3．—過性脳虚血発作の脳卒中リスクスコア

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- —過性脳虚血発作患者のトリアージには，脳卒中リスクスコアが有用である．
- プライマリーケアにおいては，ABCD²スコアを用いて早期再発リスクの層別化を行う．
- ABCD²スコアに画像所見などの項目を組み込んだ新たな脳卒中リスクスコアが提唱されている．

Key Words　—過性脳虚血発作，ABCD²スコア，ABCD²Iスコア，ABCD³スコア，ABCD³Iスコア

—過性脳虚血発作（transient ischemic attack：TIA）は，その後の脳梗塞発症に対する警告発作である．発症直後のTIAは特に脳梗塞の危険が高く，最近の欧米の報告をまとめると，TIA患者のおおむね20%前後が3ヵ月以内に完成型脳梗塞を発症し，そのうちの約半数は最初の2日以内である．したがって，症状が消失したからといって決して軽視してはならないし，ハイリスク症例はただちに専門施設で加療しなければならない．何よりも「スピード」が重要である．一旦脳梗塞を発症し，後遺症により損なわれる患者自身のQOLや周囲の介護の負担などを鑑みると，迅速な対応によって未然に脳梗塞への移行を防ぐことができたならば，TIAの診療意義は非常に大きいといえるだろう．

TIAと脳梗塞（急性脳血管症候群）は同一スペクトラム上の疾患であり，心血管における狭心症と心筋梗塞（急性冠症候群）の関係と相同である．循環器領域では狭心症のなかでも特にリスクの高い不安定狭心症を区別して扱うように，TIA患者においても脳梗塞発症リスクの高い患者を抽出し，早期評価・早期治療を実践することが重要である．本稿では特に，ハイリスク症例の選別（トリアージ）の指標となる脳卒中リスクスコアについて解説したい．

□ ABCD²スコア

ABCD²スコアはA（age：年齢），B（blood pressure：血圧），C（clinical features：臨床症候），D（duration：症状の持続時間），D（diabetes：糖尿病）の頭文字を取って名付けられた代表的な脳卒中リスクスコアである（**表1**）．これらの合計点数（5項目・0〜7点）はTIA発症後早期の脳卒中再発リスクに相関することが明らかにされている[1]．**図1**に示したとおり，2日以内の再発率は，0〜3点の低リスク群で1.0%，4〜5点の中リスク群で4.1%，6〜7点の高リスク群では8.1%にも及ぶ．さらには7日以内，30日以内，90日以内の累積リスクも同様に増加することが示されている．

ABCD²スコアは特殊な検査項目や専門的な事項を含まないという点で優れたスコア法であり，専門外の医師や一般医によるプライマリーケアの場でも広く活用することが可能である．TIAを疑う患者を診たら，ABCD²スコアから脳梗塞再発リスクを推定し，専門医へのコンサルトや入院が必要な症例を選別する必要がある．米国心臓協会（American Heart association：AHA）/米国脳卒中協会（American Stroke Association：ASA）はTIA患者の入院の適応をABCD²スコアに基づいて推奨している．それによれば，①発症72時間以内でABCD²スコアが3点以上のケース，もしくは，2点以下でも，②外来での精査が2日以内に可能かどうか不明なケース，③発作の原因が局所脳虚血であることが確定的であるケース，はただちに入院すべきとしている[2]．

さらにはABCD²スコアが高値であるほど真のTIAである確率が高まるという報告もある[3]．

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TIA 患者の多くは診察時には症状が消失しているため，その診断には一定の不確実性を伴うものだが，ABCD²スコアが TIA と他の非血管性イベントとの鑑別に有用である可能性がある．また，ABCD²スコア高値は再発イベントの重症度に関連することも指摘されている[4]．

□ 新たな脳卒中リスクスコア

ABCD²スコアの項目以外にも，MRI 拡散強調画像（diffusion weighted image：DWI）での陽性所見（すなわち梗塞巣）や MRA での主幹動脈の閉塞病変を有する症例もリスクが高いことが従来から報告されていた．また，発作を繰り返している「crescendo TIA」例では早期再発リスクが高いことも知られている．これらの事実を踏まえて，ABCD²スコアに新たな因子を組み込むことで，よりハイリスク症例の判別に優れたスコアを作成する試みがなされている．

Giles らは，ABCD²スコアに「MRI DWI での陽性所見」または「CT での脳梗塞巣」の有無を加えた「ABCD²I スコア」（表 2）の有用性を報告した[5]．それによれば，MRI DWI での陽性所見，CT での脳梗塞巣はともに独立した早期再発の予測因子であり（それぞれ OR 14.9，95%，CI 7.4～30.2；OR 4.2，95%，CI 2.6～6.9），従来の ABCD²スコアに「I」（infarction：梗塞）として点数を加算することで，7 日以内の再発イベントとの関連が向上したという．さらに「I」の点数の加重についても検討したところ，3 点とした場合にもっともリスクスコアとしての精度に優れていることが示唆された（図 2）．

Merwick らは，ABCD²スコアに D（dual TIA：反復性の TIA＝最近 1 週間以内に先行す

表 1　ABCD²スコア

	ABCD²スコア
A：年齢　≥60 歳	1
B：血圧　≥140/90 mm Hg	1
C：臨床症候	
脱力を伴わない言語障害	1
片麻痺	2
D：症状の持続時間	
10～59 分	1
≥60 分	2
糖尿病	1
合計点の範囲	0～7

（Johnston SC, et al.：Lancet 369：283-292, 2007[1]より引用改変）

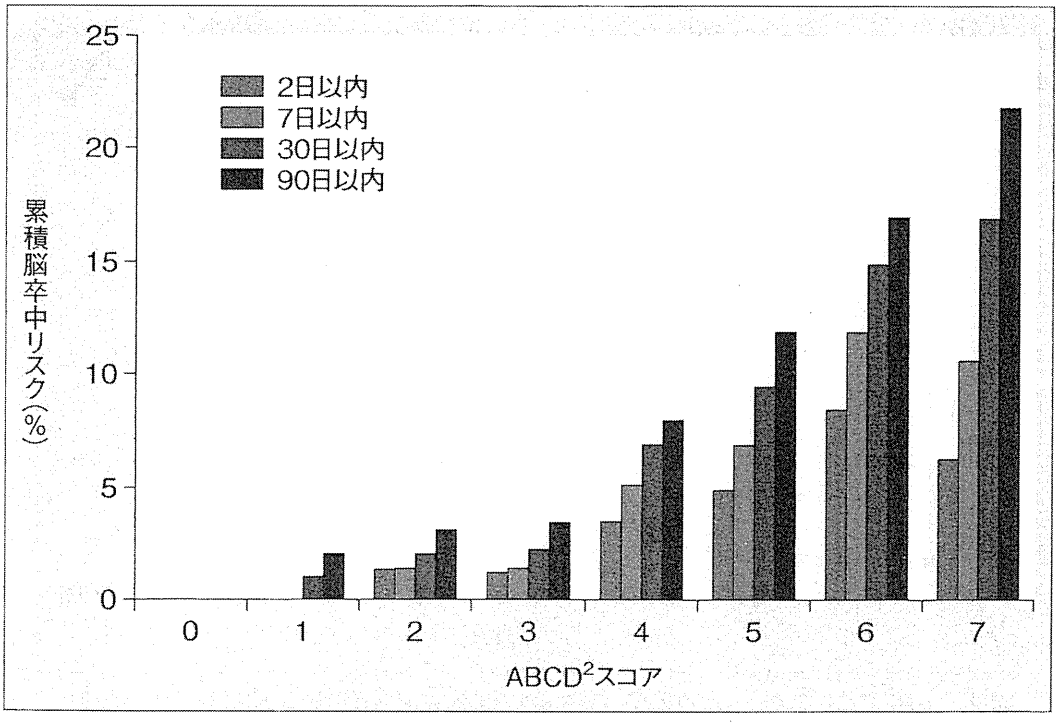

図 1　ABCD²スコアと TIA 発症後の累積脳卒中リスク
（Johnston SC, et al.：Lancet 369：283-292, 2007[1]より引用改変）

る発作があったこと）を加えたABCD^{3}スコア（表3），さらにそれにI（imaging：頸動脈の50%以上の有意狭窄，MRI DWIでの陽性所見）を加えたABCD^{3}Iスコア（表3）を検討している[6]．その結果，病院ベースコホートの解析においては，従来のABCD^{2}スコアよりもABCD^{3}スコアとABCD^{3}Iスコアのほうが早期再発患者の予測に優れていることが示された．しかしながら，同様に一般住民のコホートを対象として検証したところ，ABCD^{2}スコアに対してABCD^{3}スコアはほぼ同等，ABCD^{3}Iスコアは優れている傾向があったものの有意ではないという結果であった．

ABCD^{2}スコアにはすでに一定のコンセンサスが得られているといえるが，これらの新たな脳卒中リスクスコアについては今後もさらなる検証が必要だろう．

表2　ABCD^{2}Iスコア

	ABCD^{2}Iスコア
A：年齢　≥60歳	1
B：血圧　≥140/90 mm Hg	1
C：臨床症候	
脱力を伴わない言語障害	1
片麻痺	2
D：症状の持続時間	
10～59分	1
≥60分	2
糖尿病	1
I：梗塞巣	
MRI DWIの高信号域またはCTで梗塞巣	3
合計点の範囲	0～10

（Giles MF, et al.：Stroke 41：1907-1913, 2010[5]より引用改変）

まとめ

TIA患者のトリアージのツールとして，プライマリーケアではABCD^{2}スコアを，セカンダリーケアではABCD^{2}IスコアやABCD^{3}Iスコアを活用できれば，ステージに即したリスクの把握やより適切な管理が可能となるであろう．しかし，これらの脳卒中リスクスコアはあくまで指標の一つとすべきであり，一様にすべての患者に当てはめられるわけではない．特に動脈硬化性因子の関与が少ない心原性TIAや若年のケースなどでは，ハイリスクであってもスコアに反映されにくいの

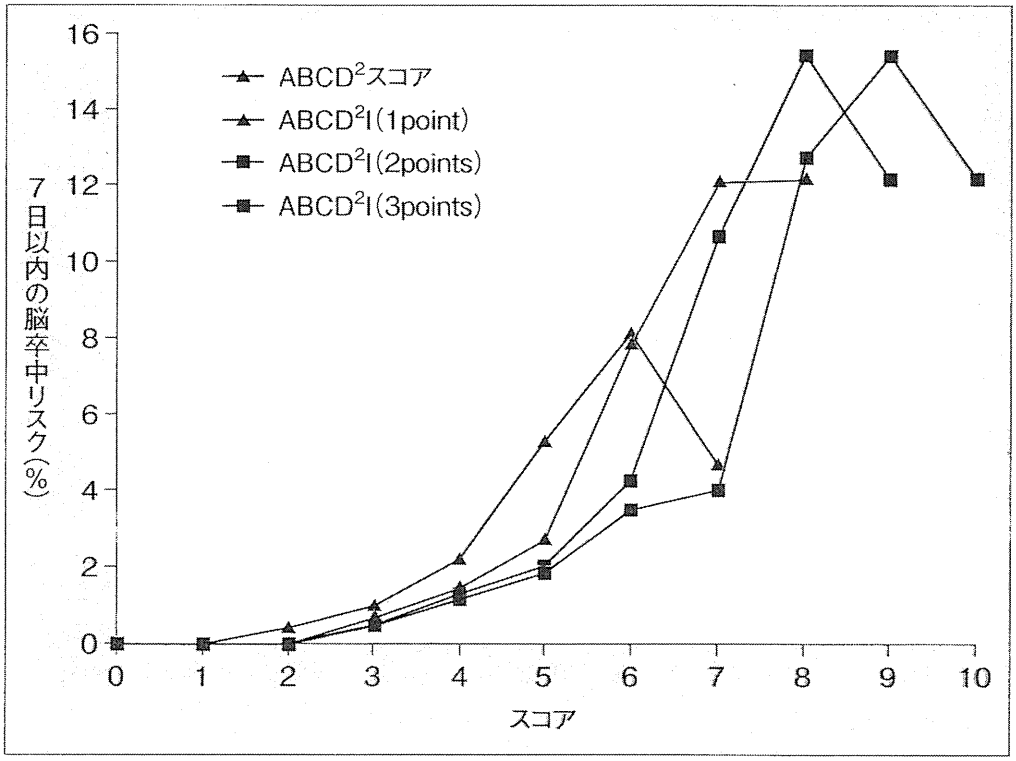

図2　ABCD^{2}スコア，Iの点数を1～3点に変化させた場合のABCD^{2}Iスコアと脳卒中リスク

（Giles MF, et al.：Stroke 41：1907-1913, 2010[5]より引用改変）

表3　ABCD^{3}I スコアと ABCD^{3}I スコア

	ABCD^3 スコア	ABCD^{3}I スコア
A：年齢　≥60 歳	1	1
B：血圧　≥140/90 mm Hg	1	1
C：臨床症候		
脱力を伴わない言語障害	1	1
片麻痺	2	2
D：症状の持続時間		
10～59 分	1	1
≥60 分	2	2
糖尿病	1	1
反復性の TIA	2	2
I：画像所見		
50%以上の頸動脈狭窄病変	—	2
MRI DWI の高信号域	—	2
合計点の範囲	0～9	0～13

（Merwick A, et al.：Lancet Neurol 9：1060-1069, 2010[6]より引用改変）

で，注意を払うべきである．

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8．急性脳血管症候群の再発予防対策

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- 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）．
- 非心原性の脳梗塞（アテローム血栓性脳梗塞，ラクナ梗塞，原因不明の脳梗塞）とTIAの再発予防には抗血小板療法が第一選択となる．
- 心原性脳塞栓症と心原性TIAの再発予防には抗凝固療法が第一選択となる．
- 頸動脈高度狭窄によるTIAに対しては，頸動脈内膜剥離術（CEA）が推奨される．
- TIAの進展予防には禁煙（グレードA），適量の飲酒（グレードC）が推奨される．適切な降圧療法（アンジオテンシン変換酵素阻害薬など）やスタチン療法は脳卒中再発リスクを有意に抑制する（グレードA）．

Key Words 急性脳血管症候群，再発予防，抗血小板療法，抗凝固療法，頸動脈狭窄

一昨年，5年ぶりに改訂された『脳卒中治療ガイドライン2009』では，新たに一過性脳虚血発作（transient ischemic attack：TIA）の治療に関する項目が加えられた（**表1**）[1]．発症直後のTIAを急性期脳梗塞とともに急性脳血管症候群（acute cerebrovascular syndrome：ACVS）[2]というコンセプトに包括し，適切な治療方針を決定する必要がある．

□ 非心原性の脳梗塞（アテローム血栓性脳梗塞，ラクナ梗塞，原因不明の脳梗塞）とTIAの再発予防には抗血小板療法の適応がある

1．アスピリン

アスピリンは医療経済効果に優れ，世界でもっとも広く用いられている抗血小板薬である．また，脳梗塞急性期治療ガイドラインで唯一推奨されている経口抗血小板薬である（**表2**）[1]．

中国で行われた，脳梗塞急性期患者約2万例を対象として，アスピリン（160 mg/日を4週間）の有効性と安全性をプラセボと比較したCAST（Chinese Acute Stroke Trial）によると，治療期間中の全死亡，脳梗塞の再発はアスピリン群で有意に低かった（おのおの $2p=0.04$，$2p=0.01$）一方，出血性脳卒中の発症は，プラセボと比較し，アスピリン群で有意な増加がなかった（$2p>0.1$）．4週間後の死亡または要介護は，アスピリン群で減少する傾向が示され（$2p=0.08$），脳梗塞急性期におけるアスピリンの有用性が示された[3]．

日本も含む世界36ヵ国で行われた，急性期脳梗塞患者を対象として，アスピリン（300 mg/日を2週間）とヘパリン（10,000単位/日または25,000単位/日）の単独または併用療法の有効性と安全性を比較したIST（International Stroke Trial）の結果によると，アスピリンは急性期の脳梗塞の再発を有意に抑制し（$2p=0.03$），6ヵ月後の死亡または要介護も有意に減少させた（$2p=0.03$）[4]．

ISTとCAST試験の複合解析の結果では，アスピリンは脳梗塞の再発と死亡を低下させ，脳出血をわずかに増加させるものの有意差はなく，全体として脳卒中または死亡を有意に抑制した[5]．また，ISTとCASTを中心としたCochrane Database Systematic Reviewによれば，発症48時間以内のアスピリン160～300 mg/日の経口投与による抗血小板療法が，早期の重大な出血合併症を増加させることなく，脳梗塞の早期再発を抑制し，長期予後も改善するとしている[6]．

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表1　脳卒中治療ガイドライン2009「TIAの急性期治療と脳梗塞発症防止」

推奨

1．一過性脳虚血発作（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ただちに開始しなくてはならない（グレードA）．
2．TIAの急性期（発症48時間以内）の再発防止には，アスピリン160～300 mg/日の投与が推奨される（グレードA）．
3．非心原性TIAの脳梗塞発症予防には抗血小板療法が推奨され，本邦で使用可能なものはアスピリン75～150 mg/日，クロピドグレル75 mg/日（以上，グレードA），シロスタゾール200 mg/日，チクロピジン200 mg/日（以上，グレードB）である．必要に応じて降圧薬（アンジオテンシン変換酵素阻害薬など），スタチンの投与も推奨される（グレードA）．
4．非弁膜症性心房細動（NVAF）を中心とする心原性TIAの再発防止には，第一選択薬はワルファリンによる抗凝固療法（目標INR：70歳未満では2.0～3.0，70歳以上では1.6～2.6）である（前者グレードA，後者グレードB）．
5．狭窄率70%以上の頸動脈病変によるTIAに対しては，頸動脈内膜剝離術（CEA）が推奨される（グレードA）．狭窄率50～69%の場合は年齢，性，症候などを勘案しCEAを考慮する（グレードB）．狭窄率50%未満の場合は，積極的にCEAを勧める科学的根拠に乏しい（グレードC1）．CEA適応症例ではあるが，心臓疾患合併，高齢などCEAハイリスクの場合は，適切な術者による頸動脈ステント留置術（CAS）を行ってもよい（グレードB）．
6．TIAおよび脳卒中発症予防に，禁酒（グレードA），適切な体重維持と運動の励行が推奨される（グレードC）．飲酒は適量であればよい（グレードC1）．

（篠原幸人，他 編：脳卒中治療ガイドライン2009．協和企画，東京，2009[1]より引用・改変）

表2　脳卒中治療ガイドライン2009「急性期抗血小板療法」

推奨

1．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）．
2．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）．

（篠原幸人，他 編：脳卒中治療ガイドライン2009．協和企画，東京，2009[1]より引用・改変）

2．オザグレルナトリウム

本邦では，発症後5日以内のアテローム血栓性脳梗塞およびラクナ梗塞に対して，オザグレルナトリウムが最大で14日間投与可能である．出血性合併症の頻度も少なく，嚥下障害のある症例にも投与できるなどの利点があるが，海外では用いられていない．

3．クロピドグレル

TIAに対する早期対応の有効性を示した試験EXPRESS（Effect of Urgent Treatment of Transient Ischaemic Attack and Minor Stroke on Early Recurrent Stroke）[7]とFASTER（Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence）[8]では，発症直後のTIAの危険性が示されたのと同時に，TIAに対する発症24時間以内の初期対応が非常に重要であることが明らかとなっている．この試験を含むアスピリンとクロピドグレルの併用療法が施行された試験のなかで，発症24時間以内の急性期治療に関する90日間の結果をメタアナリシスにより解析した結果では，アスピリンとクロピドグレルの併用により，脳卒中を含む血管イベントおよび全死亡は34%の減少が認められた[7]．

欧米において何らかの危険因子を有する軽症脳梗塞またはTIA患者を対象としたクロピドグレル単剤療法とクロピドグレル・アスピリン併用療法を比較したMATCH（Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke）[9]，およびアテローム血栓症およびその予備軍を対象としたアスピリン・クロピドグレル併用療法とアスピリン単独療法を比較したCHARISMA（Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance）[10]の成績によれば，クロピドグレル・アスピリン併

用療法は出血リスクを上回るベネフィットはなかったことから，長期の脳梗塞再発予防には推奨できない．

一方，同側頭蓋内外の50%以上の血管狭窄を伴い，微小塞栓子（microembolic signals：MES）を認める急性期脳梗塞またはTIA患者を対象として，アスピリン単独療法（75～160 mg）と，アスピリン（75～160 mg）とクロピドグレル（1日目300 mg，その後2～7日目75 mg投与）併用療法におけるMESに対する効果を比較したCLAIR（Clopidogrel Plus Aspirin versus Aspirin Alone for Reducing Embolisation in Patients with Acute Symptomatic Cerebral or Carotid Artery Stenosis）試験[11]によると，併用療法群において有意なMESの減少を認めた（RRR：42.4%，p＝0.025）．このCLAIRと3ヵ月以内の脳梗塞あるいはTIA患者を対象として行われた同様の試験（Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis：CARESS）[12]をメタ解析した結果では，脳卒中の再発は併用療法群で6%有意に低いことが示された（p＝0.03）[11]．

これらのエビデンスからは，脳梗塞急性期における抗血小板療法の一つとして，クロピドグレルとアスピリン併用療法の有効性に期待が持てる結果と考えられる．

現在，軽症脳梗塞あるいはTIA発症後12時間以内の患者を対象として，アスピリン単独療法（50～325 mg）とアスピリン（50～325 mg）とクロピドグレル（1日目600 mg，その後75 mgを90日目まで投与）併用療法の脳梗塞再発予防効果を比較検討するPOINT（Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke）とCHANCE（Clopidogrel-Aspirin Regimen versus Aspirin Alone for the Treatment of High-Risk Patients with Acute Nondisabling Cerebrovascular Event）が進行中であり，その結果に期待が寄せられている．

4．シロスタゾール

シロスタゾールは，出血性合併症のリスクが少なく[13]，脳卒中の再発予防効果がアスピリンと比較し有意に高いことがCSPS（Cilostazol Stroke Prevention Study）Ⅱ[14]で示され，また，CASISP（Cilostazol vs Aspirin for Secondary Ischaemic Stroke Prevention）とのメタ解析においても，有意な再発予防効果が示されている（RRR＝33%）[15]．

脳梗塞急性期に関しては，進行性運動障害を伴う大径ラクナ梗塞患者を対象として，従来治療群（アルガトロバン，オザグレルナトリウム，ヘパリン，ウロキナーゼなどを単独あるいは併用投与）と併用治療群（従来治療にエダラボンとシロスタゾール200 mg/日併用投与）において，進行性運動障害予防および機能転帰改善における有用性を検討した報告がある[16]．その結果，併用治療群では，進行性運動障害予防効果は示されなかったものの，従来治療群と比べ転帰が有意に良好であった．

脳卒中後の合併症として肺炎は，頻度が高く急性期においても入院期間延長やコスト増加が問題視されている．日本人脳梗塞患者対象のプラセボ比較試験CSPSのサブ解析[17]では，脳梗塞後の誤嚥性肺炎の発症率が有意に低い（RRR＝78.3%）ことから，『脳卒中治療ガイドライン2009』および『成人院内肺炎診療ガイドライン』において，誤嚥性肺炎の予防・治療対策の一つとして記載があり[18]，脳卒中後の入院期間短縮やコスト抑制につながる可能性がある．

□ 非弁膜症性心房細動（NVAF）を中心とする心原性脳塞栓症と心原性TIAの再発予防には抗凝固療法（目標INR：70歳未満では2.0～3.0，70歳以上では1.6～2.6）が第一選択となる

NVAF患者における脳卒中の危険因子として，脳卒中・TIAの既往か，高齢（75歳以上），高血圧，うっ血性心不全，糖尿病のいずれか2つ以上を有する高リスクのNVAF患者には，アスピリンによる脳卒中予防効果は期待できず，ワルファリンによる抗凝固療法の適応となる．

NVAF患者における脳卒中予防試験をメタ解析した最新の結果によれば，ワルファリン療法は未治療例に比べ64%の相対リスク減少を認めた[19]．しかし，アスピリンはプラセボまたは未治

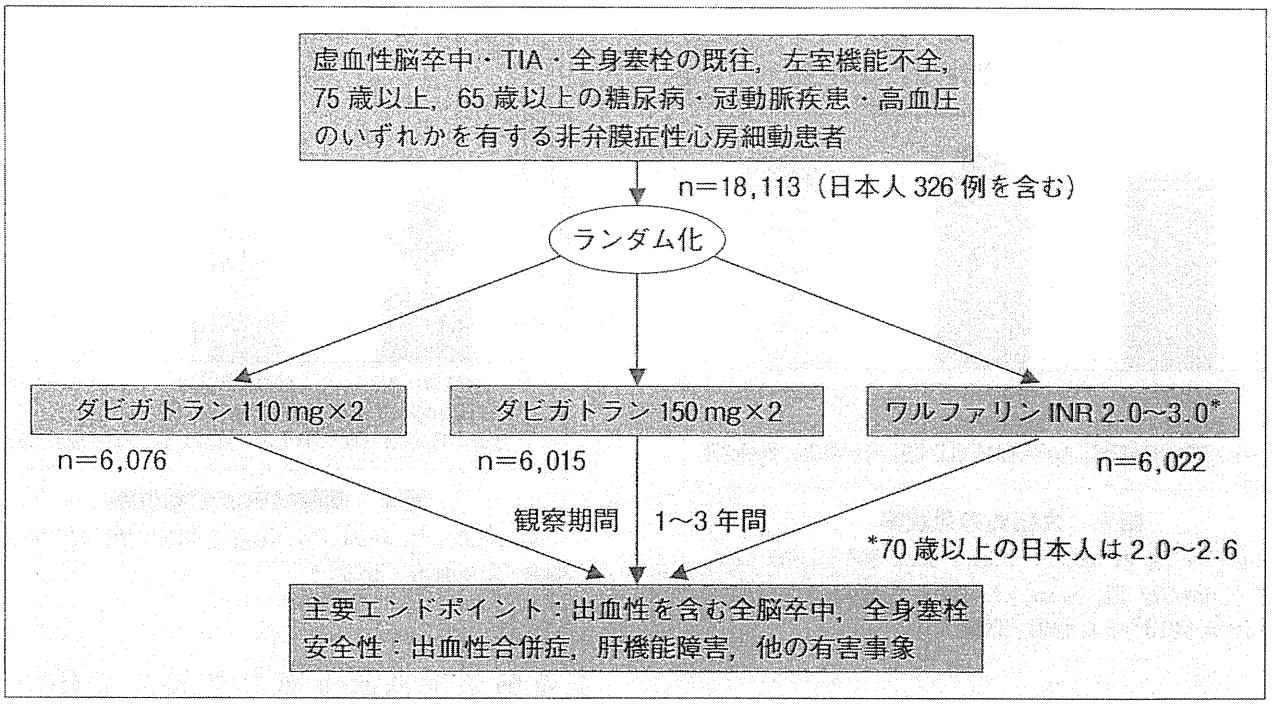

図1　RE-LYの試験デザイン
(Connolly SJ, et al.：N Engl J Med 361：1139-1151, 2009[21]より引用・改変)

療例に比べ19%の相対リスク低下にとどまった．また，ワルファリン療法は，アスピリンによる抗血小板療法に比べ38%の相対リスク低下を認め，ワルファリン療法の優位性が示される結果となった．NVAFを伴うTIA/脳梗塞を対象としたEuropean Atrial Fibrillation Trial（EAFT）によれば，年間脳卒中発症率はプラセボ群12%に対して抗凝固療法群4%と，有意に再発が低かった（ハザード比0.34）[20]．

今春，本邦においてもダビガトランが発売され，ワルファリンコントロール不良例や，定期的なINR評価が困難な患者における再発予防効果が期待される．心房細動患者において2用量のダビガトランのワルファリンとの非劣勢を検証するRE-LY（Randomized Evaluation of Long-Term Anticoagulation Therapy）試験が行われ（**図1**）[21]，高用量のダビガトランのワルファリンを上回る有効性と，低用量のダビガトランのワルファリンを上回る安全性が示された（**図2，3**）[21,22]．ダビガトランはワルファリンより頭蓋内出血の発現頻度が低いことから脳出血リスクの高い症例にも推奨される（**図4**）[21]．

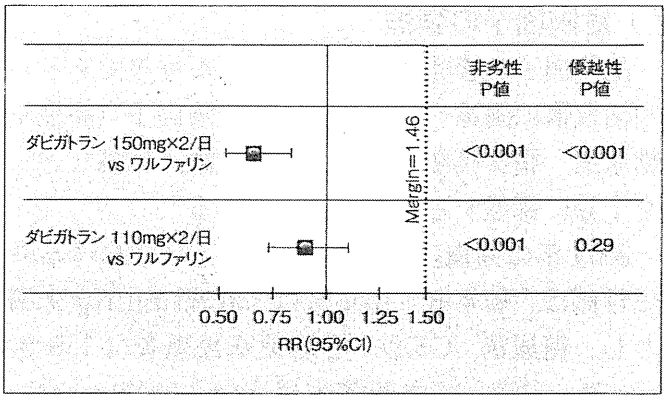

図2　主要評価項目―脳卒中または全身性塞栓症―
(Connolly SJ, et al.：N Engl J Med 361：1139-1151, 2009[21]/Connolly SJ, et al.：N Engl J Med 363 (19)：1875-1876, 2010[22]より引用・改変)

□ 狭窄率70%以上の頸動脈病変による軽症脳梗塞やTIAに対しては，頸動脈内膜剝離術（CEA）が推奨される

慢性期の軽症脳梗塞やTIAにおいてNASCET法で70%以上の頸動脈狭窄例に対しては，頸動脈内膜剝離術（CEA）が推奨される（グレードA，50～69%狭窄に対してはグレードB）．急性期の緊急CEAについてはエビデンスがなくグレードCにとどまっている[1]．心臓疾患合併，高齢などCEAハイリスクの場合，ステント留置術（CAS）が，適切な術者により行われること

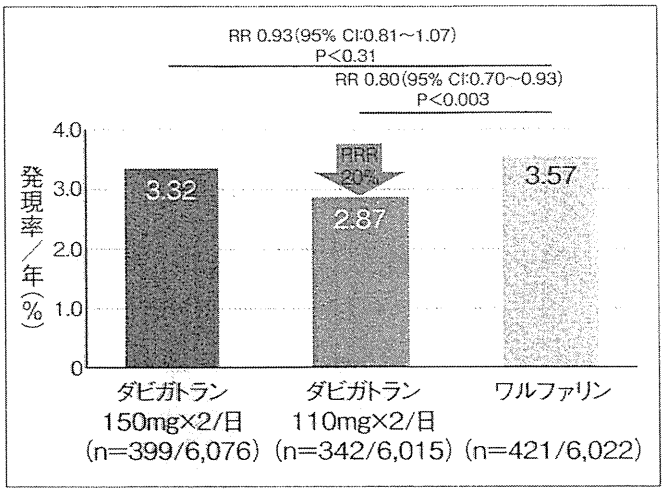

図3　大出血の発現率

(Connolly SJ, et al.：N Engl J Med 361：1139-1151, 2009[21]/Connolly SJ, et al.：N Engl J Med 363 (19)：1875-1876, 2010[22]より引用・改変)

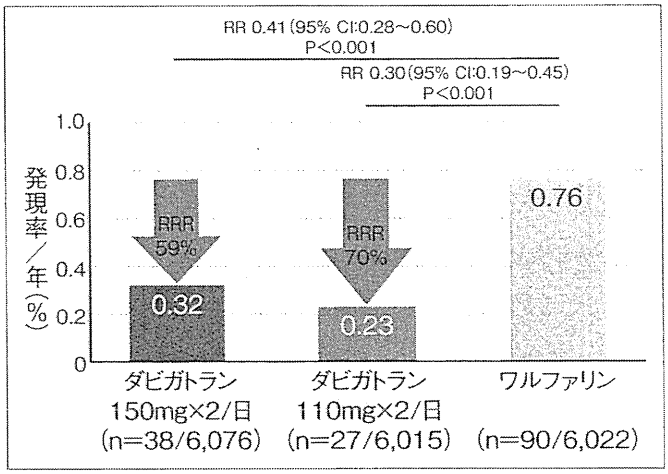

図4　頭蓋内出血の発現率

(Connolly SJ, et al.：N Engl J Med 361：1139-1151, 2009[21]より引用・改変)

が考慮されるが，国際的にはCEAを上回る有効性に関して十分な検証はされていない[23]．

□ 危険因子の管理

危険因子の管理は脳卒中予防に不可欠であり，生活習慣に関連した修正可能な危険因子（高血圧，糖尿病，脂質異常，喫煙，大量飲酒，肥満など）を十分に管理することが必要である[1]．

2009年の高血圧治療ガイドラインにおける降圧目標は，若年者・中年者は130/85 mmHg未満とし，糖尿病，CKD，心筋梗塞後患者は130/80 mmHg未満，脳血管障害患者は140/90 mmHg未満，高齢者においても最終降圧目標は140/90 mmHgとするが，75歳以上の後期高齢者では慎重な降圧治療を行うことが必要[24]とされている．急性期脳梗塞を対象としたAcute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) 試験によれば，アンギオテンシンII受容体拮抗薬であるカンデサルタンを入院初日から早期投与することにより，1年後の死亡および血管イベントが有意に低かった（オッズ比0.475）[25]．しかしながら，最近行われたSCAST (Scandinavian Candeartan Acute Stroke Trial)[26]の成績によれば，脳卒中発症直後からの積極的降圧は長期予後をかえって悪化させたことから，脳梗塞発症後は慎重で，緩徐な降圧が推奨される．

高コレステロール血症治療薬であるスタチンによる脳卒中再発予防を検討したSPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) の結果，致死的・非致死的脳卒中の発症は，アトルバスタチン投与にて16%低下した[27]．2007年に発表された動脈硬化性疾患予防ガイドラインでは，冠動脈疾患の一次予防として，生活習慣の改善によっても管理目標値が達成できない高LDL-コレステロール血症に対して，スタチンの投与を推奨している．脳梗塞の合併するカテゴリーIII（高リスク群：LDLコレステロール以外の主要危険因子が3以上）では，LDLコレステロール120 mg/dL以下を管理目標値としている[28]．

まとめ

TIAのみを対象とした臨床試験はほとんどなく，大部分がTIAと脳梗塞を合わせた虚血性脳卒中として行われている．抗血小板薬の併用に関する臨床試験も現在進行中であり，急性期治療への有用性と安全性のエビデンスが待たれる．

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話題のキーワード解説

ACVS

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一過性脳虚血発作(transient ischemic attack：TIA)は，治療なしに短時間で回復するため患者や家族に無視または軽視されがちである．また，TIAは医師にさえ軽症の脳卒中として後回しにされやすい．しかしながら，TIAは発症直後ほど脳梗塞を発症する危険性が大きいので，早急な評価と治療の開始が必要である(図1)[1]．TIAは24時間以内に完全回復する局所脳虚血症状と定義されるが，その後1時間以内に変更する定義も提唱された．しかしながら，TIAの持続時間の分布は連続的であり，持続時間のみでTIAと虚血性脳卒中を区別するのは意味がないと考える．TIAと虚血性脳卒中(acute ischemic stroke：AIS)は同一スペクトラム上にある病態と認識すべきである．不安定狭心症と急性心筋梗塞を急性冠症候群(acute coronary syndrome：ACS)と総称して救急診療体制を整備することにより救命率が飛躍的に向上したという前例がある．そこで，我々はTIAとAISを急性脳血管症候群(acute cerebrovascular syndrome：ACVS)と総称する新しい疾患概念を提唱している(図2)．ACVSは救急疾患であり，24時間・365日診療するTIA clinicのような救急診療体制を整備する必要がある．

英国で行われたEXPRESS研究[2]では，一次診療医はTIAが疑われたらファックスで専門医に紹介しており，TIAを緊急入院させなければならないとは考えてもいなかったが，TIAが疑われたら直ちにTIA clinicを受診させ，専門医の緊急診療を受ける体制に改めたところ，TIA発症後3ヵ月間の脳梗塞発症率は10%以上から4%に激減したという実績がある(図3)[2]．また，フランスで行われたSOS-TIA研究[3]では，9時から17時までを専門看護師がカバーし，17時から9時までと週末を脳卒中神経内科医がカバーすることにより，24時間・365日ホットラインでTIA患者に対応するTIA clinic体制を構築することで大きな成果をもたらしたことが報告さ

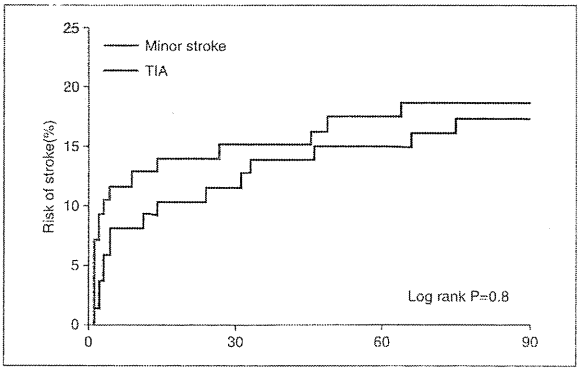

図1 TIAまたは軽症脳卒中発症後早期の脳卒中リスク

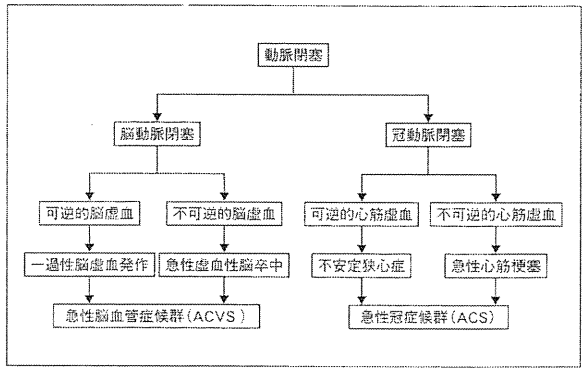

図2 急性脳血管症候群と急性冠症候群

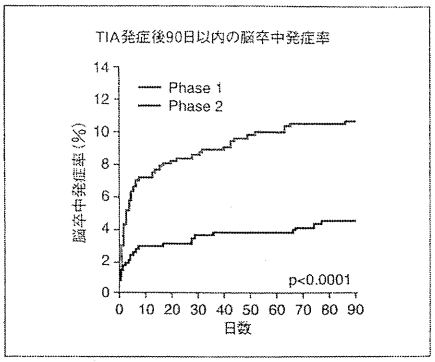

図3　EXPRESS研究の成績
Phase 1: 2002年4月1日～2004年10月20日，一次診療医はTIAが疑われたらFAXで紹介していたが，TIAで入院が必要とは考えていなかった．
Phase 2: 2004年10月1日～2007年3月31日，一次診療医はTIAクリニックへ直接患者を送るよう要請した．

表　ABCD²スコア

A: Age（年齢）>60歳（1点）	
B: Blood pressure（血圧）>140/90 mmHg（1点）	
C: Clinical feature（臨床像）；片麻痺（2点），言語障害（1点）	
D: Diabetes（糖尿病）（1点）	
Duration（症状の持続時間）；（60分未満1点，60分以上2点）	

れている．

2009年に発表された米国心臓協会（AHA）と米国脳卒中協会（ASA）の学術声明[4]によれば，TIAの脳卒中リスク評価に用いられているABCD²スコア（表）[5]が3点以上で発症後72時間以内のTIAは緊急入院させることが推奨されている．脳卒中治療ガイドライン2009でも，TIAが初めて独立した項目として記載され，「一過性脳虚血発作（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ければならない」ことが推奨文に明記された．

現在，発症後7日以内のTIAまたは軽症AIS（modified Rankin Scale 0または1）を5,000例登録して5年間観察する医師主導型の国際共同前向き登録観察研究（TIAregistry.org）[6]が行われている．本研究は，本学を含む日本の6施設も参加し，2008年に第1回運営会議が開催されてその骨子が固まり，2009年から登録が開始され，日本でも2010年4月から6施設の登録が開始された．現在，海外でも日本でも順調に症例登録が進んでおり，2011年7月には目標症例数の達成が期待できそうである．本研究の主目的は，発症後7日以内のTIAまたは軽症AIS（Rankin 0または1）（急性脳血管症候群）患者における脳卒中，心筋梗塞，血管死の発症率を調査することと，臨床症状，危険因子，MRI所見，頸動脈所見，アテローム血栓性疾患の合併（冠動脈，末梢動脈疾患，頭蓋内動脈），を調査して脳卒中発症の予知因子を特定することにある．また，本研究では，TIA発症から診療開始までの時間，ガイドラインの順守率，危険度評価スコア，発症メカニズム，医療経済効果なども検討項目に含まれている．本研究は，TIA診療体制の各国の実情を把握し，TIA救急診療体制の整備に大いに貢献することが期待されている．

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Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial

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Summary

Background The antiplatelet drug cilostazol is efficacious for prevention of stroke recurrence compared with placebo. We designed the second Cilostazol Stroke Prevention Study (CSPS 2) to establish non-inferiority of cilostazol versus aspirin for prevention of stroke, and to compare the efficacy and safety of cilostazol and aspirin in patients with non-cardioembolic ischaemic stroke.

Methods Patients aged 20–79 years who had had a cerebral infarction within the previous 26 weeks were enrolled at 278 sites in Japan and allocated to receive 100 mg cilostazol twice daily or 81 mg aspirin once daily for 1–5 years. Patients were allocated according to a computer-generated randomisation sequence by means of a dynamic balancing method using patient information obtained at registration. All patients, study personnel, investigators, and the sponsor were masked to treatment allocation. The primary endpoint was the first occurrence of stroke (cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage). The predefined margin of non-inferiority was an upper 95% CI limit for the hazard ratio of 1·33. Analyses were by full-analysis set. This trial is registered with ClinicalTrials.gov, number NCT00234065.

Findings Between December, 2003, and October, 2006, 2757 patients were enrolled and randomly allocated to receive cilostazol (n=1379) or aspirin (n=1378), of whom 1337 on cilostazol and 1335 on aspirin were included in analyses; mean follow-up was 29 months (SD 16). The primary endpoint occurred at yearly rates of 2·76% (n=82) in the cilostazol group and 3·71% (n=119) in the aspirin group (hazard ratio 0·743, 95% CI 0·564–0·981; p=0·0357). Haemorrhagic events (cerebral haemorrhage, subarachnoid haemorrhage, or haemorrhage requiring hospital admission) occurred in fewer patients on cilostazol (0·77%, n=23) than on aspirin (1·78%, n=57; 0·458, 0·296–0·711; p=0·0004), but headache, diarrhoea, palpitation, dizziness, and tachycardia were more frequent in the cilostazol group than in the aspirin group.

Interpretation Cilostazol seems to be non-inferior, and might be superior, to aspirin for prevention of stroke after an ischaemic stroke, and was associated with fewer haemorrhagic events. Therefore, cilostazol could be used for prevention of stroke in patients with non-cardioembolic stroke.

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Introduction

Platelets have a pivotal role in the pathogenesis of atherothrombosis, and findings of randomised trials and meta-analyses have shown the efficacy of antiplatelet therapies for secondary prevention after ischaemic stroke.[1] Comparisons of several antiplatelet regimens have shown statistically significantly different outcomes, though only marginal clinical benefit, in stroke prevention,[2,3] and few regimens have proven significantly more effective than has aspirin alone. Dual antiplatelet therapy has been intensively studied, and in the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management, and Avoidance (CHARISMA) trials combined aspirin and clopidogrel was not more effective for reduction of the risk of vascular events than was either drug alone, but did result in more haemorrhagic events.[4,5] Treatments targeting platelets alone have restricted clinical effectiveness, and attempts to augment antiplatelet effects seem to increase the risk of haemorrhage.[6]

Cilostazol is an antiplatelet drug that inhibits phosphodiesterase 3, increases cAMP concentrations and consequently inhibits platelet aggregation.[7] Cilostazol also has vasodilatory activity, inhibits vascular smooth muscle proliferation, and protects the vascular wall and endothelium in vivo and in vitro.[8] In several randomised trials, cilostazol significantly improved symptoms of intermittent claudication in patients with peripheral artery disease.[9] The TASC II international guideline recommends cilostazol as the first-line drug for treatment of intermittent claudication.[10] In the first Cilostazol Stroke Prevention Study (CSPS) in 1052 patients in

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Japan, compared with placebo cilostazol was significantly associated with lower incidence of recurrent cerebral infarction without increased occurrence of cerebral haemorrhage.[11] Cilostazol was also more effective than placebo for prevention of secondary cerebral infarction, particularly in patients with lacunar infarction and in high-risk patients with diabetes or hypertension.[12] On the basis of this evidence, cilostazol is used in Japan for secondary prevention of cerebral infarction and is listed in the Japanese guideline for the management of stroke.[13] In a clinical trial in 720 Chinese patients with cerebral infarction, cilostazol lowered rates of both stroke and any haemorrhagic event compared with aspirin,[14] although follow-up was quite short. We designed CSPS 2 to establish non-inferiority of cilostazol compared with aspirin, and to assess the safety and efficacy of cilostazol compared with aspirin for prevention of stroke in patients with non-cardioembolic cerebral infarction.

Methods

Patients

Patients were enrolled from 278 sites in Japan between December, 2003, and October, 2006, and were treated between December, 2003, and December, 2008. Inclusion criteria were a non-cardioembolic cerebral infarction (NINDS-III classification[15]) in the previous 26 weeks with evidence on a CT or MRI scan, clinical stability before randomisation, and age of 20–79 years. Patients were excluded if they had contraindications to one of the antiplatelet agents, including increased risk of haemorrhage, congestive heart failure, and peptic ulcer. Patients were also excluded if they had blood, hepatic, or renal disorders or cardiac diseases associated with cardioembolism, or had undergone or were scheduled to undergo percutaneous transluminal angioplasty or revascularisation for treatment of cerebral infarction. Patients who were taking thienopyridine derivatives or any other investigational drug were also excluded. Concomitant antiplatelet drugs, anticoagulants, thrombolytic agents, non-steroidal anti-inflammatory drugs, and drugs that inhibit the effects of aspirin were not permitted. No restriction was imposed on diet or rehabilitation therapy. The evaluation committee validated the eligibility of every patient.

The study was done in accordance with ethical principles originating from the Declaration of Helsinki and in compliance with good clinical practice guidelines. The study was approved by the institutional review board of every participating institution. All patients provided written informed consent.

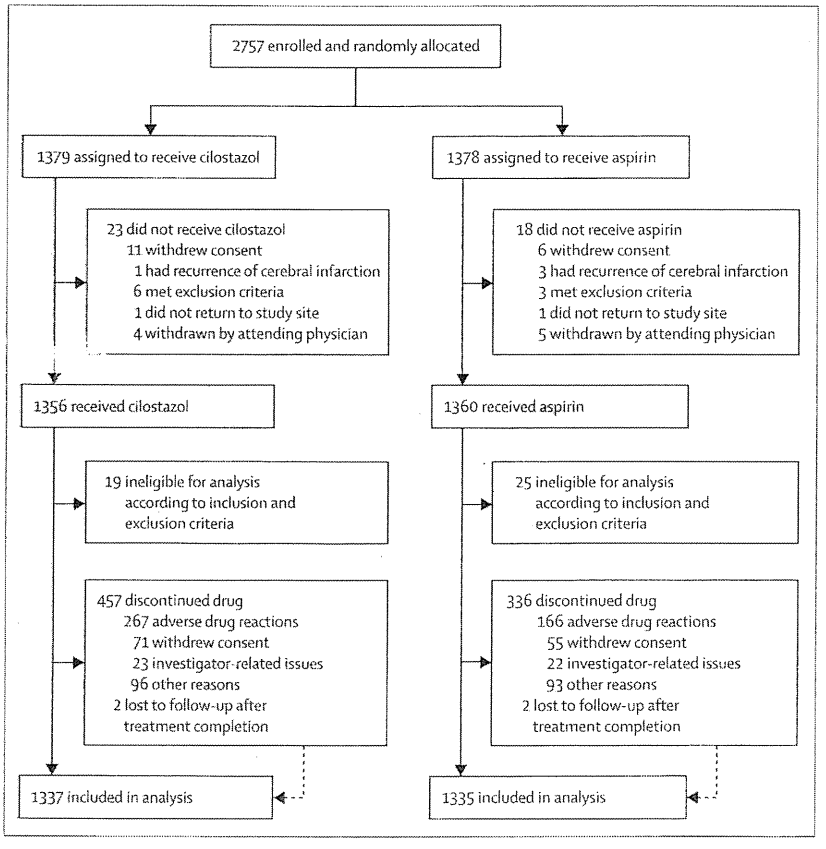

Figure 1: Trial profile

Randomisation and masking

Patients were randomly assigned to receive 100 mg cilostazol twice daily or aspirin 81 mg once daily by use of a double-dummy method. Placebo tablets were identical in appearance to that of the drug that the patient was not assigned to. The randomisation table was generated with SAS (version 8.2) by the personnel responsible for drug allocation from the contract research organisation and random allocation was done with a dynamic balancing method with stratification by age, sex, and study institution to minimise differences in the distribution of baseline variables between the two groups. A randomisation number was pre-assigned to every drug pack. Patients were assigned a treatment number that was matched to a numbered drug pack by the personnel responsible for drug allocation from the contract research organisation at the registration centre. All patients, study personnel, investigators, and the sponsor were masked to treatment allocation throughout the study. The person responsible for drug allocation sealed the assignment list immediately after assignment, and kept it sealed until the designated point for unmasking.

Procedures

Patients were assessed at baseline, week 12, and every 24 weeks thereafter until the end of the trial. At each visit, haematological and biochemical laboratory analyses, blood pressure measurement, and electrocardiography (ECG) were done. All endpoint events were recorded by assessment of clinical records. Study treatment was continued for a minimum of 1 year and a maximum of 5 years.

The evaluation committee, whose members were unaware of patients' treatment assignment, adjudicated all trial endpoints. The primary endpoint was the first occurrence of stroke (recurrence of cerebral infarction, or occurrence of cerebral haemorrhage or subarachnoid haemorrhage). Secondary endpoints were the first recurrence of cerebral infarction, ischaemic cerebrovascular events including cerebral infarction or transient ischaemic attack, death from any cause, and the composite of completed stroke (cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage), transient ischaemic attack, angina pectoris, myocardial infarction, heart failure, or haemorrhage requiring hospital admission (excluding cerebral haemorrhage and subarachnoid haemorrhage). We also did a subgroup analysis of the stroke subtypes included in the composite primary endpoint.

All adverse events were recorded and those that occurred within 10 days of discontinuation or completion of treatment were included in the analyses. Only permanent discontinuations were recorded as discontinuations. The rate of haemorrhagic events (cerebral haemorrhage, subarachnoid haemorrhage, or haemorrhage requiring hospital admission) was analysed to assess drug safety. Follow-up to confirm the occurrence of fatal adverse events was done for 38 days after treatment completion or discontinuation.

Statistical analysis

The number of patients and length of the study period were set on the basis of the number of events needed to confirm the non-inferiority of cilostazol to aspirin. According to the results of a meta-analysis of antiplatelet therapy in patients with cerebral infarction,[1] aspirin did not reduce the risk of stroke by more than 40% compared with placebo, and the hazard ratio (HR) of aspirin to placebo based on exposure was estimated as about 0·6. In the first CSPS, cilostazol reduced the risk of recurrent cerebral infarction by 40% compared with placebo,[7] and on the basis of this result, the HR of cilostazol to placebo for stroke onset was also estimated to be about 0·6.

We calculated that if the upper 95% CI limit for the HR of cilostazol to aspirin was 1·33 (4/3) or lower, cilostazol would be non-inferior to aspirin. With the assumption that the margin of non-inferiority is an HR of cilostazol versus placebo of 1·33, the HR versus placebo would be 0·8 (0·6×1·33=0·798), so the results of the first CSPS could be reconfirmed. The statistical power was set at 80%. We used Freedman's method[16] to calculate that a total of 385 events would be needed. On the assumption that the incidence of stroke would be 5% per year, an estimated 2600 patients would be needed in total to secure at least 385 events over a 4-year registration period and a 5-year study period.

After the end of follow-up, efficacy analyses were done on the full analysis set of patients, as predetermined in the protocol. The full analysis set excluded patients who failed to satisfy inclusion criteria, violated exclusion criteria, did not take the study drugs, or had no follow-up of study-specified events after the start of the study drug. Patients who prematurely discontinued study treatment for any reason other than onset of the primary endpoint

	Cilostazol (n=1337)	Aspirin (n=1335)
Men	959 (72%)	957 (72%)
Age (years)	63·5 (9·2)	63·4 (9·0)
Body-mass index (kg/m²)	24·0 (3·1)	23·9 (3·1)
Stroke subtype		
Atherothrombotic	435 (33%)	420 (31%)
Lacunar	869 (65%)	874 (65%)
Undetermined	33 (3%)	41 (3%)
Days after onset*		
≤28	414 (31%)	419 (31%)
29–56	354 (26%)	338 (25%)
57–112	343 (26%)	320 (24%)
>113	226 (17%)	258 (19%)
Stroke severity (modified Rankin scale)		
0	207 (15%)	186 (14%)
1	612 (46%)	613 (46%)
2	406 (30%)	432 (32%)
3	73 (5%)	69 (5%)
4	39 (3%)	35 (3%)
Drug use		
Cilostazol	304 (23%)	358 (27%)
Aspirin	794 (59%)	749 (56%)
Present smoker	385 (29%)	403 (30%)
Does not abstain from drinking alcohol	640 (48%)	624 (47%)
Complications		
Hypertension	976 (73%)	991 (74%)
Ischaemic heart disease	11 (1%)	18 (1%)
Diabetes mellitus	382 (29%)	393 (29%)
Dyslipidaemia	560 (42%)	599 (45%)

Data are number (%) or mean (SD). *Days from onset of cerebral infarction to start of treatment.

Table 1: **Demographic and clinical characteristics at baseline**

	Cilostazol (n=1337)	Aspirin (n=1335)	p value
Antihypertensive drugs	900 (67%)	999 (75%)	<0·0001
Angiotensin II receptor blockers	617 (46%)	723 (54%)	<0·0001
Calcium channel blockers	627 (47%)	753 (56%)	<0·0001
Angiotensin-converting-enzyme inhibitors	111 (8%)	121 (9%)	0·48
Lipid-lowering drugs	401 (30%)	452 (34%)	0·03
Statins	362 (27%)	402 (30%)	0·08
Antidiabetic drugs	271 (20%)	278 (21%)	0·72
Digestive drugs	863 (65%)	908 (68%)	0·06

Table 2: **Concomitant drug treatments during the study**

were handled as censored cases. We calculated the HRs (95% CIs) of cilostazol to aspirin for occurrence of the primary and secondary endpoints, including subgroup analysis by stroke subtypes, with the log-rank test. On the basis of the principle of a closed testing procedure, the log-rank test was used to verify the superiority of cilostazol to aspirin only if non-inferiority was verified. Because the independent data monitoring committee did a single unmasked interim analysis for safety only and two analyses for efficacy and safety according to the predetermined plan, the adjusted significance level for the superiority test of the primary endpoint was set at 0·0471 (two-tailed) according to the O'Brien-Fleming method.[17] The cumulative incidence rates were estimated and plotted by use of Kaplan-Meier analysis. The occurrence rate per year was calculated in each group based on the log-transformed normal approximation. For the safety analysis, we used the χ^2 test to compare the cumulative incidences of adverse events in the two groups. All analyses were done with SAS (version 9.1).

This trial is registered with ClinicalTrials.gov, number NCT00234065.

Role of the funding source

The funding source had a role in the study design, data collection, and data analysis, but not in data interpretation or writing of the report. Data were collected by the sponsor and entrusted to a contract research organisation (EPS) under a blinded condition. The contract research organisation did statistical analyses under the supervision of the trial statistician (CH) who was independent from the sponsor. Both the corresponding author and CH had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit this paper for publication.

Results

2757 patients were enrolled and randomly assigned, of whom 41 did not receive any study drug, mostly because of withdrawal of informed consent (figure 1). A further 44 patients were judged to be ineligible according to exclusion criteria or violation of inclusion criteria that was missed at the enrolment stage, so 2672 patients were included in analyses. Of patients included in analyses, 34% in the cilostazol group and 25% in the aspirin group discontinued the study drug during the treatment period, and two patients (<1%) in each group were lost to follow-up after treatment completion. Reasons for discontinuation of the study treatment included adverse drug reactions, withdrawal of informed consent, and investigator-related issues.

Mean duration of follow-up was 29 months (SD 16, range 1–59 months). Demographic and clinical characteristics were well balanced between the treatment groups at baseline, including receipt of cilostazol or aspirin (table 1). A significantly higher proportion of patients in the aspirin group took concomitant antihypertensive drugs and lipid-lowering drugs during the treatment period than in the cilostazol group (table 2). The proportions of patients taking statins and, conversely, antidiabetic drugs were also higher in the aspirin group than the cilostazol group but the differences were not significant. The antidiabetic

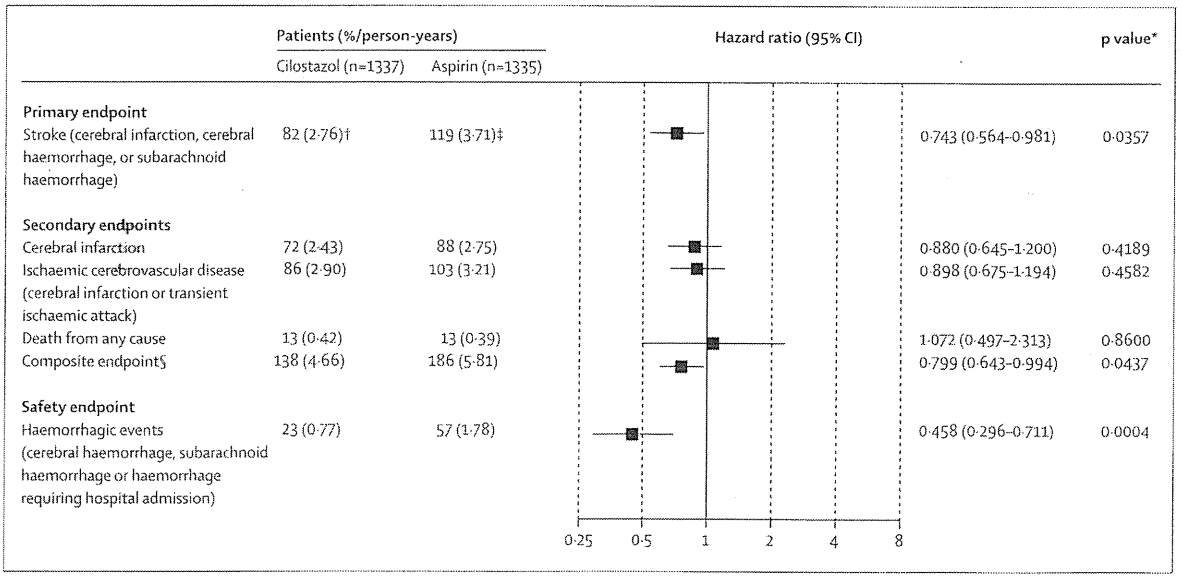

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Figure 2: **Incidences of primary and secondary endpoints**

*Log-rank test. †72 patients had cerebral infarction, eight had cerebral haemorrhage, and two had subarachnoid haemorrhage. ‡88 patients had cerebral infarction, 27 had cerebral haemorrhage, and four had subarachnoid haemorrhage. §Composite of stroke (cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage), transient ischaemic attack, angina pectoris, myocardial infarction, heart failure, or any haemorrhage requiring hospital admission.

drug pioglitazone was used in 58 patients (4%) in the cilostazol group and 78 (6%) patients in the aspirin group.

The primary endpoint occurred at a higher yearly rate in the aspirin group than in the cilostazol group, and cilostazol reduced the risk of stroke by 25·7% compared with aspirin (figure 2, figure 3A). Because the upper 95% CI limit was lower than the prespecified non-inferiority margin of 1·33, cilostazol seems to be non-inferior to aspirin for the prevention of stroke; because the p value for the primary analysis (p=0·0357) was lower than the adjusted significance level for superiority testing (p=0·0471), cilostazol also seems to be superior to aspirin. In the analysis of stroke subtypes, cilostazol was associated with a relative risk reduction of 32·0% for atherothrombotic stroke and 24·8% for lacunar stroke versus aspirin, although the differences between the drugs were not significant (figure 4). Although all analyses were done on the full analysis set, intention-to-treat analysis of the primary endpoint in 1379 patients on cilostazol and 1378 on aspirin confirmed the findings of our study (HR 0·749, 95% CI 0·568–0·988; p=0·0404).

In the secondary endpoint analysis, the composite endpoint occurred in significantly fewer patients in the cilostazol group than in the aspirin group (figure 2, figure 3B). Cilostazol reduced the risk of these events by 20·1% compared with aspirin. For occurrences of all other secondary endpoints, differences between treatment groups were not significant (figure 2).

Haemorrhagic events occurred in significantly fewer patients in the cilostazol group than in the aspirin group (figure 2, figure 3C), and cilostazol reduced the risk of these events by 54·2%. Haemorrhagic events were recorded more frequently in the aspirin group than in the cilostazol group for both the composite of symptomatic cerebral haemorrhage, intraventricular haemorrhage, thalamus haemorrhage, putamen haemorrhage, and cerebellar haemorrhage (27 *vs* 8, p=0·0027) and gastrointestinal haemorrhage that required hospital admission (21 *vs* 8, p=0·0257). Overall, haemorrhagic adverse events occurred in 161 patients (12%) in the cilostazol group and 240 (18%) patients in the aspirin group. Other haemorrhagic adverse events that were most frequently reported were nasal haemorrhage, conjunctival haemorrhage, and subcutaneous haemorrhage (webappendix pp 1–2).

However, several adverse events other than haemorrhage were significantly more common in cilostazol recipients than in aspirin recipients (in descending order of occurrence in the cilostazol group): headache, diarrhoea, palpitations, dizziness, and tachycardia (table 3). Investigator-designated increase in blood pressure and constipation occurred in a higher proportion of patients in the aspirin group than in the cilostazol group (table 3). 267 patients (20%) in the cilostazol group and 166 (12%) in the aspirin group discontinued treatment owing to adverse drug reactions.

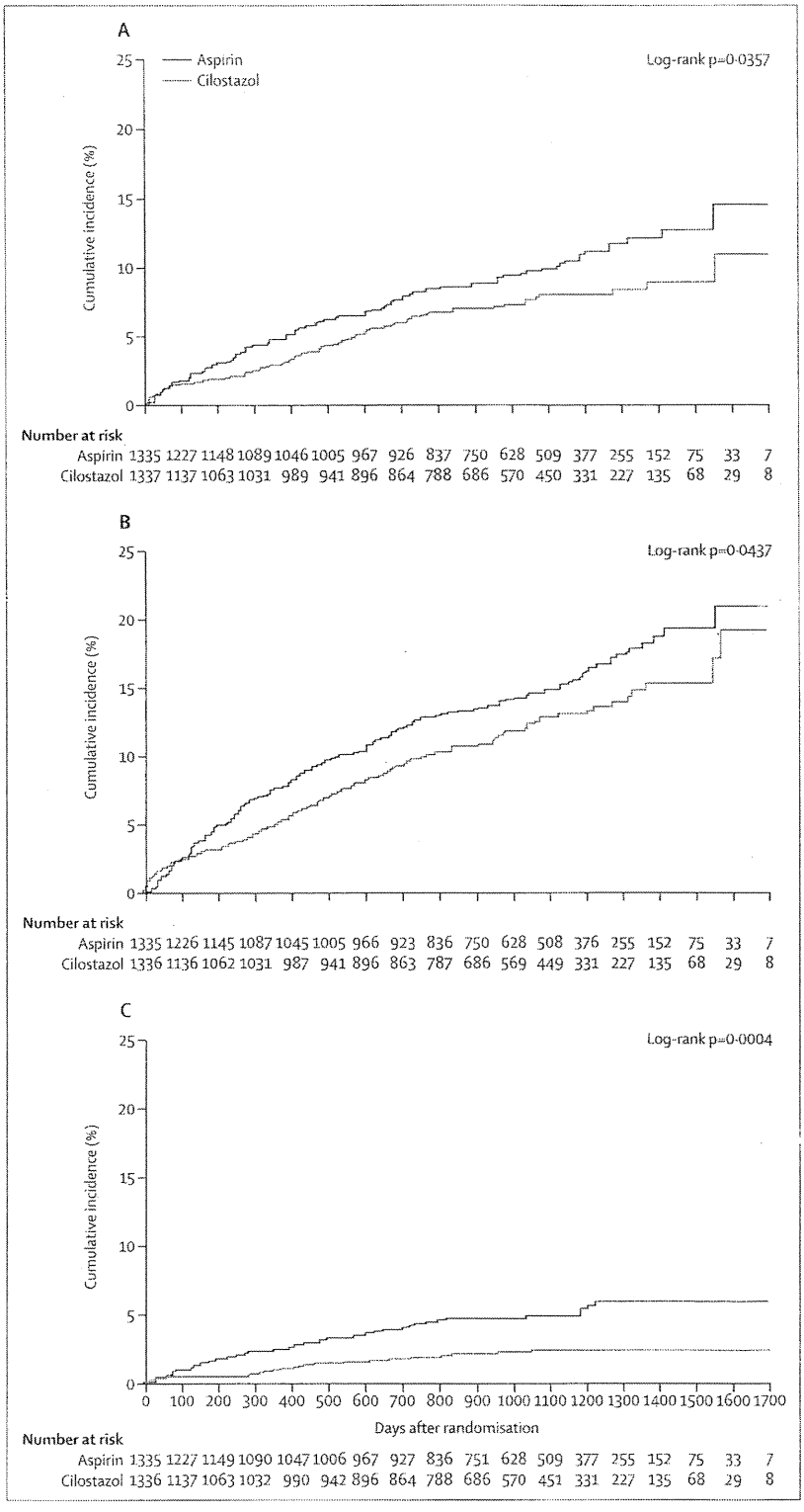

Figure 3: **Cumulative incidences of primary and secondary endpoints**
(A) Primary endpoint: cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage. (B) Secondary composite endpoint: stroke (cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage), transient ischaemic attack, angina pectoris, myocardial infarction, heart failure, or any haemorrhage requiring hospital admission. (C) Safety endpoint of haemorrhagic events: cerebral haemorrhage, subarachnoid haemorrhage, or haemorrhage requiring hospital admission.

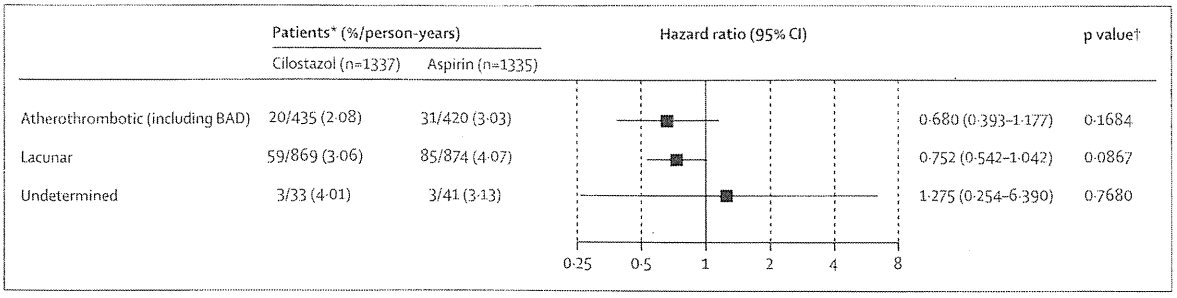

Figure 4: **Incidence of stroke by ischaemic stroke subtype**
*n of total N of patients with the stroke subtype at baseline. †Log-rank test. BAD=branch atheromatous disease.

	Cilostazol (n=1337)	Aspirin (n=1335)	p value*
Headache			
Events	313 (23%)†	217 (16%)	<0·0001
Discontinuations	64 (5%)	6 (<1%)	..
Diarrhoea			
Events	164 (12%)	85 (6%)	<0·0001
Discontinuations	4 (<1%)	1 (<1%)	..
Palpitations			
Events	156 (12%)	71 (5%)	<0·0001
Discontinuations	39 (3%)	2 (<1%)	..
Dizziness			
Events	129 (10%)‡	97 (7%)§	0·0268
Discontinuations	3 (<1%)	2 (<1%)	..
Tachycardia			
Events	89 (7%)	21 (2%)	<0·0001
Discontinuations	14 (1%)	0	..
Investigator-designated increase in blood pressure			
Events	120 (9%)	185 (14%)	<0·0001
Discontinuations	3 (<1%)	1 (<1%)	..
Constipation			
Events	110 (8%)	155 (12%)	0·0034
Discontinuations	0	0	..

*χ^2 test. †One event was a serious adverse event. ‡Seven events were serious adverse events. §Six events were serious adverse events.

Table 3: **Adverse events other than haemorrhage**

37 patients (3%) in each treatment group had serious cardiac adverse events (43 events in the cilostazol group and 41 in the aspirin group), including angina pectoris (10 and 11), myocardial infarction (14 and 11), heart failure (8 and 7), arrhythmias (8 and 5), and others (3 and 7), with no significant differences in occurrence between the groups. Cardiac events resulted in death in four patients (<1%) in the cilostazol group and two patients (<1%) in the aspirin group.

Although use of antihypertensive drugs was significantly more common in the aspirin group than in the cilostazol group, mean blood pressure during treatment was fairly well controlled in both groups. Descriptive statistics for blood pressure (webappendix pp 3–4), transition of blood pressure (webappendix p 5), and analysis of values for blood pressure with a mixed-effect model (webappendix p 6) showed significant differences in systolic blood pressure and no significant differences in diastolic blood pressure between the treatment groups, but we recorded no interaction between treatment group and measurement timepoints for systolic or diastolic blood pressure. Because increase in blood pressure was recorded more frequently in the aspirin group than in the cilostazol group, two further post-hoc analyses were done to investigate the association of blood pressure and the safety endpoint: the first adjusted treatment effect for time-varying blood pressure by use of Cox regression model with systolic blood pressure measurements as time-dependent covariates (webappendix p 7); and the second adjusted treatment effect for investigator-designated increase in blood pressure elevation (webappendix p 8).

Discussion

In CSPS 2, the incidence of stroke, the primary endpoint, was extremely low in both the cilostazol and aspirin groups, in accordance with the known benefits of antiplatelet therapy and risk factor management for prevention of stroke. Nevertheless, cilostazol significantly lowered the risk of stroke compared with aspirin, and seemed to be non-inferior and superior to aspirin for prevention of stroke in patients with cerebral infarction, with significantly fewer haemorrhagic events (panel). Cilostazol also seemed to be superior to aspirin for prevention of a cluster of secondary endpoints, including stroke, transient ischaemic attack, angina pectoris, myocardial infarction, heart failure, and haemorrhage requiring hospital admission.

The effectiveness of aspirin or thienopyridine derivatives for prevention of secondary vascular events has been validated in patients with ischaemic stroke.[1] However, according to calculations from Antiplatelet Trialists' Collaboration[18] and Antithrombotic Trialists' Collaboration data,[1] the number needed to treat (NNT) for these antiplatelet drugs is about 26–28 in a 2·4–3-year treatment period, which is not satisfactory. The NNT for cilostazol was about 18·7 per 3 years,[12] which is a little better than for conventional antiplatelet drugs, although the patients might have had different subtypes of

ischaemic stroke. Therefore, CSPS 2 was designed for direct comparison of cilostazol and aspirin.

Our findings are consistent with those of CASISP,[14] a pilot study done before CSPS 2, in which cilostazol seemed to be superior to aspirin with a relative risk reduction of 38·1% (p=0·185), but the sample size was too small (720 patients) and the trial period was too short (740 person-years) to establish a significant difference. In the CAPRIE study in patients with cerebral infarction, myocardial infarction, or peripheral artery disease, clopidogrel was significantly superior to aspirin in terms of the incidence of ischaemic events, but the risk reduction was only 8·7% (p=0·043).[2] Moreover, in a subgroup analysis of patients with ischaemic stroke, the risk reduction by clopidogrel for vascular events was about 7% compared with aspirin, and this difference was not significant. In the TASS study of patients with a history of transient ischaemic attack or mild cerebral infarction,[3,19] ticlopidine treatment led to significantly lower occurrence of non-fatal stroke and death (primary endpoint) than did aspirin, but the risk reduction was only 12%. Although ticlopidine resulted in a 21% reduction in the risk of fatal and non-fatal stroke (a secondary endpoint) compared with aspirin, a greater risk reduction was recorded with cilostazol versus aspirin in CSPS 2.

In studies comparing combined clopidogrel and aspirin with clopidogrel alone (MATCH trial[4]) and aspirin alone (CHARISMA trial[5]), clopidogrel plus aspirin did not show an evident suppressive effect on vascular events, and conversely resulted in an increase in haemorrhagic events. The results of these large-scale trials indicated that treatments targeting platelets alone to prevent stroke or other vascular events have restricted clinical efficacy and inevitably increase the risk of haemorrhage. Rudolf Virchow pointed out the importance of endothelial cell functions of the vessel wall as another treatment target for the prevention of thrombus formation.[20] Caplan and colleagues[21] supported Virchow's idea that three components (blood constituents, vessel wall, and blood flow) should be considered together as a treatment target to prevent thrombus formation. Treatment with a combination of dipyridamole and aspirin has been reported to be more effective than aspirin alone.[22] In PRoFESS,[23] however, combined dipyridamole and aspirin was not more efficacious than clopidogrel alone for prevention of recurrent cerebral infarction, so the benefit of dipyridamole as an adjunct to antiplatelet monotherapy has not been proven.

We believe that the reduced risk of stroke with cilostazol in CSPS 2 can be ascribed not only to the antiplatelet effect, but also to effects on other factors associated with thrombus formation. These effects include improvement of endothelial function and dilation of blood vessels by increased production of nitric oxide, an endogenous vasodilating factor, and reduction of intracellular calcium ion concentrations.[24] Cilostazol also inhibits smooth muscle proliferation[25] and inflammation[26,27]—the processes underlying atherosclerosis—in various vascular beds, including the intracranial,[28] carotid,[29] coronary,[30] and peripheral arteries.[31] These actions are thought to contribute to the prevention of secondary vascular events with this drug.

In our study, we also assessed the cardiac safety of cilostazol in relation to the increase in heart rate. We did not record increases in myocardial infarction, angina pectoris, heart failure, or serious arrhythmias associated with increased heart rate, at least in this group of patients with non-cardioembolic stroke and without congestive heart failure. Some adverse events other than haemorrhage occurred more frequently in the cilostazol group than in the aspirin group, but none was serious, and all symptoms resolved after discontinuation or dose tapering of cilostazol. Incremental increases in dose from 50 mg cilostazol might avoid these events in some patients. The higher rate of haemorrhagic events in our study than in studies done in white patients might be attributable to the high proportion of patients with lacunar stroke in our study. This high rate of haemorrhagic events is consistent with results from the S-ACCESS study[32] in a Japanese population and the CHARISMA subanalysis,[33] which showed that bleeding tendency was higher in Asian than in white patients. Findings of the post-hoc analyses of the association of blood pressure with the safety

Panel: Research in context

Systematic review

Trials of antiplatelet drugs, including cilostazol and aspirin, were identified by searches of Medline (January, 1950, to January, 2010) and PubMed (January, 1950, to January, 2010). We also hand-searched relevant journals, reference lists of included papers, and guidelines. For discussion of efficacy and safety of antiplatelet therapies, we restricted searches to human studies and included the results of only large-scale clinical trials or meta-analyses of more than 1000 patients, apart from the preliminary study CASISP.

Interpretation

Treatments targeting platelets alone to prevent stroke or other vascular events seem to have restricted clinical efficacy and increase the risk of haemorrhage. However, the results of this study provide evidence that cilostazol reduces the occurrence of stroke, especially haemorrhagic stroke, compared with aspirin, which might be attributable to the antiplatelet effect and other actions such as improvement of endothelial function. This study adds to the evidence supporting the recommendation of the antiplatelet cilostazol as an option for the prevention of stroke in patients with ischaemic stroke, particularly those with increased risk of haemorrhage.

endpoint showed that blood pressure was not related to haemorrhagic side-effects.

The results of CSPS 2 suggest that cilostazol can be recommended as an option for the prevention of stroke in Asian patients with non-cardioembolic stroke who can tolerate long-term treatment with this drug. However, cilostazol also seems to be effective for patients of different ethnic origin who have peripheral artery disease—for example, in a study in the USA, cilostazol reduced cerebrovascular events versus placebo.[34] Because significantly fewer haemorrhagic events were recorded in the cilostazol group than in the aspirin group, cilostazol might be particularly useful in patients with increased risk of haemorrhage.

Contributors

YS, YKa, SU, TY, and TS contributed to the study concept and design, and supervised the study. All authors contributed to acquisition of data. YS, YKa, SU, TY, YO, NT, HY, SH, KM, TS, and CH did data analysis and interpretation. YS and CH drafted the report, and all other authors critically revised the report for important intellectual content. CH did the statistical analysis, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest

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