].

Warfarin was included as the target oral anticoagulant and aspirin, ticlopidine and cilostazol (a selective phosphodiesterase inhibitor) were included as the target oral antiplatelets. During the study period, clopidogrel was not commercially available in Japan.

The following patient baseline characteristics were assessed: gender, age, previous symptomatic ICH, previous symptomatic ischemic stroke, hypertension [systolic blood pressure (BP) $\geq$140/diastolic BP $\geq$90 mm Hg before ICH onset or history of antihypertensive medication], diabetes mellitus (fasting blood glucose $\geq$126 mg/dl or positive 75-gram oral glucose tolerance test before ICH onset or in the chronic phase after ICH, or a history of antidiabetic medication), hypercholesterolemia (serum total cholesterol $\geq$220 mg/dl or a history of antihypercholesterolemic medication), current or previous smoking, alcohol consumption $\geq$2 drinks/day ($\geq$150 g ethanol/week) [20], heart diseases (including arrhythmia), liver diseases and neoplasm. The number of major arteriosclerotic comorbidities and risk factors (previous symptomatic ICH or ischemic stroke, hypertension, diabetes mellitus, hypercholesterolemia, current or previous smoking, and heart diseases) was also assessed. On admission, the systolic and diastolic BP, blood glucose, total cholesterol, platelets, fibrinogen, activated partial thromboplastin time and the international normalized ratio (INR) for prothrombin time were determined.

The neurological deficits on admission were evaluated using the National Institutes of Health Stroke Scale (NIHSS) score. Activities of daily living before and 3 weeks after ICH onset were assessed using the modified Rankin Scale score.

Continuous values are expressed as means $\pm$ SD. The clinical characteristics of patients with CH were compared to those with other ICH using the χ^2 test and Mann-Whitney U test, as appropriate. Two-way factorial analysis of variance (ANOVA) followed by Fisher's PLSD post hoc analysis was used to analyze the subgroups receiving warfarin, antiplatelets and no antithrombotics. To identify the independent predictors of predilection of ICH for the cerebellum, we did a multivariate logistic regression analysis using the clinical characteristics that showed a statistically significant ($p < 0.05$) or a marginally significant ($0.05 \leq p < 0.1$) relationship with CH as independent variables on univariate analyses, with adjustments for gender and age.

Results

Of the 327 ICH patients, 38 (12%) developed CH, 180 (55%) developed ICH in the basal ganglia, 84 (26%) developed ICH in a hemispheric lobe, and 25 (7%) developed ICH in the brainstem.

With respect to baseline characteristics, patients with CH more frequently had previous symptomatic ischemic stroke ($p = 0.002$) and heart disease ($p = 0.018$) compared to patients having other ICH (table 1). The median number of major arteriosclerotic comorbidities and risk factors was 3 (range 0–6) for patients with CH and 2 (0–6) for those with other ICH ($p = 0.0003$). On admission, patients with CH more frequently had a systolic BP >200 mm Hg ($p = 0.035$) and had a higher blood glucose level ($p = 0.0002$) than those with other ICH (table 1).

Twenty-four patients (7%) were taking warfarin, and 5 of them were also taking aspirin or ticlopidine (table 2). The admission INR values differed between the patients with CH and those with other ICH (CH 2.50 $\pm$ 0.82 vs. other 1.87 $\pm$ 0.59, $p = 0.042$, fig. 1). Sixty-six patients (20%) were taking oral antiplatelet agents daily before ICH onset. The indications for antithrombotic therapy in

Table 1. Clinical characteristics of patients with ICH

	Cerebellar hemorrhage (n = 38)	Other hemorrhage (n = 289)	p value
Baseline characteristics			
Male gender	23 (61)	174 (61)	0.970
Age, years	70 ± 10	67 ± 12	0.114
Hypertension	35 (92)	235 (81)	0.099
Diabetes mellitus	11 (29)	50 (17)	0.083
Hypercholesterolemia	12 (32)	53 (18)	0.054
Smoking habit	16 (42)	118 (41)	0.894
Alcohol consumption	7 (18)	67 (23)	0.503
Comorbidities			
Symptomatic ICH	7 (18)	31 (11)	0.164
Symptomatic ischemic stroke	15 (39)	53 (18)	0.002
Heart diseases	13 (34)	52 (18)	0.018
Atrial fibrillation	7 (18)	27 (9)	0.085
Ischemic heart disease	5 (13)	21 (7)	0.207
Liver diseases	1 (3)	19 (7)	0.340
Neoplasm	4 (11)	30 (10)	0.978
Number of major comorbidities and risk factors			
Median	3	2	0.0003
Range	0–6	0–6	
Physiological status on admission			
Systolic BP, mm Hg	182 ± 38	176 ± 32	0.259
Systolic BP >200 mm Hg	14 (37)	62 (21)	0.035
Diastolic BP, mm Hg	96 ± 23	95 ± 16	0.650
Blood glucose, mg/dl	188 ± 95	144 ± 64	0.0002
Platelets, × 1,000/μl	235 ± 78	210 ± 74	0.058
Fibrinogen, mg/dl	351 ± 116	326 ± 108	0.239
APTT, s	29.2 ± 6.4	31.2 ± 16.5	0.495

APTT = Activated partial thromboplastin time. Figures in parentheses indicate percentages.

Table 2. Use of antithrombotic agents before onset of ICH

	Cerebellar hemorrhage (n = 38)	Other hemorrhage (n = 289)	p value
Warfarin alone	7 (18)	12 (4)	0.0004
Warfarin plus aspirin (81–100 mg)	0	4 (1)	0.466
Warfarin plus ticlopidine (200 mg)	1 (3)	0	0.006
Aspirin alone	4 (11)	38 (13)	0.650
Ticlopidine alone	4 (11)	8 (3)	0.017
Cilostazol alone	1 (3)	2 (1)	0.238
Multiple antiplatelets	1 (3)	8 (3)	0.961

Figures in parentheses indicate percentages.

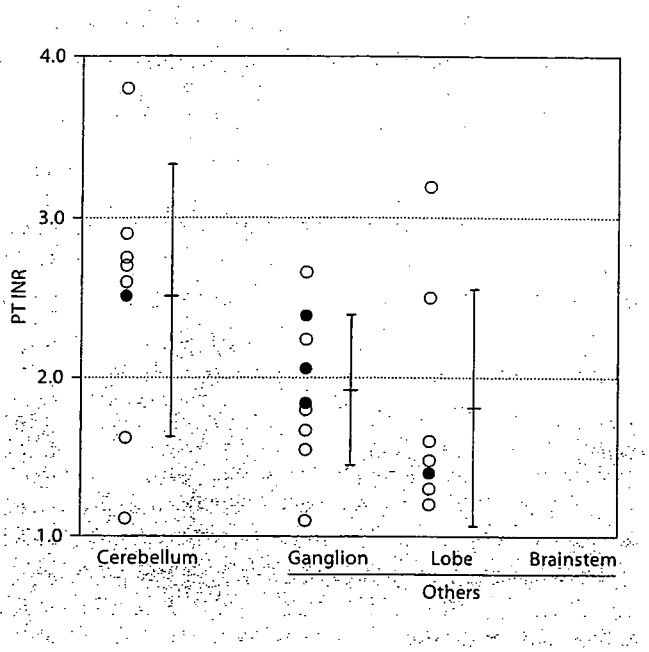
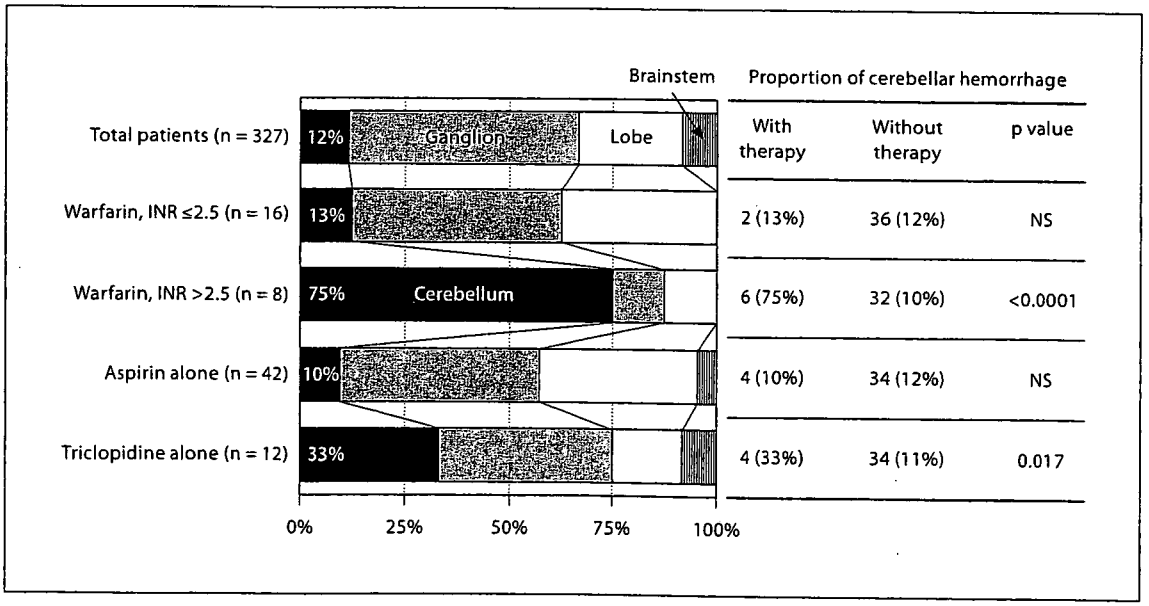


Fig. 1. Admission INR for prothrombin time (PT) for patients on warfarin therapy. Closed circles indicate patients who were also taking antiplatelets. Bars indicate means ± SD. The Mann-Whitney U test shows a significant difference in the INR between patients with CH and other hemorrhage.

patients with CH included cardioembolic stroke in 4 (all of whom received warfarin), other ischemic stroke in 11 (2 on warfarin therapy and 9 on antiplatelet agents), nonvalvular atrial fibrillation without previous stroke in 2 (all of whom received warfarin) and other peripheral vascular diseases in 1 patient (treated with aspirin). The proportion of CH to total ICH increased from 12% of the total patients to 75% of the patients on warfarin therapy with INR >2.5 ($p < 0.0001$) and to 33% of the patients on ticlopidine ($p = 0.017$, fig. 2).

On multivariate analysis using 'any antithrombotic therapy before stroke onset' and the items in table 1 that were statistically significantly or marginally significantly different between the 2 groups as variables, only high blood glucose on admission was independently related to CH (table 3, model 1). The results were similar when either warfarin or ticlopidine use was included instead of any antithrombotic therapy. On the other hand, when warfarin therapy with an INR >2.5 was included instead of any antithrombotic therapy, it was found to be an independent predictor of CH, as was high blood glucose (odds ratio 1.83, 95% confidence interval 1.10–3.06). The total number of major arteriosclerotic comorbidities and risk factors was also independently predictive of CH after



	Proportion of cerebellar hemorrhage		
	With therapy	Without therapy	p value
Total patients (n = 327)			
Warfarin, INR ≤2.5 (n = 16)	2 (13%)	36 (12%)	NS
Warfarin, INR >2.5 (n = 8)	6 (75%)	32 (10%)	<0.0001
Aspirin alone (n = 42)	4 (10%)	34 (12%)	NS
Triclopidine alone (n = 12)	4 (33%)	34 (11%)	0.017

Fig. 2. Hematoma location in patients on various oral antithrombotic therapies at stroke onset. The table shows the proportion of CH to all ICH in patients with and without each type of antithrombotic therapy. Patients receiving both antiplatelet and warfarin therapy were included in the warfarin group. Data on treatment with cilostazol alone (n = 3) and multiple antiplatelets (n = 9) are not shown due to the small number of patients.

Table 3. Multivariate analysis of independent predictors of predilection for CH

Items	p value	OR	95% CI
Model 1			
Hypercholesterolemia	0.10	2.00	0.88–4.57
Symptomatic ischemic stroke	0.27	1.68	0.67–4.18
Heart diseases	0.12	1.99	0.83–4.78
Systolic BP >200 mm Hg	0.11	1.91	0.87–4.17
High blood glucose (by 100 mg/dl)	0.03	1.76	1.07–2.89
Platelet count (by 50,000/μl)	0.21	1.19	0.90–1.58
Preexisting antithrombotic therapy			
Any	0.63	1.26	0.50–3.19
Warfarin	0.08	2.95	0.86–10.1
Warfarin with an INR >2.5	0.001	19.5	3.32–114.9
Ticlopidine	0.24	2.28	0.58–8.96
Model 2			
Number of major comorbidities and risk factors	0.002	1.63	1.19–2.24
Warfarin with an INR >2.5	0.001	16.7	3.09–90.6

Adjusted by gender and age (by 10 years).

Model 1: analysis using each comorbidity and risk factor plus various types of preexisting antithrombotic therapy. Odds ratios (OR) and 95% confidence intervals (CI) of the first 6 items were determined in case of any antithrombotic therapy. Hypertension and diabetes mellitus were not included in the analysis although they showed marginally significant differences in table 1, because systolic BP >200 mm Hg and high blood glucose were used instead.

Model 2: using 'number of major comorbidities and risk factors' and 'warfarin with an INR >2.5'.

adjustment for gender, age and warfarin therapy with an INR >2.5 (table 3, model 2).

Ventricular bleeding on the initial CT was more frequent (p = 0.046), and severe initial neurological deficits (NIHSS ≥16) tended to be more frequent in patients with CH than in patients with other ICH (p = 0.063, table 4). Patients with CH on warfarin therapy had larger hematomas but did not have a higher NIHSS score than those receiving antiplatelet therapy or those not taking any antithrombotic therapy (fig. 3a, b). Patients with CH on ticlopidine did not have a statistically significantly different hematoma volume or NIHSS score compared to other patients (data not shown).

Three weeks after ICH onset, patients with CH tended to be less independent (p = 0.066) and more frequently required hematoma evacuation than those with other ICH (p = 0.035, table 4). The outcome did not differ among patients with a CH who were taking warfarin, antiplatelet agents or those who were not taking any antithrombotic therapy (fig. 3c).

Discussion

In this study, we focused on the important causal relationship between warfarin and CH during this period of widespread antithrombotic therapy. Our major new finding was that warfarin therapy with an INR >2.5 and the number of major arteriosclerotic comorbidities and risk factors were independently predictive of the more frequent occurrence of CH as compared to other ICH. Among antiplatelet agents, ticlopidine increased the proportion of CH to total ICH.

Kase et al. [13] studied the predilection for the cerebellum (9/24, 38%) as a bleeding location in patients on anticoagulant therapy based on their original data and prior small population studies. However, they did not offer a clear explanation for their findings. Our study confirmed their observations and highlighted the association of an INR >2.5 with an increase in CH compared to other ICH. However, we could not identify any causal pathological or pathophysiological characteristics. Cerebellar microbleeds were visualized in 29 of 98 Korean stroke patients (30%) who had microbleeds somewhere in

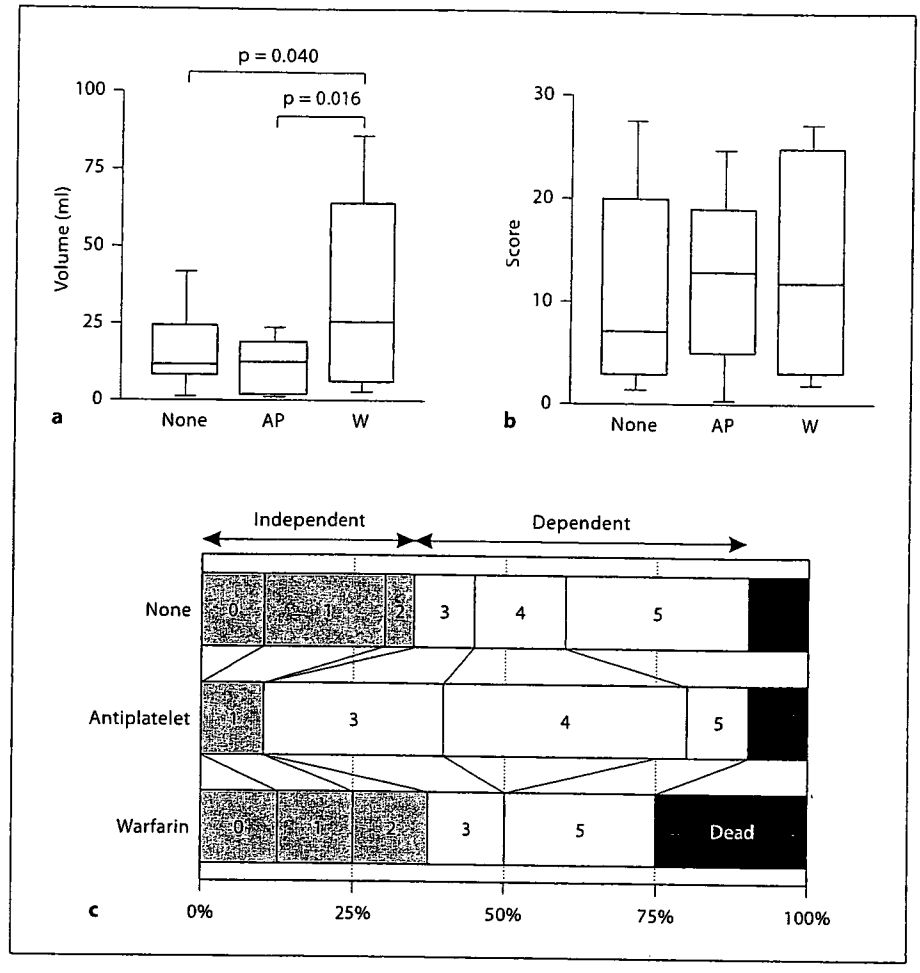


Fig. 3. Comparison of hematoma volume on admission (**a**), the NIHSS score on admission (**b**) and the modified Rankin Scale score, including acute death, at 3 weeks (**c**) among patients with a CH on antiplatelet (AP), warfarin (W) and no antithrombotic therapy (none). **a** Two-way factorial ANOVA shows a significant difference in hematoma volume among the 3 groups ($p = 0.042$) with post hoc differences shown.

Table 4. CT findings, neurological status and outcome of patients with ICH

	Cerebellar hemorrhage (n = 38)	Other hemorrhage (n = 289)	p value
CT findings			
Multiple hematoma	1 (3)	6 (2)	0.824
Volume of hematoma	19.8 ± 21.4	25.5 ± 38.5	0.373
Ventricular bleeding	18 (47)	90 (31)	0.046
ICH onset to CT <3 h	18 (49)	134 (46)	0.793
Neurological status			
mRS before ICH ≥ 3	4 (11)	14 (5)	0.149
NIHSS on admission ≥ 16	15 (39)	73 (25)	0.063
Outcome at 3 weeks			
Independent, mRS ≤ 2	11 (29)	129 (45)	0.066
Dependent, mRS ≥ 3	22 (58)	131 (45)	0.144
Dead	5 (13)	29 (10)	0.553
Required surgical evacuation	14 (37)	62 (21)	0.035

mRS = Modified Rankin Scale. Figures in parentheses indicate percentages.

the brain on T_2*-weighted gradient-echo MRI [21], which suggests a relatively high frequency of cerebellar microbleeds in the Asian population. Thus, chronic warfarin might cause subclinical cerebellar microbleeds to grow to symptomatic CH [18], thus explaining the increased prevalence of cerebellar involvement in warfarin-related ICH. A similar predilection for the cerebellum was not found in patients after coronary thrombolysis using tissue plasminogen activator or streptokinase; in these patients, the primary bleeding location was a hemispheric lobe [22–24]. After cerebrovascular thrombolysis using prourokinase, hemorrhages were found to occur primarily in the area of the preceding infarcts and not in the cerebellum [25]. Thus, different mechanisms may be operative in patients with postthrombolysis ICH compared to patients who have ICH during warfarin therapy.

Our study found that ticlopidine was associated with CH, although the result was based on data derived from a small number of patients. Aspirin was not associated with CH in this and in previous studies [26]. This difference between aspirin and ticlopidine might partly be due to a different intensity of treatment or a different mechanism of action with respect to antiplatelet function between these 2 agents.

High blood glucose on admission was independently associated with CH. This finding may be partly due to the high frequency of diabetic patients in the CH group. The prevalence of diabetes mellitus in patients with CH, as well as that of previous ischemic stroke, heart disease and hypercholesterolemia, would appear to be at least partly due to the use of antithrombotic therapy for these arteriosclerotic comorbidities. Interestingly, the proportion of CH increased with a greater number of comorbidities or risk factors. The existence of multiple comorbidities may complicate the acute management of these patients.

Although warfarin treatment appeared to contribute to greater initial hematoma size, this did not adversely affect the 3-week post-CH outcome. The effect of warfarin in patients with high INR values was primarily reversed using vitamin K or prothrombin complex concentrate including coagulation factors II, VII, IX and X [17, 27]. This strategy might have prevented hematoma growth and the associated poor outcome. The limitations of this analysis included the small patient sample and the fact that 3-week outcome might not be fully correlated with long-term outcome.

Despite these limitations, our study found that preexisting warfarin use increased the risk of CH. Recently, ultra-early use of recombinant activated factor VII after ICH has been reported to limit hematoma growth and improved the long-term outcome in patients without disorders of hemostasis [28]. This agent counteracts the effect of warfarin and may also be useful in patients on antiplatelet therapy, although currently there is no effective means to counteract the effects of antiplatelet therapy.

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Early Recurrence of Ischemic Stroke in Japanese Patients: The Japan Standard Stroke Registry Study

Kazunori Toyoda[a] Yasushi Okada[b] Shotai Kobayashi[c]
for the Japan Standard Stroke Registry Study group

[a]Department of Medicine, Cerebrovascular Division, National Cardiovascular Center, Suita,
[b]Department of Cerebrovascular Disease and Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, and [c]Shimane University Hospital, Izumo, Japan

Key Words
Stroke recurrence, risk factors · Stroke subtype · Cerebral infarction · Atherothrombotic stroke · Diabetes mellitus

Abstract
Background: To determine the factors that contribute to early ischemic stroke recurrence in Japanese patients. ***Methods:*** A multicenter stroke registration study based on a computerized database from 54 Japanese institutes, involving 8,036 patients with brain infarction who were hospitalized within 48 h after symptom onset between January 2000 and March 2004. ***Results:*** Within 30 days after the initial stroke, 395 patients (4.9%) developed a recurrent stroke. Recurrence most frequently occurred in atherothrombotic patients (6.6%), followed by cardioembolic patients (6.2%). Overall, hypertension (OR 1.348, 95% CI 1.071–1.696) and atrial fibrillation (OR 1.503, 95% CI 1.177–1.918), but not diabetes mellitus, were independently predictive of early recurrence. In atherothrombotic patients, diabetes mellitus (OR 1.485, 95% CI 1.058–2.085) and atrial fibrillation (OR 1.998, 95% CI 1.231–3.244) were independently related to early recurrence. At hospital discharge, the modified Rankin Scale score was higher in patients who had an early recurrence ($p < 0.0001$). ***Conclusions:*** This study was based on a large number of Japanese patients and confirmed that hypertension and atrial fibrillation contribute to early ischemic stroke recurrence. In addition, analysis by stroke subtype showed that diabetes mellitus was independently related to early recurrence in atherothrombotic patients.

Introduction

Stroke recurrence continues to be a major risk for stroke survivors, despite advances in stroke prevention strategies and treatments [1]. Atherothrombotic ischemic stroke, atrial fibrillation, and both high and low admission blood pressures are known to be predictors of early stroke recurrence [1–3].

The incidence of stroke in Japan surpasses that of ischemic heart disease [4]. A high incidence of lacunar stroke and intracerebral hemorrhage [4, 5] has been documented; this is unique to Japan. To further clarify the characteristics of stroke in Japan, a large hospital-based registration study using a computerized database that included 16,280 patients from 54 institutes was conducted (the Japan Standard Stroke Registry Study: JSSRS) [6]. Using data from this database, we sought to identify the clinical features that were predictive of early ischemic stroke recurrence.

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Kazunori Toyoda, MD
Department of Medicine, Cerebrovascular Division, National Cardiovascular Center
5-7-1 Fujishirodai
Suita, Osaka 565-8565 (Japan)
Tel. +81 6 6833 5012, Fax +81 6 6872 7486, E-Mail toyoda@hsp.ncvc.go.jp

Table 1. Baseline clinical characteristics

	All patients			Atherothrombotic stroke		
	recurrent	nonrecurrent	p value	recurrent	nonrecurrent	p value
Patients	395	7,641		174	2,471	
Age, years	72.0 ± 11.5 (395)	71.2 ± 11.9 (7,641)	0.1888	71.3 ± 10.8 (174)	71.7 ± 11.0 (2,471)	0.5825
Male gender, %	61.6 (393)	59.8 (7,633)	0.4815	66.5 (173)	63.0 (2,469)	0.3625
Previous ischemic stroke, %	35.2 (383)	29.8 (7,471)	0.0222	39.1 (169)	32.7 (2,422)	0.0876
Hypertension, %	66.6 (392)	60.6 (7,620)	0.0188	73.4 (173)	64.4 (2,466)	0.0167
Diabetes mellitus, %	25.7 (393)	24.5 (7,605)	0.5932	37.6 (173)	28.3 (2,466)	0.0090
Hyperlipidemia, %	22.5 (386)	22.6 (7,496)	0.9635	29.7 (172)	26.7 (2,419)	0.3999
Atrial fibrillation, %	33.4 (392)	24.8 (7,613)	0.0001	13.3 (173)	7.9 (2,463)	0.0122
Ischemic heart disease, %	13.3 (376)	11.8 (7,324)	0.3939	13.9 (166)	12.9 (2,372)	0.7112
Aortic aneurysm, %	1.6 (376)	1.0 (7,324)	0.3039	0.0 (166)	1.2 (2,372)	0.1592
Peripheral artery disease, %	0.8 (376)	0.3 (7,324)	0.1515	0.6 (166)	0.4 (2,372)	0.7317
Chronic kidney diseases, %	4.2 (334)	4.2 (6,440)	0.9786	4.2 (143)	4.3 (2,046)	0.9521
Hemodialysis, %	0.6 (334)	1.4 (6,440)	0.2002	1.4 (143)	1.4 (2,046)	0.9853
Alcohol consumption[1], %	9.7 (361)	9.4 (6,936)	0.8443	9.6 (157)	11.0 (2,183)	0.5646
Smoking habit[2], %	36.1 (352)	37.6 (6,770)	0.5564	41.6 (154)	39.7 (2,139)	0.6559
Prestroke medication						
Anticoagulants, %	10.1 (286)	7.3 (5,595)	0.0776	4.9 (142)	5.3 (1,892)	0.8547
Antiplatelets, %	24.1 (286)	17.6 (5,595)	0.0052	29.6 (142)	18.1 (1,892)	0.0007
Antihypertensives, %	55.1 (392)	47.0 (7,620)	0.0017	58.4 (173)	49.4 (2,466)	0.0229
Insulin, %	4.1 (393)	3.8 (7,605)	0.8054	6.4 (173)	4.5 (2,466)	0.2487
Prestroke mRS: 0–1, %	80.5 (220)	81.1 (4,318)	0.7975	84.7 (111)	80.7 (1,484)	0.3053

Numbers in parentheses indicate the number of patients whose data were available. [1] ≥2 drinks per day. [2] Current or previous.

Methods

Between January 2000 and March 2004, 10,261 patients with acute brain infarction were hospitalized within 48 h after stroke onset and were registered in the JSSRS. In 8,036 of these patients, there was appropriate documentation in the database to ascertain whether there was stroke recurrence within 30 days after the onset of the initial stroke; thus, these patients were eligible to be included in this study.

The subtype of the initial stroke was determined based on the patients' neurological, radiological, cardiological, and hematological profiles, principally according to the TOAST subtype classification system [7]: large-artery atherosclerosis (atherothrombotic), cardioembolism, small-artery occlusion (lacunar), and stroke of other determined or undetermined etiology. Patients were diagnosed as having a recurrent stroke based on the occurrence of additional neurological deficits or the progression of neurological deficits in conjunction with the appearance of a new infarct or hematoma that corresponded to the deficits; radiological confirmation was useful for differentiating stroke recurrence from progressing stroke. The patients' baseline characteristics and features of the initial stroke are listed in table 1. The severity of white matter lesions and periventricular hyperintensity was scored using scales developed in previous studies [8, 9]. Independent activity of daily living before the initial stroke corresponded to a modified Rankin Scale (mRS) score of 0 and 1. Patient outcome at discharge was evaluated using the mRS.

Values are expressed as mean ± SD. The baseline characteristics and stroke features were compared between patients with and without stroke recurrence using the χ^2-test, paired t test, and Mann-Whitney's U test, as appropriate. To identify the independent predictors of stroke recurrence, a multivariate logistic regression analysis was done using the baseline characteristics and stroke features that showed a statistically significant ($p < 0.05$) or a marginally significant ($0.05 \leq p < 0.15$) relationship with recurrence on univariate analyses as independent variables, with adjustments for age and gender. If >20% of patient data for a particular characteristic was missing on univariate analysis, then that characteristic was not used in the multivariate analysis. We also determined which stroke subtypes were independently related to recurrence.

Results

Of the 8,036 patients that were studied, 395 patients (4.9%) had a recurrent stroke within 30 days after the initial stroke. Recurrent strokes were most frequent in atherothrombotic stroke patients (174/2,645, 6.6%), followed by patients with cardioembolic stroke (143/2,318, 6.2%), stroke of other etiology (36/630, 5.7%), and lacunar stroke (42/2,443, 1.7%). Of the 254 patients in whom the day of

Cardioembolic stroke			Lacunar stroke			Stroke of other etiology		
recurrent	nonrecurrent	p value	recurrent	nonrecurrent	p value	recurrent	nonrecurrent	p value
143	2,175		42	2,401		36	594	
73.9 ± 11.8 (143)	73.9 ± 11.3 (2,175)	0.9873	71.2 ± 10.8 (42)	69.4 ± 11.5 (2,401)	0.3162	69.0 ± 13.6 (36)	66.4 ± 15.6 (594)	0.3191
58.5 (142)	55.0 (2,172)	0.4194	57.1 (42)	59.9 (2,398)	0.7195	55.6 (36)	63.6 (594)	0.3290
31.4 (137)	27.7 (2,119)	0.3451	39.0 (41)	29.7 (2,346)	0.1942	27.8 (36)	25.7 (584)	0.7806
61.0 (141)	52.5 (2,166)	0.0501	69.0 (42)	66.5 (2,398)	0.7259	52.8 (36)	51.0 (590)	0.8374
16.2 (142)	17.8 (2,160)	0.6325	23.8 (42)	28.5 (2,389)	0.5000	8.3 (36)	17.1 (590)	0.1692
14.0 (136)	14.4 (2,134)	0.8934	26.2 (42)	26.8 (2,355)	0.9302	16.7 (36)	19.2 (588)	0.7053
73.9 (142)	70.7 (2,170)	0.4150	4.9 (41)	5.3 (2,390)	0.9018	2.8 (36)	5.9 (590)	0.4300
14.8 (135)	14.6 (2,078)	0.9529	15.4 (39)	8.9 (2,295)	0.1635	2.8 (36)	9.2 (579)	0.1897
3.0 (135)	0.8 (2,078)	0.0091	2.6 (39)	0.9 (2,295)	0.2670	2.8 (36)	2.1 (579)	0.7753
1.5 (135)	0.4 (2,078)	0.0933	0.0 (39)	0.1 (2,295)	0.8213	0.0 (36)	0.5 (579)	0.6651
5.9 (119)	3.8 (1,880)	0.2500	2.6 (38)	4.2 (1,968)	0.6379	0.0 (34)	4.9 (546)	0.1842
0.0 (119)	1.3 (1,880)	0.2150	0.0 (38)	1.6 (1,968)	0.4281	0.0 (34)	1.5 (546)	0.4773
8.8 (133)	8.2 (2,005)	0.5503	16.2 (37)	9.0 (2,166)	0.1275	14.7 (34)	8.8 (582)	0.2413
27.3 (128)	30.6 (1,936)	0.4338	44.4 (36)	40.7 (2,128)	0.6450	35.3 (34)	42.0 (567)	0.4427
21.1 (95)	15.6 (1,427)	0.1561	0.0 (29)	3.7 (1,874)	0.2925	10.0 (20)	4.7 (402)	0.2898
20.0 (95)	16.5 (1,427)	0.3817	24.1 (29)	17.8 (1,874)	0.3789	5.0 (20)	18.4 (402)	0.1258
53.2 (141)	44.2 (2,166)	0.0371	57.1 (42)	48.7 (2,398)	0.2783	44.4 (36)	40.3 (590)	0.6263
1.4 (142)	2.4 (2,160)	0.4634	4.8 (42)	5.1 (2,389)	0.9292	2.8 (36)	1.5 (590)	0.5607
75.0 (76)	78.3 (1,081)	0.5068	75.0 (20)	84.3 (1,454)	0.2609	84.6 (13)	78.6 (299)	0.6029

stroke recurrence was documented, 162 patients (63.8%) developed a recurrence within the initial 7 days post onset (fig. 1). Of the 294 patients for whom the recurrent stroke type was documented, 280 patients (95.2%) had an ischemic stroke.

Baseline clinical characteristics and features of the initial stroke for all patients and by subtype are shown in tables 1 and 2. Overall, compared to patients who did not have a recurrent stroke, patients who had an early recurrence more frequently had: a previous ischemic stroke ($p = 0.0222$), hypertension ($p = 0.0188$), atrial fibrillation ($p = 0.0001$), antiplatelet ($p = 0.0052$) and antihypertensive ($p = 0.0017$) medication prior to the initial stroke, and progression of symptoms within 48 h ($p < 0.0001$).

Overall, on multivariate analysis, hypertension and atrial fibrillation were independently related to early stroke recurrence (table 3). In atherothrombotic stroke patients, diabetes mellitus and atrial fibrillation were independently related to recurrence. In cardioembolic stroke patients, hypertension and aortic aneurysm were independently related to recurrence. No independent predictors for early recurrence could be identified in patients with a lacunar stroke and in those with a stroke of other etiology.

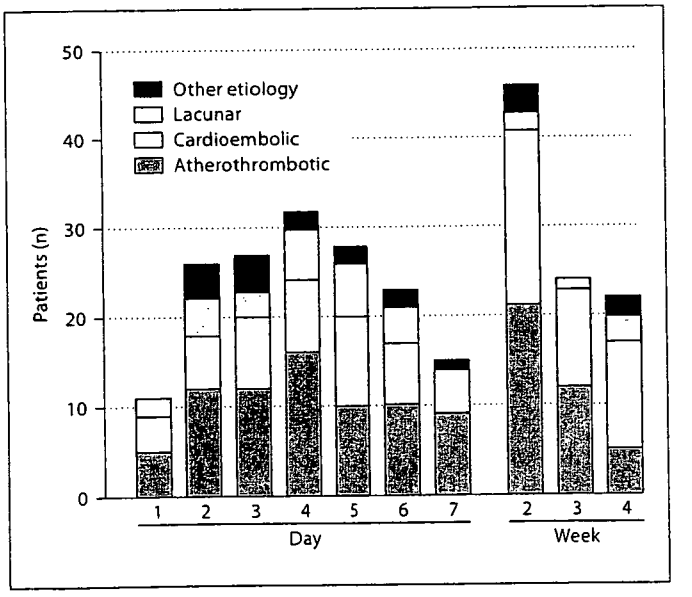

Fig. 1. Timing of stroke recurrence after stroke onset according to the initial stroke subtypes.