20. Li Y, Li J, Segal S, Wegiel J, De Santi S, Zhan J, de Leon MJ (2006) Hippocampal cerebrospinal fluid spaces on MR imaging: relation to aging and Alzheimer disease. AJNR Am J Neuroradiol 27:912–918
21. Lindsberg PJ, Mattle HP (2006) Therapy of basilar artery occlusion. A systematic analysis comparing intra-arterial and intravenous thrombolysis. Stroke 37:922–928
22. Linfante I, Llinas RH, Schlaug G, Chaves C, Warach S, Caplan LR (2001) Diffusion-weighted imaging and National Institutes of Health Stroke Scale in the acute phase of posterior-circulation stroke. Arch Neurol 58:621–628
23. Nuutinen J, Liu Y, Laakso MP, Karonen JO, Roivainen R, Vanninen RL, Partanen K, Østergaard L, Sivenius J, Arounen HJ (2006) Assessing the outcome of stroke: a comparison between MRI and clinical stroke scales. Acta Neurol Scand 113:100–107
24. Puetz V, Sylaja PN, Coutts SB, Hill MD, Dzialowski I, Mueller P, Becker U, Urban G, O'Reilly C, Barber PA, Sharma P, Goyal M, Gahn G, von Kummer R, Demchuk AM (2008) Extent of hypoattenuation on CT angiography source images predicts functional outcome in patients with basilar artery occlusion. Stroke 39:2485–2490
25. Renard D, Landragin N, Robinson A, Brunel H, Bonafe A, Heroum C, Milhaud C (2008) MRI-based score for acute basilar artery thrombosis. Cerebrovasc Dis 25:511–516
26. Schaefer PW, Yoo AJ, Bell D, Barak ER, Romero JM, Nogueira RG, Lev MH, Schwamm LH, Gonzalez RG, Hirsch JA (2008) CT angiography-source image hypoattenuation predicts clinical outcome in posterior circulation strokes treated with intra-arterial therapy. Stroke 39:3107–3109
27. Schonewille WJ, Wijman CAC, Michel P, Rueckert CM, Weimer C, Mattle HP, Engelter ST, Tanne D, Muir KW, Molina CA, Thijs V, Audebert H, Pfefferkorn T, Szabo K, Lindsberg PJ, de Freitas G, Kappelle LJ, Algra A, on behalf of the BASICS study group (2009) Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study. Lancet Neurol 8:724–730
28. Schwarz S, Egelhof T, Schwab S, Hacke W (1997) Basilar artery embolism. Clinical syndrome and neuroradiologic patterns in patients without permanent occlusion of the basilar artery. Neurology 49:1346–1352
29. Tei H, Uchiyama S, Ohara K, Kobayashi M, Uchiyama Y, Fukuzawa M (2000) Deteriorating ischemic stroke in 4 clinical categories classified by the Oxfordshire Community Stroke Project. Stroke 31:2049–2054
30. Tei H, Uchiyama S, Usui T (2006) Predictors of good prognosis in total anterior circulation infarction within 6 h after onset under conventional therapy. Acta Neurol Scand 113:301–306
31. Tei H, Uchiyama S, Usui T (2007) Clinical-diffusion mismatch defined by NIHSS and ASPECTS in non-lacunar anterior circulation infarction. J Neurol 254:340–346
32. The National Institute of Neurological Disorders, Stroke (NINDS) rt-PA Stroke Study Group (2000) Effects of intravenous recombinant tissue plasminogen activator on ischemic lesion size measured by computed tomography. Stroke 31:2912–2919
33. Thijs VN, Lansberg MG, Beaulieu C, Marks MP, Moseley ME, Albers GW (2000) Is early ischemic lesion volume on diffusion-weighted imaging an independent predictor of stroke outcome? A multivariable analysis. Stroke 31:2597–2602
34. Toyoda K, Fujii K, Kamouchi M, Nakane H, Arihiro S, Okada Y, Ibayashi S, Iida M (2004) Free radical scavenger, edaravone, in stroke with internal carotid artery occlusion. J Neurol Sci 221:11–17
35. van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J (1990) Grading white matter lesions on CT and MRI: a simple scale. J Neurol Neurosurg Psychiatry 53:1080–1083
36. Wardlaw JM, Keir SL, Bastin ME, Armitage PA, Rana AK (2002) Is diffusion imaging appearance an independent predictor of outcome after ischemic stroke? Neurology 59:1381–1387

教育講演

8. 脳卒中予防を目的とした抗血栓療法の大規模臨床試験

内山真一郎

Key words：クロピドグレル，シロスタゾール，ジピリダモール，ダビガトラン

はじめに

最近，脳卒中の一次・二次予防効果を安全性とともに検討した抗血栓療法の大規模臨床試験とメタ解析の成績を紹介し，ガイドラインと日常診療へのインパクトについて考えてみたい．

1. クロピドグレル

クロピドグレルはチクロピジンより血液障害や肝機能障害などの重大な副作用が少ないことから海外ではチクロピジンに代わるチエノピリジン系抗血小板薬として用いられており，日本でも長い間承認が待望されていた[1]．日本では海外より大幅に遅れ，2006年にようやく脳梗塞再発抑制薬として承認されたが，海外ではクロピドグレルとチクロピジンを直接比較した臨床試験は行われたことがなく，エビデンスがなかったことから，日本人の脳梗塞患者を対象に行われた両薬剤の安全性を有効性とともに比較するランダム化比較試験を統合解析した[2]．

最初の試験は1996年～1997年，749例を対象に26週間，二番目の試験は2001年～2005年，1,172例を対象に52週間にわたって行われた．症例の選択基準は，年齢が20～80歳，発症後8日以上経過した非心原性脳梗塞の既往があり，CT（computed tomography）かMRI（magnetic resonance imaging）で脳梗塞が確認されていることとなっており，薬剤の用量はクロピドグレルが75 mg/日，チクロピジンが200 mg/日であり，これらが全て両試験に共通していたことから統合解析が可能となった．

白血球減少や血小板減少などの血液障害，日本人に多い肝機能障害，大出血などの重篤な有害事象はクロピドグレルでチクロピジンより明らかに約40％少なかった（ハザード比0.610，95％信頼区間0.529～0.703，$p<0.001$）（図1）[2]．これに対して血管性イベント（脳梗塞，心筋梗塞，血管死）の発症率は，クロピドグレル75 mgとチクロピジン200 mgは同等の血小板ADP（adenosine diphosphate）凝集抑制効果があるので当然な結果ではあるが，両群間で有意差はなかった（ハザード比0.918，95％信頼区間0.518～1.626，$p=0.769$）[2]．すなわち，クロピドグレルはチクロピジンより安全性に優れ，有効性はチクロピジンと同等なので，有用性がチクロピジンより優れているということになる．これらのエビデンスに基づき，脳卒中治療ガイドライン2009[3]では，非心原性脳梗塞の再発予防にはクロピドグレルがグレードAで新たに推奨され，チクロピジンの推奨レベルはグレードBに格下げされ

うちやま　しんいちろう：東京女子医科大学神経内科学

本講演は，平成22年4月10日（土）東京都・東京国際フォーラムにて行われた．

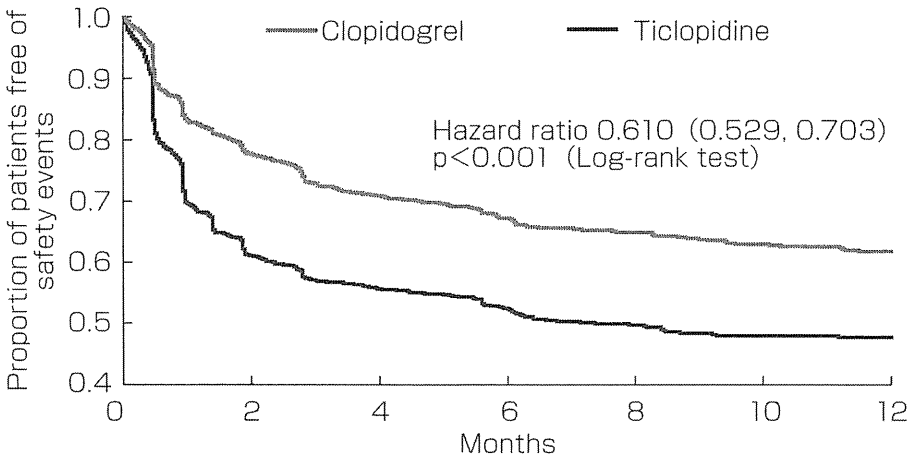

図 1. クロピドグレルとチクロピジンの副作用発現頻度（文献 2 より引用・改変）
日本人脳梗塞患者においてクロピドグレルとチクロピジンを直接比較した 2 件の第 3 相ランダム化比較臨床試験の統合解析の成績．重篤な肝障害，白血球減少症，血小板減少症，大出血などの有害事象の累積発現率はクロピドグレル投与群（35.0%）でチクロピジン投与群（48.7%）より有意に 39% 少なかった．

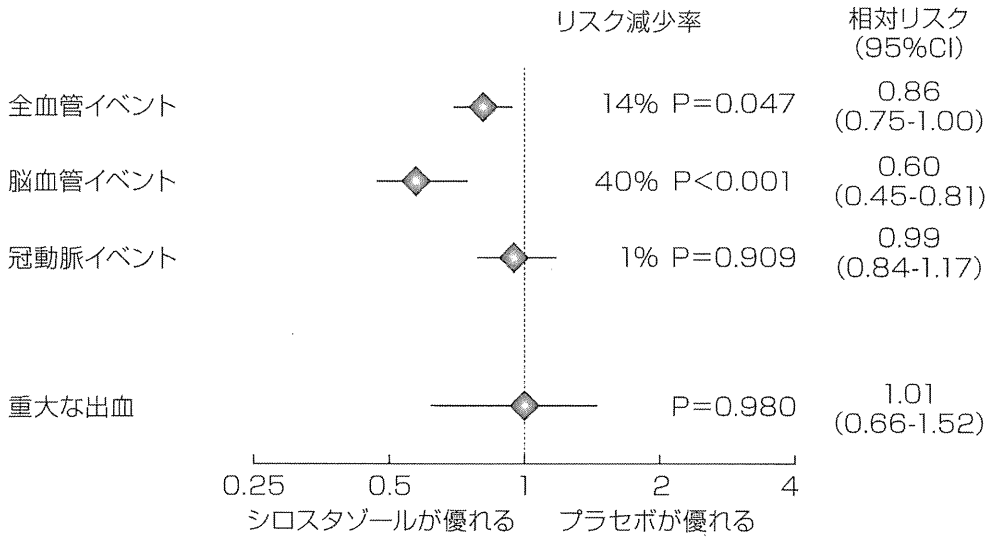

図 2. アテローム血栓症におけるシロスタゾールのプラセボ対照ランダム化比較試験のメタ解析（文献 4 より引用・改変）
13 件（末梢動脈疾患 10 件，脳血管障害 2 件，冠動脈疾患 1 件）のプラセボ対照ランダム化比較試験に登録された 6,194 例のメタ解析．

た．したがって日常診療においては，チエノピリジンの適応となる新規処方例にはチクロピジンよりクロピドグレルを優先すべきである．

2. シロスタゾール

著者らは，アテローム血栓症（虚血性脳血管障害，冠動脈疾患，末梢動脈疾患）を対象に行われたシロスタゾールのプラセボ対照ランダム化比較試験をメタ解析した[4]．解析対象は，10 件の末梢動脈疾患，2 件の脳梗塞，1 件の冠動脈ステント留置患者を対象にした合計 13 件の試験に登録された 6,194 例であった．いずれの背景因子にもシロスタゾール投与群とプラセボ投与群

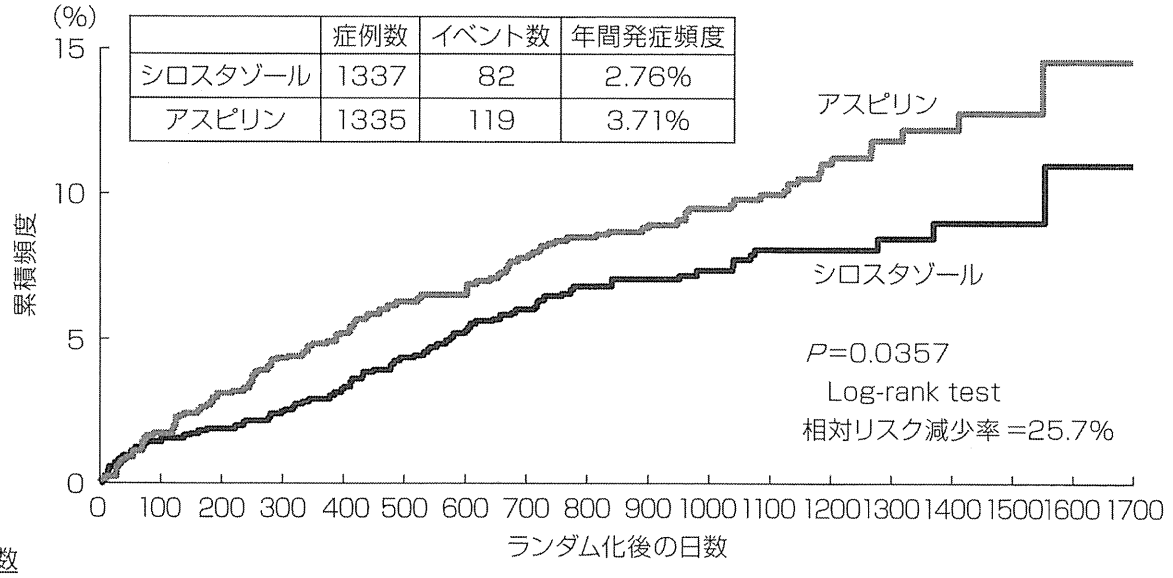

図3. Cilostazol Stroke Prevention Study Ⅱ（CSPS Ⅱ）における脳卒中の累積発症率（文献5より引用）
CSPS Ⅱにおけるシロスタゾール投与群とアスピリン投与群の全脳卒中（虚血性脳卒中と出血性脳卒中）の累積発症頻度の比較.

に有意差はなかった．全血管イベントは，シロスタゾール群でプラセボ群より有意に14%少なかった(図2)[4]．このシロスタゾールによる有意な血管イベントの低減効果は，脳血管イベントの著明な減少によりもたらされていた(図2)[4]．もう一つの顕著な特徴は，重大な出血性合併症がシロスタゾール投与群とプラセボ投与群に全く差がないという結果であった(図2)[4]．すなわち，シロスタゾールは出血リスクを増加させることなく，著明な脳血管障害の予防効果を有する薬剤であることが特徴であるといえる．

2010年2月にテキサス州のサンアントニオで開催されたInternational Stroke ConferenceにおいてCilostazol Stroke Prevention Study Ⅱ（CSPS Ⅱ）の成績が発表された[5]．対象は，CTまたはMRIで確認された，発症後26週間までの非心原性脳梗塞2,672例であり，シロスタゾール200 mg/日投与群かアスピリン81 mg/日投与群に無作為割り付けし，平均29カ月間追跡調査した．一次エンドポイントである全脳卒中（脳梗塞，脳出血，くも膜下出血）は，シロスタゾール投与群で年間2.76%．アスピリン投与群で3.71%であり，シロスタゾール投与群で有意に少なかった（相対リスク減少25.7%，P＝0.0357）(図3)[5]．二次エンドポイントである脳梗塞，一過性脳虚血発作（TIA），心筋梗塞，心不全または入院を要する出血は，シロスタゾール投与群4.66%，アスピリン投与群5.81%であり，やはりシロスタゾール投与群で有意に少なかった（相対リスク減少20.1%，p＝0.043）．また，出血性合併症（脳出血，くも膜下出血，入院を要する出血）は，シロスタゾール投与群0.77%，アスピリン投与群1.78%であり，シロスタゾール投与群で著しく少なかった(相対リスク減少54.4%，p＝0.0004)(図4)[5]．副作用は，頭痛，下痢，動悸，めまい，頻脈がシロスタゾール投与群で有意に多く，高血圧，便秘がアスピリン投与群で有意に多かった．

CSPS Ⅱの結果より，非心原性脳梗塞患者においてシロスタゾールはアスピリンより全脳卒中の発症予防効果が優れており，重大な出血リスクも少ないことが示されたことから，日常臨床

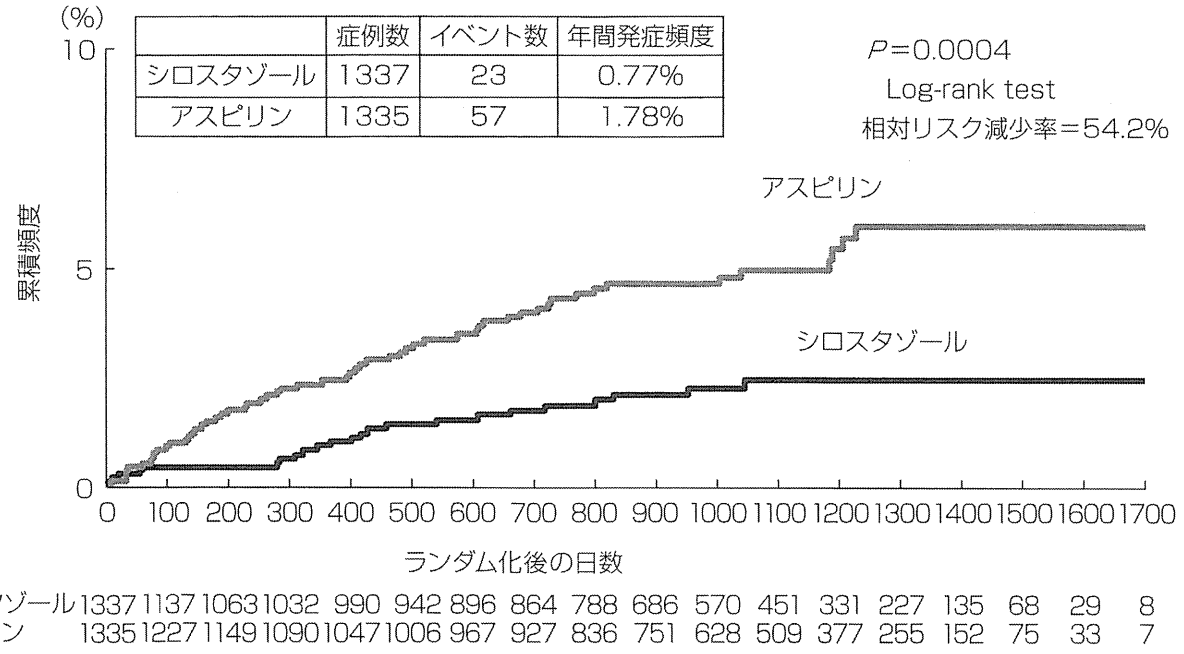

図4. Cilostazol Stroke Prevention Ⅱ（CSPS Ⅱ）における重大な出血（脳出血，くも膜下出血，入院を要する出血）の累積発症頻度[5]

CSPS Ⅱにおけるシロスタゾール投与群とアスピリン投与群の重大な出血（出血性脳卒中と入院を要する出血）の累積発症頻度の比較．

においても第一選択の抗血小板薬の一つと位置付けられる．特に，出血リスクの高い脳梗塞患者にはシロスタゾールが推奨される．

3. ジピリダモール

発症後90日以内か，90～120日以内で2つ以上の血管性危険因子を有し，CTまたはMRIで確認された50歳以上の，日本人を含む非心原性脳梗塞患者20,332例を対象として，ジピリダモールとアスピリンの合剤をクロピドグレルと比較するPrevention Regimen for Effectively Avoiding Second Strokes（PRoFESS）研究が行われた[6]．PRoFESSは2×2要因デザインにより徐放型ジピリダモール200 mgとアスピリン25 mgの合剤の1日2回投与群かクロピドグレル75 mg/日投与群に無作為割り付けされ，平均2.5年間追跡調査された．

一次エンドポイントである脳卒中の再発は，両群間で差がなかったが，頭蓋内出血はジピリダモール・アスピリン併用群でクロピドグレル投与群より有意に多かった（図5）．過去に行われたEuropean Stroke Prevention Study 2（ESPS 2）やEuropean/Australasian Stoke Prevention in Reversible Ischmaemia Trial（ESPRIT）の成績によれば，アスピリンとジピリダモールの併用がアスピリン単独より明らかに頭蓋内出血のような，重大な出血性合併症を増加させたというエビデンスはないので，両群間における頭蓋内出血の発現頻度の差は主にアスピリンとクロピドグレルの差を反映している可能性がある．

4. 心房細動患者における抗血小板療法と抗凝固療法

血管イベントの危険因子を有する心房細動14,000例のうち，ガイドラインで抗凝固療法の適応とされている高リスクの心房細動患者においてクロピドグレル・アスピリン併用療法とワルファリン療法（INR：international normalized ratio 2～3）を比較したAtrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vas-

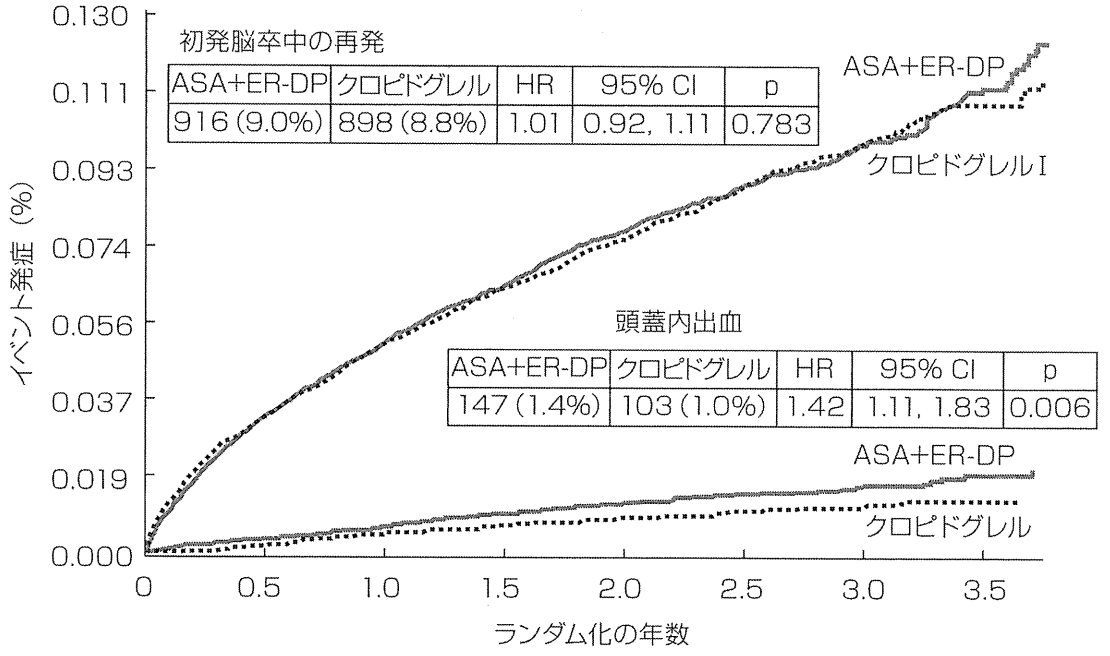

図5. PRoFESSにおける脳卒中の再発と頭蓋内出血の累積発症頻度（文献6より引用・改変）

PRoFESS試験において脳卒中の再発は両群間で差はなかったが，頭蓋内出血はアスピリン・ジピリダモール併用群で有意に42%多かった．ASA+ER-DP；アスピリン＋徐放型ジピリダモール，HR；ハザード比，CI；信頼区間．

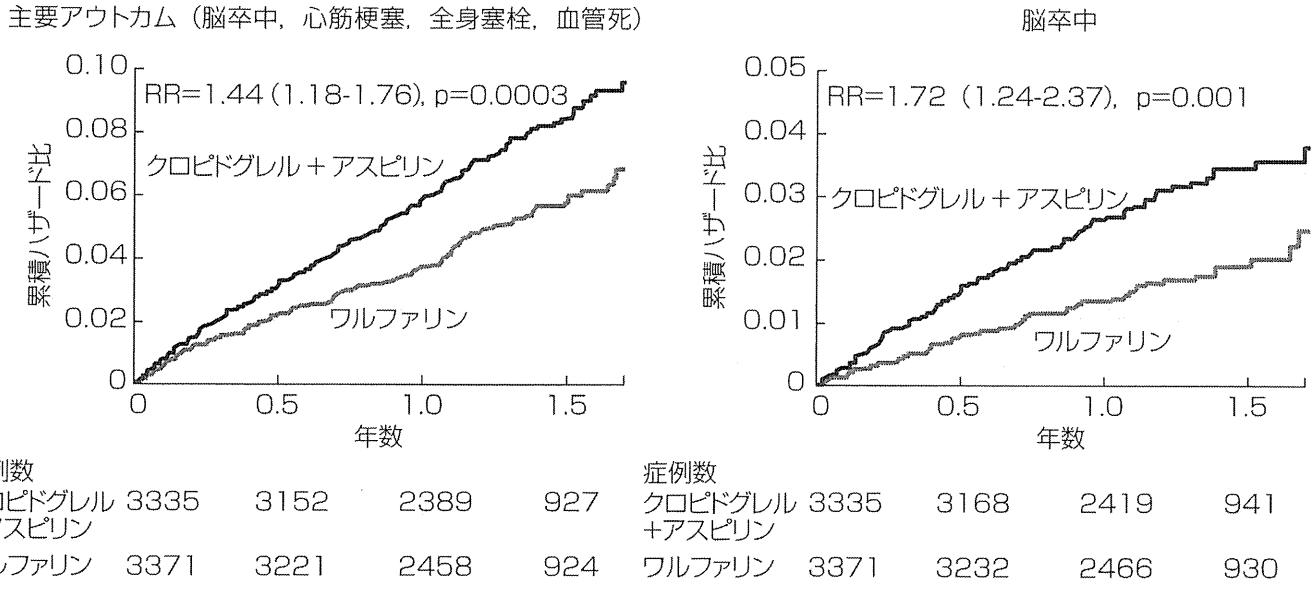

図6. ACTIVE Wの成績（文献7より引用・改変）

高リスクの心房細動患者において主要アウトカム（脳卒中，心筋梗塞，全身塞栓，血管死）と脳卒中の発症はいずれもクロピドグレル・アスピリン併用療法でワルファリン療法（INR2～3）よりはるかに多かった．

cular Events (ACTIVE) Wの成績によれば，アスピリン・クロピドグレル併用療法は脳卒中や全身塞栓症の予防効果がワルファリン療法よりはるかに劣っていた（図6）[7]．

一方，ガイドラインでアスピリンでもよいとされている低リスクのNVAF(non-valvular atrial fibrillation)患者においてアスピリン単独療法とアスピリン・クロピドグレル併用療法を比較し

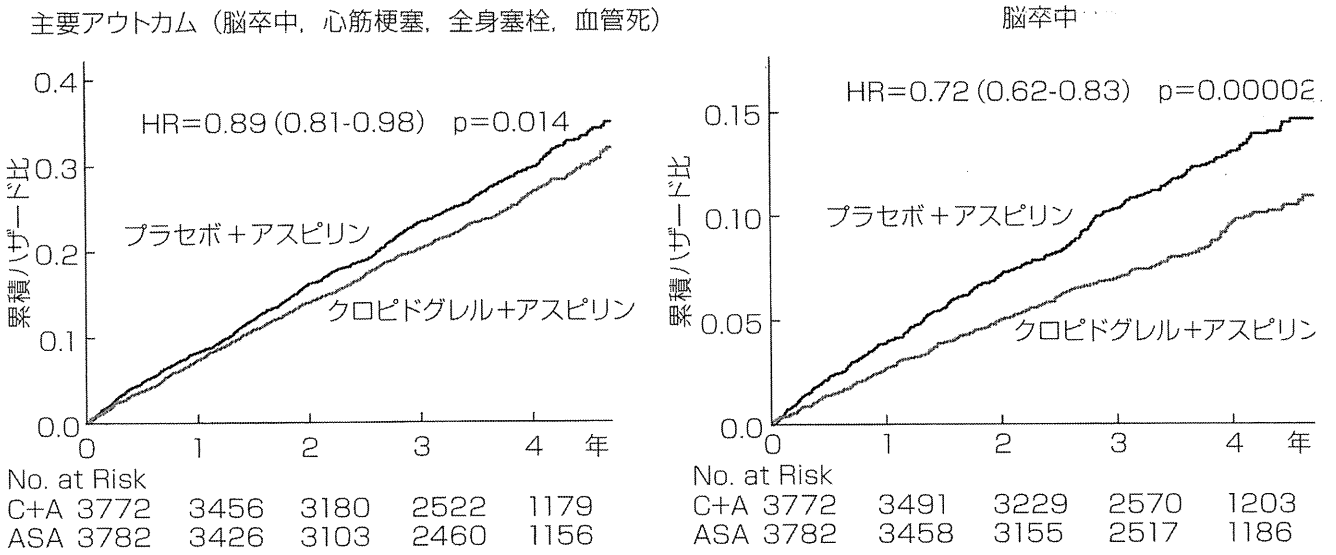

図7. ACTIVE Aの成績（文献8より引用・改変）
低リスクの心房細動患者において主要アウトカム（脳卒中，心筋梗塞，全身塞栓，血管死）と脳卒中の発症はいずれもクロピドグレル・アスピリン併用療法でアスピリン単独療法より有意に少なかった．

表．ACTIVE Aにおける出血性合併症の発現頻度（文献8より引用・改変）

出血合併症	クロピドグレル＋アスピリン		アスピリン		クロピドグレル＋アスピリン対アスピリン単独		
	数	年間発症率	数	年間発症率	相対リスク	95% 信頼区間	P
大出血	251	2.0	162	1.3	1.57	1.29-1.92	< 0.001
高度	190	1.5	122	1.0	1.57	1.25-1.98	< 0.001
致死的	42	0.3	27	0.2	1.56	0.96-2.53	0.07
頭蓋内	54	0.4	29	0.2	1.87	1.19-1.94	0.006
頭蓋外	200	1.6	134	1.1	1.51	1.21-1.88	< 0.001

たACTIVE Aの成績によれば，アスピリン・クロピドグレル併用療法はアスピリン単独療法より脳卒中や血栓塞栓リスクが有意に少なかった（図7）[8]．したがって，ワルファリンの適応とならない低リスクのNVAF患者にはアスピリン・クロピドグレル併用療法が推奨されるが，出血性合併症も併用療法では増加するという結果が示されているのでリスク・ベネフィットを勘案して適応を決定する必要があろう（表）[8]．

5. ダビガトラン

ワルファリンには血液凝固モニター，ビタミンK摂取制限，他剤との相互作用などの煩雑さがあり，本来適応となる患者にも十分使用されていないのが現状である．ワルファリンはビタミンK依存性の凝固因子の合成を抑制することによりトロンビンの生成を抑制する間接的トロンビン阻害薬であり，その代謝が遺伝子の制御下にあり，食事や薬剤の影響を受けやすいので治療域が狭いため時間と経費を要する血液凝固モニターが必要となる．これに対して，新規抗凝固薬は血液凝固カスケード発生の阻害，凝固進展阻止によるトロンビン生成の抑制，トロンビン阻害によるフィブリン形成の抑制といった，血液凝固の特異的な段階を標的としているため用量反応性に優れ，抗凝固活性の個人差が少なく，ビタミンK摂取の影響や薬物相互作用がなく，血

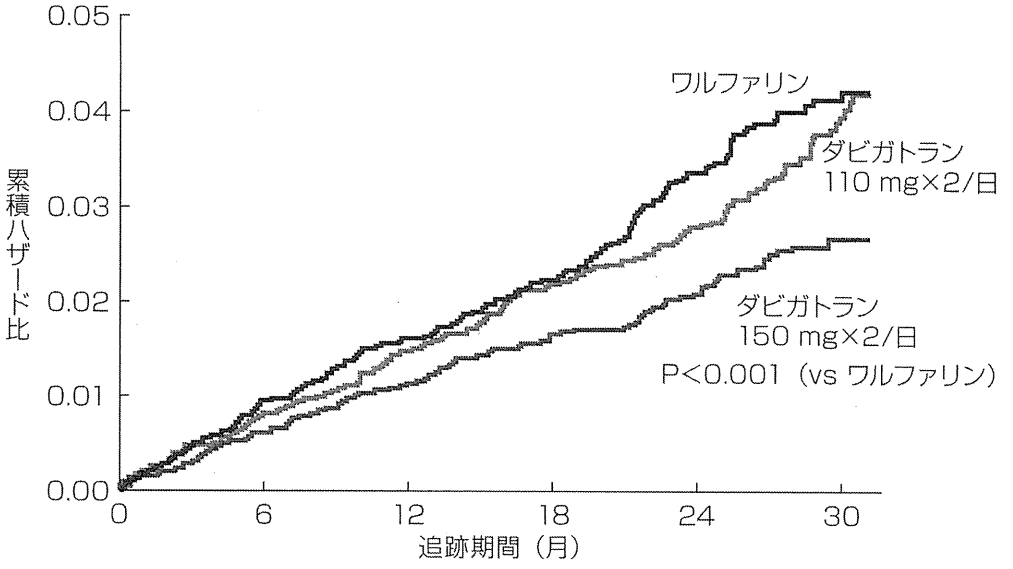

図8. RE-LY試験における主要評価項目（脳卒中または全身塞栓症）の成績（文献9より引用・改変）
脳卒中または全身塞栓症は高用量のダビガトラン投与群でワルファリン投与群より有意に少なく，低用量のダビガトラン投与群でワルファリン投与群と同等であった．

液凝固モニターを必要としない．

これらの新規抗凝固薬の中で心房細動患者における臨床開発がもっとも進んでいた経口薬がトロンビン阻害薬のダビガトラン（dabigatran）であり，心房細動患者においてワルファリン（INR 2～3）との有効性と安全性を比較する第3相臨床試験（Randomized Evaluation of Long Term Anticoagulant Therapy：RE-LY）が行われ，注目すべき成績が発表された．

RE-LY試験の対象患者は，少なくとも一つの危険因子（脳卒中，TIAまたは全身塞栓症の既往，左室機能不全，75歳以上，高血圧・冠動脈疾患・糖尿病のいずれかを有する65歳以上）を有するNVAF患者18,000例であり，日本人患者も含まれており，6,000例にダビガトラン110 mg 1日2回，6,000例にダビガトラン150 mg 1日2回，6,000例にワルファリン（INRの目標値2.0～3.0，日本人のみINR 2.0～2.6）を投与し，1～3年間追跡調査した．

本研究の目的はワルファリンに対するダビガトランの非劣性を証明することにあったが，結果はいずれの用量のダビガトランも非劣性が証明されたのみならず，高用量の有効性と低用量の安全性はワルファリンを有意に上回っていた．すなわち，脳卒中または全身塞栓症はワルファリン投与群（1.69%/年）よりダビガトラン150 mg 2回投与群（1.11%/年）で有意に少なく，ダビガトラン110 mg 2回投与群（1.53%/年）で同等であり（図8）[9]，大出血はダビガトラン110 mg 2回投与群でワルファリン投与群より有意に少なく（図9）[9]，出血性脳卒中はいずれのダビガトラン投与群もワルファリン投与群より有意に少なかった（図10）[9]．

本研究結果は，60年以上続いたワルファリンの時代に終止符を打ち，本来抗凝固療法の適応となるべき高リスクの心房細動患者に適正な抗凝固療法が安全かつ簡便に行えることを示唆しており，医師と患者の両者から大きな期待が寄せられている．

おわりに

本講演で紹介した大規模臨床試験はガイドラインに大きな影響を及ぼすものであり，特に新規抗凝固薬の成績は治療のパラダイムシフトをもたらすインパクトがある．抗血栓療法は，死

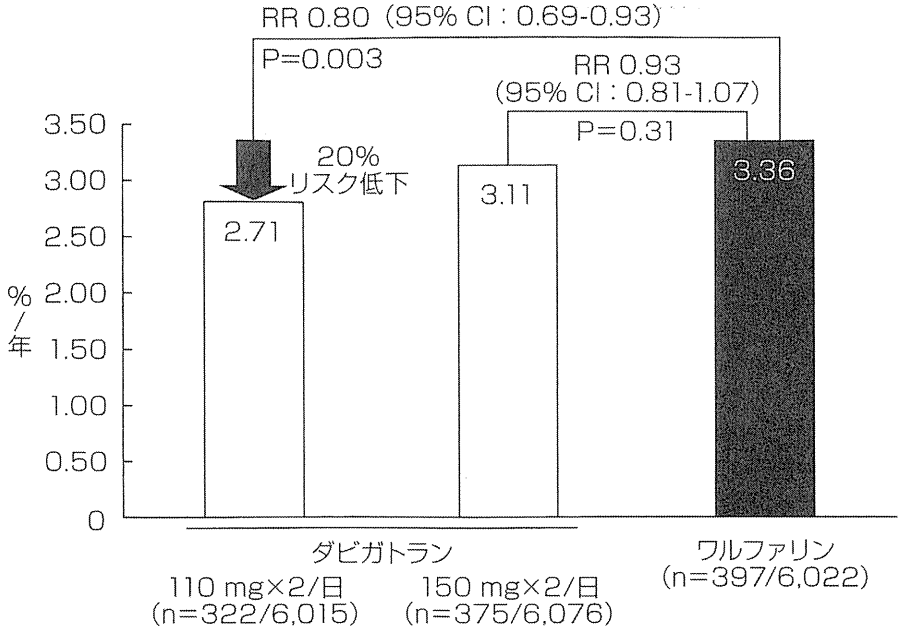

図 9. RE-LY 試験における大出血の発現率（文献 9 より引用・改変）
大出血（ヘモグロビン 20 g/l 以上の減少を示す出血，2 単位以上の輸血を必要とする出血，または重要な部位や臓器における症候性の出血）は低用量のダビガトラン投与群でワルファリン投与群より有意に少なく，高用量のダビガトラン投与群でワルファリン投与群と同等であった．

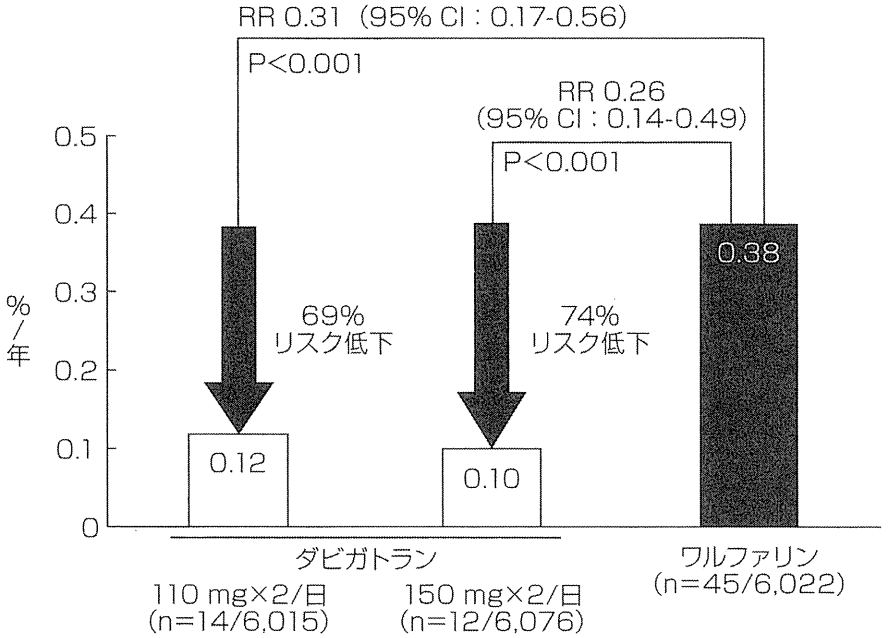

図 10. RE-LY 試験における出血性脳卒中の発症率（文献 9 より引用・改変）
出血性脳卒中はいずれの用量のダビガトラン投与群もワルファリン投与群よりはるかに少なかった．

亡または身体障害の原因となる，人類最大の疾患である血栓症の治療法であるが，宿命的な副作用として出血性合併症が常に問題となる[10]．このジレンマを解決し，有効性と安全性を高めるため，ゲノム薬理学の進歩とともに分子標的薬が次々と開発されており，今後も多くの大規模

臨床試験が行われ，ガイドラインの変更を迫るような，新たなエビデンスがもたらされるものと期待される．

文　献

1) Uchiyama S, et al : New modalities and aspects of antiplatelet therapy for stroke prevention. Cerebrovascr Dis 21 (suppl 1) : 7–16, 2006.
2) Uchiyama S, et al : The safety and efficacy of clopidogrel versus ticlopidine in Japanese stroke patients : combined results of two phase III, multicenter, randomized clinical trials. J Neurol 256 : 888–897, 2009.
3) 日本脳卒中学会，他：脳卒中治療ガイドライン．脳卒中ガイドライン作成委員会編．2009.
4) Uchiyama S, et al : Stroke prevention by cilostazol in patients with atherothromobosis : meta-analysis of placebo-controlled randomized trials. J Stroke Cereborvasc Dis 18 : 482–490, 2009.
5) Shinohara Y, et al : Cilostazol is superior to aspirin for secondary stroke prevention : results of CSPS II. International Stroke Conference 2010, San Antonio. Lancet Neurol, 2010. in press.
6) Sacco RL, et al for the PRoFESS Study Group : Aspirin and extended release dipyridamole versus clopidogrel for recurrent stroke. New Engl J Med 359 : 1238–1251, 2008.
7) ACTIVE Writing Group of the ACTIVE Investigators : Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation. Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W) : a randomized controlled trial. Lancet 67 : 1903–1912, 2006.
8) The ACTIVE Investigators : Effect of clopidogrel added to aspirin in patients with atril fibrillation. N Engl J Med 360 : 2066–2078, 2009.
9) Connolly SJ, et al : Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361: 1139–1151, 2009.
10) Uchiyama S, et al : Risk factor profiles of stroke, myocardial infarction, and atrial fibrillation : a Japanese multicenter cooperative registry. J Stroke Crebrovasc Dis 19 : 190–197, 2010.

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Cardiovascular event rates in patients with cerebrovascular disease and atherothrombosis at other vascular locations: Results from 1-year outcomes in the Japanese REACH Registry

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ABSTRACT

The REduction of Atherothrombosis for Continued Health (REACH) Registry is a large, international, prospective cohort of patients with atherothrombosis or multiple (≥3) risk factors (MRFs) for atherothrombosis.
Japanese patients ($n=5193$) were enrolled into the REACH registry between August and December 2004. One-year event rate in patients with cerebrovascular disease (CVD) was compared with that of patients with symptomatic atherothrombosis at other locations.
After one year ($n=5021$), patients with CVD ($n=1962$) experienced a higher rate of non-fatal strokes than patients with coronary artery disease (CAD), peripheral artery disease (PAD) or MRFs alone (2.77% vs. 1.28%, 2.07% and 1.56%, respectively), but a lower rate of non-fatal myocardial infarction (0.45% vs. 1.31%, 0.77% and 0.66%, respectively). Patients with CVD plus disease in ≥1 other vascular bed had higher rates of cardiovascular events than patients with CVD alone. Overall, event rates including non-fatal stroke, non-fatal myocardial infarction and cardiovascular death were higher for patients with CVD and PAD than for patients with CVD and CAD. Asymptomatic carotid stenosis ≥70% and ankle-brachial index <0.9 were significant predisposing factors for stroke.
Patients with CVD and co-existing atherothrombotic diseases had a high risk of recurrent events, including events arising in other vascular beds than originally diagnosed.

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1. Introduction

Atherothrombosis (coronary artery disease [CAD], cerebrovascular disease [CVD], and peripheral arterial disease [PAD]) contributes to the major causes of death worldwide. While age-standardized rates of death from these conditions are decreasing in leading industrialized countries, such as the USA, the increasing age of these populations has ensured that the absolute numbers of deaths have continued to increase [1].

The situation in Japan is no better than the rest of the world, with high mortality rates for atherothrombotic disease. CAD and CVD constitute the second and third most common causes of death in Japan, respectively [2]. Measures need to be considered to improve these statistics and alleviate the burden that atherothrombotic diseases have on affected individuals.

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Clarification of the characteristics of atherothrombotic conditions, their risk factors, and the rate of cardiovascular (CV) events may help to develop prevention and treatment strategies in the future. However, for such strategies to be effective, they may need to be specifically tailored for the populations of individual countries because the background characteristics of atherothrombotic disease vary between countries.

In Japan, CVD has a relatively major impact, with reports indicating that the prevalence is higher than observed elsewhere in the world [2,3]. A greater understanding of the causes of CVD should provide healthcare professionals with essential information so that strategies for its prevention and treatment in the Japanese population can be improved.

As part of the information-gathering process, the REduction of Atherothrombosis for Continued Health (REACH) Registry describes contemporary patients with a diagnosis of atherothrombosis or with risk factors for the development of atherothrombosis, together with their medical management and their risk of CV events. As this registry spans the globe and follows consistent enrollment criteria, it allows comparison of patients with atherothrombosis across the world. The methodology of this study and the baseline characteristics of enrolled patients (globally and in Japan) have been described previously [3,4].

This purpose of this report is to present the 1-year follow-up results for the REACH Registry in Japan, with particular emphasis on the importance of cerebrovascular events in the Japanese population.

2. Methods

The study design, including the strategy for selecting physicians, collecting follow-up data, and ensuring data quality, and the inclusion criteria of the REACH Registry have been described previously [4]. Briefly, patients were ≥45 years old either with established atherothrombotic disease (CAD, CVD, or PAD) or with multiple risk factors (MRFs) alone (≥3 atherothrombotic risk factors). To avoid selection bias, patients were enrolled consecutively (August to December 2004). Documented CAD was defined as a history of at least one of the following conditions: stable or unstable angina, percutaneous coronary intervention, coronary artery bypass surgery, or myocardial infarction (MI). A documented history of either transient ischemic attack (TIA) or symptomatic cerebral infarction defined CVD. PAD was defined as intermittent claudication confirmed by an ankle-brachial index (ABI) <0.9 at the time of enrollment, a history of intermittent claudication with relevant intervention, or both. Polyvascular disease was defined as patients with a diagnosis of more than one of CAD, CVD, or PAD.

Atherothrombotic risk factors for enrollment included: type 1 or type 2 diabetes mellitus; diabetic nephropathy; ABI <0.9 in either leg at rest; asymptomatic carotid stenosis ≥70%; carotid intima-media thickness >2 times that at adjacent sites; systolic blood pressure of ≥150 mm Hg despite therapy for ≥3 months; hypercholesterolemia treated with medication; current frequent smoking (≥15 cigarettes per day); and age ≥65 years (men) or ≥70 years (women). Patients already in a clinical trial or those who might have difficulty returning for a follow-up visit were excluded. Patients with ongoing events were not enrolled and hospitalized patients were specifically excluded.

To ensure that the risk of inclusion bias was reduced, patients were enrolled from rural, suburban, and urban Japan through various specialty physicians (including general practitioners, cardiologists, neurologists, and vascular surgeons) from a variety of institutions (including private clinics, community hospitals, and university hospitals) [3]. Physicians and their specialties were selected to be representative of healthcare utilization by patients with or at risk of atherothrombotic conditions. The number of subjects recruited was limited to 15 per physician.

2.1. Follow-up

At 12 (±3) months after enrollment, patients' clinical outcomes, vascular procedures, employment status, body weight, current smoking status, and regular medications since baseline were recorded by participating physicians. To ensure that diagnosis of ischemic stroke or TIA was reliable, such data were only accepted from a neurologist or hospital department. The current report is based on a database lock of July 21, 2006.

CV death was defined as fatal stroke, fatal MI, or other CV death. Other CV death was defined death due to another cardiac origin; pulmonary embolism; any sudden death, including unobserved and unexpected death (e.g., while sleeping) unless proven otherwise by autopsy; death following a vascular operation, vascular procedure, or amputation (except for trauma or malignancy); death attributed to heart failure; death following a visceral or limb infarction; and any other death that could not be definitely attributed to a nonvascular cause or hemorrhage. Any MI or stroke followed by death from any cause in the subsequent 28 days was considered as a fatal MI or fatal stroke. Major CV events were defined as CV death, MI, stroke, or hospitalization for TIA, unstable angina, or another ischemic arterial event including worsening of PAD.

2.2. Statistical analysis

Annualized event rates were calculated, adjusted for age and sex. This adjustment was accomplished through the corrected group prognosis method in the Cox proportional hazards model described previously [5]. Patients were only included in an endpoint analysis if they had complete outcome and covariate information. Multiple logistic regression analysis was used to determine the effect of different risk factors on the likelihood of recurrent stroke.

3. Results

Of the 5193 Japanese patients who were enrolled in the REACH Registry, 5185 entered the follow-up phase; 6 patients (0.12%) withdrew their consent early and 2 patients (0.04%) were found to be ineligible. At the time of the database lock on July 21, 2006, 1-year follow-up data were available for 5021 patients (96.84%). Data were unavailable for 117 patients (2.26%) who missed visits and for 47 patients (0.91%) whose physician withdrew from the study.

Demographics and baseline characteristics of patients enrolled in the REACH Registry with 1-year follow-up have been described previously for other regions of the world [6]. The characteristics of all Japanese REACH patients compared with those who had CVD at the 1-year follow-up are shown in Table 1. Patients with CVD included 371 patients with TIA and 1749 patients with symptomatic cerebral infarction; of these, 158 patients had both a TIA and symptomatic cerebral infarction. Compared with the all-patient group, the proportions of patients with CVD who had diabetes (45.81% vs. 36.44%, respectively) or hypercholesterolemia (46.43% vs. 35.63%, respectively) at baseline were lower, while the proportion of patients with CVD who had hypertension were higher (70.88% vs. 74.41%, respectively) (Table 1).

One-year CV event rates for Japanese patients are shown in Table 2. In the all-patient population, the rate of non-fatal stroke (1.90%) was higher than the rate of non-fatal MI (0.87%). There was a trend for higher all-cause mortality at 1 year in patients with established atherothrombotic disease compared with patients with MRFs alone (1.66% vs. 0.77% of patients, respectively; $p=0.116$). In the patients with established atherothrombotic disease, approximately 1 in 14 patients had a major CV event (CV death/MI/stroke/hospitalization), which was significantly greater than the 1 in 41 patients with MRFs alone who had a major CV event ($p<0.001$).

Among patients diagnosed with atherothrombosis in a particular vascular bed, there was a substantial rate of recurrence of an event at

Table 1
Characteristics of Japanese patients in the 1-year follow-up analysis.

Variable	Total patients ($n=5021$)	Patients with CVD ($n=1962$)	Patients with PAD ($n=603$)	Patients with CAD ($n=2252$)	Patients with MRFs ($n=831$)
Mean age ((years) ± SD)	70.31 ± 8.72	70.87 ± 8.77	72.18 ± 7.96	69.79 ± 8.91	70.72 ± 8.23
Male (%)	69.25	69.47	83.42	76.02	48.26
Diabetes (%)	45.81	36.44	41.29	40.54	85.92
Hypertension (%)	70.88	74.41	78.11	68.16	73.16
Hypercholesterolemia (%)	46.43	35.63	36.48	52.66	62.70
Overweight (BMI 25–>30 kg/m_2) (%)	29.36	28.64	22.72	30.99	30.81
Obese (BMI >30 kg/m^2) (%)	4.00	3.31	1.49	3.64	6.98
Former smoker (%)	45.18	45.56	60.62	53.77	20.75
Current smoker (%)	16.86	16.14	21.93	11.86	26.04
Antiplatelet agent (%)	76.60	84.40	86.57	89.39	27.08
Aspirin	57.20	56.98	40.46	79.57	18.77
Other antiplatelet agent	35.13	43.37	67.99	32.55	11.31
Aspirin and other antiplatelet agent	14.78	14.58	20.73	22.02	2.65
Antihypertensive agent (%)	82.02	77.62	80.43	89.83	77.26
Calcium channel blockers	59.79	59.33	61.86	61.46	58.97
Beta blockers	20.81	14.12	15.75	33.53	11.19
Diuretics	15.10	12.28	14.10	20.29	14.20
Angiotensin II receptor blockers	37.64	37.56	35.82	36.50	44.40
Angiotensin-converting enzyme inhibitors	20.00	17.99	20.73	22.78	18.53
Other antihypertensives	6.45	7.95	8.46	4.75	8.06
Statins (%)	47.62	36.34	35.82	56.08	60.53

BMI = body mass index; CAD = coronary artery disease; CVD = cerebrovascular disease; MRFs = multiple risk factors; PAD = peripheral artery disease; SD = standard deviation.

the original site of diagnosis. However, patients also experienced events in other vascular beds. Patients with CVD experienced an annual rate of stroke (fatal and non-fatal) of 2.96% (2.77% non-fatal), but had a non-fatal MI rate of 0.45% (six-fold lower than non-fatal stroke). The rate of non-fatal stroke was also higher than the rate of non-fatal MI in patients with PAD (2.07% vs. 0.77%) and in those with MRFs alone (1.56% vs. 0.66%).

In patients with prior CAD, the annualized event rate for non-fatal stroke and non-fatal MI was similar (1.28% and 1.31% of patients, respectively). In addition, patients with CAD had the highest rates of CV death and non-fatal MI, followed by those with PAD and then by those with MRFs only. Patients with CVD had the lowest occurrence of non-fatal MI over 1 year.

Patients with PAD had the highest incidence of the composite endpoint of CV death/MI/stroke/hospitalization and also of new diagnosis/worsening of claudication, which were reported by approximately 1 in 10 patients and 1 in 24 patients, respectively (Table 2). The annual rate of hospitalization was 7.44% among patients with PAD compared with 4.87% and 2.27% among patients with CAD or CVD, respectively.

The rate of bleeding events leading to hospitalization was low, occurring in 0.40% of patients over 1 year. Bleeding events were seen in approximately 1 in 189 patients with established atherothrombotic disease, whereas none of the patients with MRFs alone reported bleeding events (Table 2).

Patients with CVD plus atherothrombotic disease in at least one additional vascular bed generally had higher rates of CV events than those with CVD alone (Table 3). In patients with CVD and comorbid PAD compared with patients with CVD alone, the rate of non-fatal stroke was almost doubled (4.82% vs. 2.58%, respectively), as too was the combined rate of hard CV events (CV death, non-fatal MI, or non-fatal stroke) (7.23% vs. 3.83%). The rate of non-fatal MI was almost four times higher in patients with CVD and PAD (1.20%) compared with patients with CVD alone (0.33%). Patients with CVD and PAD also had higher event rates

Table 2
One-year CV event rates for the total population and the main subsets (adjusted for sex and age[a]).

Event	Total events (n)	Patients with event (%)						
		Total ($n=5021$)	Total established disease[b] ($n=4190$)	CVD[c] ($n=1962$)	CAD ($n=2252$)	PAD ($n=603$)	MRFs alone ($n=831$)	p-value[d]
All-cause mortality	65	1.51	1.66	1.46	1.75	1.25	0.77	0.116
Major CV event								
CV death	33	0.81	0.86	0.82	0.87	0.55	0.48	0.524
Non-fatal MI	32	0.87	0.91	0.45	1.31	0.77	0.66	0.967
Non-fatal stroke	80	1.90	1.97	2.77	1.28	2.07	1.56	0.335
CV death/MI/stroke	141	3.47	3.59	3.90	3.32	3.08	2.77	0.408
CV death/MI/stroke/hospitalization	306	6.44	7.26	6.17	8.19	10.52	2.45	<0.001
Other CV outcomes leading to hospitalization								
Unstable angina	45	0.95	1.20	0.86	1.87	0.84	0.00	0.983
Transient ischemic event	17	0.36	0.43	0.63	0.34	0.15	0.10	0.154
Other ischemic arterial event[e]	38	0.80	0.99	0.86	1.24	1.76	0.10	0.026
Chronic heart failure	37	0.79	0.88	0.57	1.42	0.88	0.27	0.119
Hemorrhagic stroke	19	0.40	0.53	0.38	0.56	0.68	0.00	0.989
New diagnosis/worsening of claudication	39	0.83	0.94	0.53	0.73	4.15	0.15	0.070

CAD = coronary artery disease; CV = cardiovascular; CVD = cerebrovascular disease; MI = myocardial infarction; MRF = multiple risk factor; PAD = peripheral arterial disease; TIA = transient ischemic attack.

[a] Calculated on the basis of the sample of patients with no missing outcomes or covariates.
[b] Established atherothrombotic disease (CAD, CVD, or PAD).
[c] Either TIA or symptomatic cerebral infarction.
[d] Comparison of the total established disease population with the MRFs alone population.
[e] Includes peripheral arterial embolism, mesenteric artery occlusion, and worsening of PAD.

Table 3
One-year CV event rates in patients with CVD alone or CVD in combination with atherothrombosis in other arterial beds.

Event	Patients (%) with event (95% CI)			
	CVD alone ($n=1514$)	CVD + CAD ($n=325$)	CVD + PAD ($n=83$)	CVD + CAD + PAD ($n=40$)
CV death	0.99 (0.56–1.63)	0.92 (0.19–2.67)	1.20 (0.03–6.53)	0 (–)
Non-fatal MI	0.33 (0.11–0.77)	0.92 (0.19–2.67)	1.20 (0.03–6.53)	0 (–)
Non-fatal stroke	2.58 (1.84–3.50)	2.15 (0.87–4.39)	4.82 (1.33–11.88)	2.50 (0.06–13.16)
CV death/MI/stroke	3.83 (2.92–4.92)	3.69 (1.92–6.36)	7.23 (2.70–15.07)	2.5 (0.06–13.16)
CV death/MI/stroke/hospitalization for atherothrombotic event(s)	5.35 (4.27–6.61)	11.38 (8.14–15.35)	16.87 (9.54–26.68)	12.50 (4.19–26.80)

CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; CVD = cerebrovascular disease; MI = myocardial infarction; PAD = peripheral arterial disease.

than patients with CVD and CAD for CV death (1.20% vs. 0.92%, respectively), non-fatal MI (1.20% vs. 0.92%, respectively), non-fatal stroke (4.82% vs. 2.15%, respectively), CV death/MI/stroke (7.23% vs. 3.69%, respectively), and CV death/MI/stroke/hospitalization (16.87% vs. 11.38%, respectively) (Table 3).

The importance of different risk factors in determining the risk of cerebrovascular events (fatal and non-fatal stroke, excluding TIA) is shown in Table 4. In univariate analysis, men aged ≥65 years and women ≥70 years or those with an ABI <0.9 were associated with a greater occurrence of cerebrovascular events. Patients with the inclusion risk factor of hypercholesterolemia treated with medication experienced a lower rate of cerebrovascular events than patients without hypercholesterolemia at baseline. Multiple regression analysis revealed that an ABI <0.9 and symptomatic carotid artery stenosis ≥70% were significant predisposing factors for cerebrovascular events.

4. Discussion

This report from the REACH Registry in Japan demonstrates the substantial number of major CV events (CV death/MI/stroke/hospitalization) that occurred in 1 year among outpatients with previously diagnosed atherothrombosis (7.26%; approximately 1 in 14 patients). Even among patients who had not experienced an event but who had been identified as having MRFs for atherothrombotic events, 2.45% (approximately 1 in 41 patients) had a major CV event in this first year of follow-up. Hospitalization, a major burden for healthcare resources and a component of our measure of major CV events, was a frequent occurrence among patients with established disease, particularly PAD. This highlights the continuing need to review and improve the treatment of atherothrombosis in Japanese patients.

Table 4
Baseline risk factors for cerebrovascular events (fatal/non-fatal stroke, excluding transient ischemic attack) analyzed by univariate and multivariate logistic regressions.

Risk factor	Odds ratio (95% CI)[a]	Adjusted odds ratio (95% CI)[b]	*p*-value
Age (male ≥65 years or female ≥70 years)	1.82 (1.08–3.05)	1.78 (0.49–6.44)	0.3796
Currently smoking >15 cigarettes/day	1.32 (0.73–2.39)	0.25 (0.03–2.10)	0.200
Diabetes mellitus	1.33 (0.88–2.01)	2.88 (0.83–9.97)	0.095
Diabetic nephropathy	1.49 (0.85–2.60)	2.38 (0.75–7.56)	0.142
Systolic blood pressure ≥150 mm Hg despite therapy for ≥3 months	1.27 (0.78–2.07)	0.86 (0.27–2.81)	0.808
Hypercholesterolemia treated with medication	0.51 (0.33–0.79)	0.87 (0.33–2.31)	0.783
Ankle-brachial index <0.9	2.44 (1.24–4.81)	3.18 (1.13–8.91)	0.028
Asymptomatic carotid stenosis ≥70%	2.08 (0.85–5.09)	5.77 (1.48–22.50)	0.012
Presence of ≥1 carotid plaque	1.13 (0.58–2.21)	0.63 (0.20–1.93)	0.4169

CI = confidence interval.
[a] Univariate analysis.
[b] Multivariate analysis.

The REACH Registry is the largest prospective registry of CV events collected from Japanese outpatients. Although randomized controlled trials (RCTs) provide the foundation for testing clinical hypotheses, the use of strict inclusion and exclusion criteria in RCTs makes it difficult to apply the so-called "evidence" to clinical practice. In particular, the long-term prognosis of disease and its treatment are particularly difficult to estimate from RCTs [7]. Registries therefore enable a real-world opportunity to correlate disease occurrence with treatments and baseline characteristics. In the case of the REACH Registry, this will allow an invaluable opportunity to evaluate whether the application of care guidelines is effective in reducing ischemic events [4,8].

Addressing the problem of CVD and stroke is a considerable challenge facing the healthcare community in Japan. The proportion of patients in Japan with CVD or prior stroke is higher than in the rest of the world [6]. According to international data provided by the REACH Registry, Japan ranked higher than areas such as North America, Latin America, and Western Europe for the proportion of the population with a previous history of CVD (39.08% vs. 21.00%, 31.93%, and 26.36%, respectively) and/or stroke (35.19% vs. 13.97%, 25.08%, and 16.99%, respectively) [6]. These demographic data, together with a reduction in the decline of the stroke mortality rate in Japan [9], highlight the importance of CVD in the Japanese population.

Accompanying risk factors can have a considerable impact on the management of disease and may also give an indication of specific risk. Analysis of patients with CVD in comparison with all Japanese patients highlights some differences in comorbid conditions (Table 1). Comorbidity with diabetes, hypertension, and hypercholesterolemia in the CVD population was higher than in a previous Japanese registry of acute stroke [10]. The study by Kobayashi (The Japan Standard Stroke Registry Study) [10] examined accompanying risk factors in hospitalized patients rather than outpatients. The REACH registry provides additional information, reflecting the broader population of patients with CVD in Japan more closely than an inpatient-only study. The higher prevalence of diabetes, hypertension, and hypercholesterolemia in the Japanese CVD population demonstrated in our study may indicate that these comorbidities are more widespread than has been previously recognized. Appropriate management of these risk factors should be re-emphasized.

One-year major CV event rates in the Japanese population were most notable in categories where stroke was a component (Table 2). Patients with CVD experienced higher rates of the composite endpoint of CV death/MI/stroke than patients with CAD or PAD and the rate of non-fatal stroke was greater than the combination of CV death and non-fatal MI. Furthermore, there was a high risk of recurrence of fatal and non-fatal stroke (2.96%) in patients with CVD. However, patients with CVD also experienced non-fatal MI and unstable angina events, indicating that these patients experience major vascular events other than cerebral infarction. This is in agreement with data from both RCTs [11] and registries [12] showing that patients with prior stroke will experience vascular events in other vascular beds.

The occurrence of MI and unstable angina in patients with CVD highlights the systemic nature of atherothrombosis. Previous results from the REACH Registry suggest that there is a substantial under-treatment of Japanese patients. Only 79.6% receive any CV agent and only 73.9% receive an antiplatelet agent. Prescription rates for both agents are below the global average [3,6]. There has been a historical assumption that bleeding was an issue for Japanese patients with CVD, which has impeded the adoption of antiplatelet or anticoagulant agents [13]. Interestingly, in this study patients with CVD had the lowest incidence of bleeding, an unexpected finding. One possible explanation for this might relate to the level of dual antiplatelet therapy in the different patient groups. Previous studies have reported that dual antiplatelet therapy is associated with a higher rate of bleeding events than single antiplatelet therapy [14,15]. In the present study, a higher proportion of patients with CAD and PAD were receiving dual antiplatelet agents than patients with CVD. Although bleeding has been identified as an issue for Japanese patients with CVD, the rates of bleeding resulting in hospitalization in patients with CVD observed in this report are not higher than those observed globally [6]. A recent comparison of the antiplatelet agents clopidogrel and ticlopidine in Japanese patients with non-cardioembolic cerebral infarction showed a similar low rate of bleeding in treated patients [16]. Similarly, a recent study of dual antiplatelet therapy in Japanese patients showed the same incidence of intracranial hemorrhage as in Western populations [15]. Therefore, net clinical benefit for antiplatelet intervention would be positive even in a Japanese patient population [16–19].

Polyvascular disease may lead to an increased number of events compared with atherothrombotic disease in a single vascular bed [6]. It has been estimated that up to 65% of patients with a history of CVD or CAD may have co-existing PAD [20]. In the REACH Registry in Japan, 23% of patients with CVD also had CAD and/or PAD [3]. The 1-year event rates reported here (Table 3) show that patients with CVD and PAD were at greatest risk of having an event. The influence of PAD on event rates in patients with CVD appeared greater than the effect of co-existing CAD, as shown by higher non-fatal stroke and non-fatal MI rates in patients with CVD and co-existing PAD rather than co-existing CAD. In a study of Chinese patients with PAD, CAD or CVD, PAD patients had the highest prevalence (25%) of >70% carotid stenosis, which was higher than CAD patients (11%) [21]. This suggests that PAD may be a stronger predictor of concurrent CVD risk than CAD. A risk-factor analysis was carried out as part of this study to determine which groups may be considered for earlier preventative intervention or increased monitoring to reduce the risk of future cerebrovascular events. Cerebrovascular events were more likely to occur in patients with an ABI <0.9 (adjusted odds ratio [OR] 3.18; 95% confidence interval [CI]: 1.13–8.91) or with asymptomatic carotid stenosis ≥70% (adjusted OR 5.77; 95% CI: 1.48–22.5). The ABI is a simple and accurate measure that is a good predictor of subsequent CV events and, therefore, could be integrated into routine screening of CV status [22]. Screening for carotid stenosis should also be recommended in Japanese patients with a history of atherothrombosis or multiple vascular risk factors because it was found to be a strong predictor of future CVD in this study.

A possible explanation for the effect of ABI and diagnosed PAD on the increased rate of events in patients with CVD might be that patients with CVD and comorbid PAD may represent a subset of patients with a systemically more advanced stage of atherothrombosis and vascular damage [23]. It might be expected that as the number of co-existing atherothrombotic conditions increases, so too does the risk of CV events [6,24]. This was not shown in the current analysis. Only a relatively small number of Japanese patients with disease in all three vascular beds were available for this analysis, so the event rates in this population may be anomalous. However, the upper limit of the 95% CI for the rate of the composite endpoint for major CV events including hospitalization was greatest for patients with disease at all three locations.

There are some limitations to this study as a result of its registry design, because comprehensive, observational databases lack the scientific rigor of RCTs. Registry-based analyses are generally influenced by recruitment biases, which are not necessarily recorded, although the REACH Registry was specifically designed to exclude such effects. All patients for the study were recruited by physicians and, as such, those recruited may not reflect the general Japanese population. It is quite feasible that physicians selected for participation in registry studies may exhibit greater adherence to guidelines and disease prevention than in the general physician population, which could result in bias. However, this bias is likely to result in better-treated patients entering the study, with the consequence of fewer events being reported than may be expected in general clinical practice [7]. Thus, multivariate modeling of the risk of stroke was potentially limited by the relatively low number of outcome events. In addition, the occurrence of CVD in the study may have been underestimated since diagnostic data were accepted only from neurologists or hospital departments. Although a diagnosis of PAD was defined as an ABI <0.9, diagnostic criteria for CAD were less restrictive, which may have affected comparison of event rates in the different patient populations. Furthermore, comparison with a wider population is limited as these data are only applicable to patients from a similar population. Despite the limitations of a registry design, a high level of follow-up data was available from this Japanese cohort — higher than observed for the overall global REACH population (96.84% vs. 95.22%, respectively) [6].

The REACH Registry is one of the largest international epidemiologic registries and clearly highlights the relative importance of CVD in Japanese patients. The knowledge gained from these data has the potential to raise the understanding and awareness of atherothrombosis, and to aid in the development of improved preventive strategies and management regimens for at-risk patients.

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Kobayashi, H. Bujo; National Hospital Organization Chiba Medical Center: N. Ishige, Z. Yamada; National Hospital Organization Chibahigashi Hospital: T. Nakazato; Nippon Medical School Chiba Hokusoh Hospital: M. Hamamoto; Asahi Chuo Hospital: T. Furuya; Kashiwa City Hospital: S. Sato; Sekiya Clinic: T. Sekiya; Watanabe Naika Clinic: N. Tadokoro; Higaki Naika Junkankika Clinic: S. Higaki; Nippon Medical School Hospital; Teikyo University Hospital: T. Teramoto; Keio University Hospital: H. Hoshino; Diabetes Center, Tokyo Women's Medical University: T. Nakagami; National Hospital Organization Tokyo Medical Center: K. Koyama, K. Osumi, Y. Nakamura; National Hospital Organization Disaster Medical Center: S. Suzuki, H. Komachi; National Hospital Organization Tokyo National Hospital: K. Segawa; National Hospital Organization Murayama Medical Center: H. Yamagata; Kanto Central Hospital of the Mutual Aid Association of Public School Teachers: H. 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Goto; National Hospital Organization Yokohama Medical Center: Y. Takemoto, M. Ujihara, M. Higashidate; National Hospital Organization Kurihama Alcoholism Center: K. Maruyama; National Hospital Organization Sagamihara National Hospital: T. Suwa; Yokohama City University Medical Center: K. Tsukahara; Yokohama Rosai Hospital: K. Kato; Yokohama Stroke and Brain Center: M. Yamamoto; Imai Clinic: T. Imai; Yoshioka Naika Clinic: K. Yoshioka; Shibazaki Naika Clinic: Y. Shibazaki; Akiyama Internal Medicine Clinic: H. Akiyama; Yokoyama Naika Clinic: N. Yokoyama; Nishiyama Ichou Junkanki Geka Clinic: H. Sairenji; Yokohama Sotetsu Blg Clinic of Internal Medicine: H. Mori; National Hospital Organization Saigata National Hospital: T. Inazu; Nagaoka Red Cross Hospital: T. Kawaguchi; Nakajima Neurosurgery Naika Clinic: T. Nakajima; Toyama University Hospital: M. Urakaze, M. Kubo; Toyama Red Cross Hospital: K. Yamatani; Yatsuo General Hospital: R. Masuda; Kanazawa Medical University Hospital: J. Matsubara; Kanazawa University Hospital: J. Koizumi; National Hospital Organization Kanazawa Medical Center: M. Endo, Y. Nakamura; National Hospital Organization Nanao National Hospital: H. Yokochi; Yamanaka-spa Medical Center; Doniwa Clinic: K. Doniwa; Iwaki Naika Clinic: N. Iwaki; Takeda Naika Clinic: Y. Takeda; Fukui General Hospital: Y. Kobayashi; University of Yamanashi Hospital; Kanemaru Internal Medicine Clinic: Y. Kanemaru; Shinshu University Hospital: H. Tsutsui; Oiwake Clinic: M. Takei; Nitta Naika Clinic: M. Nitta; Gifu University Hospital: K. Nishigaki, S. Yoshimura; Mori Naika Clinic: N. Mori; National Hospital Organization Shizuoka Medical Center: T. Umemoto, M. Shida; Nagoya University Hospital: M. Kuzuya; Nagoya University Graduate School of Medicine; Nagoya University Hospital: M. Kobayashi; Aichi Medical University Hospital: T. Ohta; National Hospital Organization Nagoya Medical Center: S. Okuda, M. Niinomi, T. Kitano, K. Yamaguchi; Kamiiida Daiichi Hospital: T. Ogawa; Chita Kosei Hospital: M. Nakatsuka; Toyohashi Heart Center; Japanese Red Cross Nagoya First Hospital: H. Kamiya; Nagoya Higashi Clinic: K. Miyatani; Inba Clinic: H. Miyai; Chukyo Clinical: A. Nakamura; Matsuyama Clinic: H. Matsuyama; Kinoshita Clinic: A. Kinoshita; Adachi Naika Junkankika Clinic: M. Adachi; Nitta Clinic: M. Nitta; National Hospital Organization National Mie Hospital: R. Araki; National Hospital Organization Mie Chuo Medical Center: U. Shintani; Nabari City Hospital: S. Okamoto; Iwasaki Hospital: M. Nakamura; Mie Heart Center: H. Nishikawa; Takanoo Clinic: Y. Higashi; Ono Junkankika Naika Clinic: N. Ono; Shiga University of Medical Science Hospital: A. Kashiwagi; Saiseikai Shiga Hospital: T. Nakamura; Yamada Naika: T. Yamada; Kawabata Clinic: T. Kawabata; University Hospital, Kyoto Prefectural University of Medicine; National Hospital Organization Utano National Hospital; National Hospital Organization Kyoto Medical Center: T. Tsukahara; National Hospital Organization Maizuru Medical Center: Y. Harada; Kyoto First Red Cross Hospital: M. Makino; Kyoto Second Red Cross Hospital: Y. Yamamoto; Daini-Okamoto General Hospital: Y. Kida; Oiwa Clinic: K. Oiwa; Kitamura Clinic: H. Kitamura; Hayashi Clinic: M. Hayashi; Katsume Clinic: H. Katsume; Tatsuoka Neurology Clinic: Y. Tatsuoka; Osaka Medical College Hospital: T. Hanafusa; Osaka University Graduate School of Medicine: H. Sato; Osaka University Hospital: K. Kitagawa, Y. Yamazaki; National Hospital Organization Osaka National Hospital: Y. Koretsune; National Hospital Organization Osaka National Center: R. Todo; National Hospital Organization Toneyama National Hospital: H. Fujimura; National Hospital Organization Osaka-minami Medical Center; Osaka Koseinenkin Hospital: H. Ueda, T. Watarai; Hoshigaoka Koseinenkin Hospital: R. Fukunaga; Nakamura Naika: M. Nakamura; Yokotani Clinic: T. Yokotani; Kobe University School of Medicine: T. 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References

[1] Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970–2002. JAMA 2005;294:1255–9.

[2] Japanese Statistics and Information Department. Abridged life tables for Japan; 2005. accessed on Feb 26, 2007.

[3] Yamazaki T, Goto S, Shigematsu H, Shimada K, Uchiyama S, Nagai R, et al. Prevalence, awareness, and treatment of cardiovascular risk factors in patients at high risk of atherothrombosis in Japan. Results from domestic baseline data of the REduction of Atherothrombosis for Continued Health (REACH) registry. Circ J 2007;71:995–1003.

[4] Ohman EM, Bhatt DL, Steg PG, Goto S, Hirsch AT, Liau CS, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events—study design. Am Heart J 2006;151:786.

[5] Chang IM, Gelman R, Pagano M. Corrected group prognostic curves and summary statistics. J Chronic Dis 1982;35:669–74.

[6] Steg PG, Bhatt DL, Wilson PW, D'Agostino RS, Ohman EM, Röther J, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 2007;297:1197–206.

[7] Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180–9.

[8] Goto S, Bhatt DL, Rother J, Alberts M, Hill MD, Ikeda Y, et al. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. Am Heart J 2008;156:855–63.

[9] Liu L, Ikeda K, Yamori Y. Changes in stroke mortality rates for 1950 to 1997: a great slowdown of decline trend in Japan. Stroke 2001;32:1745–9.

[10] Kobayashi S. Stroke Databank. Tokyo: Nakayama Shoten K.K; 2005.

[11] CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329–39.

[12] Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. Stroke 2000;31:2080–6.

[13] Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. Stroke 2000;31:817–21.

[14] Diener HC, Bogousslavsky J, Brass LM, Cimminiello CsibaL, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attach in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:331–7.

[15] Toyoda K, Yasaka M, Iwade K, Nagata K, Koretsune Y, Sakamoto T, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective multicenter observational study. Stroke 2008;39:1740–5.

[16] Fukuuchi Y, Tohgi H, Okudera T, Ikeda Y, Miyanaga Y, Uchiyama S, et al. A randomized, double-blind study comparing the safety and efficacy of clopidogrel versus ticlopidine in Japanese patients with noncardioembolic cerebral infarction. Cerebrovasc Dis 2008;25:40–9.

[17] Liao JK. Secondary prevention of stroke and transient ischemic attack: is more platelet inhibition the answer? Circulation 2007;115:1615–21.

[18] Plosker GL, Lyseng-Williamson KA. Clopidogrel: a review of its use in the prevention of thrombosis. Drugs 2007;67:613–46.

[19] Bhatt DL, Kapadia SR, Yadav JS, Topol EJ. Update on clinical trials of antiplatelet therapy for cerebrovascular diseases. Cerebrovasc Dis 2000;10(Suppl 5):34–40.

[20] Missault L, Krygier C, Lukito G, Mary-Rabine L. Occurrence of peripheral arterial disease in a Belgian cohort of patients with cardiovascular history of atherothrombosis. Acta Chir Belg 2007;107:508–14.

[21] Cheng SW, Wu LL, lau H, Ting AC, Wong J. Prevalence of significant carotid stenosis in Chinese patients with peripheral and coronary artery disease. Aust N Z Surg 1999;69:44–7.

[22] Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ 1996;313:1440–4.

[23] Hiatt WR. Preventing atherothrombotic events in peripheral arterial disease: the use of antiplatelet therapy. J Intern Med 2002;251:193–206.

[24] Ferrières J, Cambou JP, Gayet JL, Herrmann MA, Leizorovicz A. Prognosis of patients with atherothrombotic disease: a prospective survey in a non-hospital setting. Int J Cardiol 2006;112:302–7.

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ORIGINAL COMMUNICATION

The safety and efficacy of clopidogrel versus ticlopidine in Japanese stroke patients: combined results of two Phase III, multicenter, randomized clinical trials

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Abstract Two Phase III studies comparing the safety and efficacy of clopidogrel with ticlopidine as antiplatelet agents for the secondary prevention of vascular events in patients with prior stroke were performed in Japan. Both studies were randomized, double-blind, double-dummy comparative trials with the primary objective of comparing the clinical safety of treatment with either clopidogrel or ticlopidine for up to 12 months. The secondary objective was to assess the incidence of a combined efficacy endpoint of cerebral infarction, myocardial infarction, and vascular death. Patients with prior stroke were recruited during July 1996–February 1998 and September 2001–November 2003 at centers across Japan. The results of the two studies were combined in this analysis. There were 1,869 patients in the safety population (clopidogrel, 941; ticlopidine, 928). Significantly, fewer patients experienced a safety event in the clopidogrel group than in the ticlopidine group ($p < 0.001$; hazard ratio, 0.610; 95% confidence interval 0.529, 0.703). Almost twice as many patients in the ticlopidine group (25.6%) experienced hepatic dysfunction than in the clopidogrel group (13.4%). There were 1,862 patients evaluable for efficacy (clopidogrel, 939; ticlopidine, 923). There was no significant difference in the incidence of the combined efficacy endpoint between clopidogrel (2.6% of patients) and ticlopidine (2.5%). Clopidogrel was better tolerated than ticlopidine. There was no difference in the efficacy of the two agents with regard to the secondary prevention of vascular events in patients with prior stroke. This was the first combined analysis of direct comparison of clopidogrel with ticlopidine in the clinical setting.

Keywords Antiplatelet agents · Clopidogrel · Ticlopidine · Cerebrovascular accident · Cardiovascular event

Introduction

Stroke is a leading cause of death and disability worldwide. In Japan, 234,000 patients are newly diagnosed with stroke every year and 1,370,000 individuals have a history of previous stroke [1]. Hemorrhagic and ischemic cerebrovascular diseases (CVD) together make up the third most common cause of death in Japan [2] with 129,055 deaths due to CVD recorded in 2005 [1].

The high prevalence of stroke in Japan emphasizes the need for effective prevention strategies. Patients who have had a previous stroke are at risk of recurrent events [3]. Currently, the use of antiplatelet agents is recommended for the prevention of recurrent noncardioembolic stroke [4, 5]. Before 2006, the antiplatelet agents approved in Japan were aspirin, ticlopidine (an adenosine diphosphate antagonist; grade A recommendation), and cilostazol (a phosphodiesterase inhibitor; grade B recommendation) [5]. Use of antiplatelet agents is relatively infrequent in patients with atherothrombotic conditions or risk factors in Japan (21.3%) compared with the rest of the world (53.9%) [6].

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The most common antiplatelet agent prescribed in Japan is aspirin [6]. However, ticlopidine has been shown to be more effective than aspirin for the secondary prevention of stroke, with a risk reduction relative to aspirin of 21% [7]. The drawback of ticlopidine therapy is that it is significantly less well tolerated than aspirin [7]. In addition to the adverse events of diarrhea, rash, and severe neutropenia, there is a high risk of hepatic dysfunction with ticlopidine treatment, particularly in Japanese patients [7, 8]. Frequent blood tests when starting ticlopidine treatment and then periodic blood tests while continuing treatment are recommended to minimize the risk of serious liver damage [8].

Clopidogrel is another antiplatelet agent that has been shown to be more effective than aspirin in the secondary prevention of atherothrombotic events [9]. The safety profile of clopidogrel is similar to that of aspirin [10]; therefore, the use of clopidogrel in place of ticlopidine for the secondary prevention of noncardioembolic stroke could be advantageous given the high risk of liver damage with ticlopidine.

Two Phase III studies, (one Phase IIIa and one Phase IIIb) have compared the safety of clopidogrel against that of ticlopidine in Japanese patients. The main results of the Phase IIIb study have been reported in a previous publication [11]. This manuscript focuses on the combined safety data from the two randomized trials.

Patients and methods

Study population

Two randomized, double-blind, double-dummy, comparative Phase III studies were conducted in Japan from July 1996 to February 1998 (Phase IIIa, 177 centers across Japan) and from September 2001 to November 2003 (Phase IIIb, 129 centers across Japan). The study protocols were approved by the local ethics committees at all the participating centers and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

The inclusion criteria were similar in the two studies; those for the Phase IIIb study have been described previously [11]. The main inclusion and exclusion criteria are shown in Table 1. The most recent stroke must have occurred >8 days before inclusion in the study, with a

Table 1 Study design

	Phase IIIa	Phase IIIb
Study period	July 1996–February 1998	September 2001–November 2003
Number of patients	749	1,172
Treatment duration	26 weeks	52 weeks
Patient inclusion criteria	20–80 years old	
	History of cerebral infarctions (excluding cardiogenic cerebral embolism)	
	Written informed consent	
	Most recent stroke >8 days before inclusion	
	Computed tomography or magnetic resonance imaging to document brain infarct	
Patient exclusion criteria	TIA since the most recent stroke	TIA since the most recent stroke
	Serious impairment that would hinder detection of recurrent stroke	Serious impairment that would hinder detection of recurrent stroke
	Bleeding disorders, risk of bleeding, or history of intracranial hemorrhage	Bleeding disorders, risk of bleeding, or history of intracranial hemorrhage
	Severe renal, or heart disease, or uncontrolled hypertension, or hepatic dysfunction	Severe renal, or heart disease, or uncontrolled hypertension, or hepatic dysfunction
	Laboratory values within the previous year that were below defined limits for WBC or platelets	Laboratory values within the previous year that were below defined limits for WBC or platelets
		Diabetic retinopathy
		History of elevated serum levels of AST, ALT, γ-GTP, AL-P, LDH, or total bilirubin
Randomization	Clopidogrel (75 mg) or ticlopidine (200 mg) once daily after a meal	
	Double blind	

AL-P alkaline phosphatase, *ALT* serum alanine aminotransferase, *AST* aspartate aminotransferase, *γ-GTP* γ-glutamyl transpeptidase, *LDH* lactate dehydrogenase, *TIA* transient ischemic attack, *WBC* white blood cells

well-documented clinical course up to inclusion. There was no limit on the maximum time since the most recent stroke. Brain infarcts were documented by computed tomography (CT) or magnetic resonance imaging (MRI)—in the case of the Phase IIIa study within 1 month of the start of treatment and in the case of the Phase IIIb study at initial screening. Imaging was also used to exclude patients with intracranial hemorrhage.

Study design

Patients were randomly assigned to either clopidogrel 75 mg or ticlopidine 200 mg once daily after a meal (preferably breakfast) for 26 weeks (Phase IIIa) or 52 weeks (Phase IIIb). Patients were given both the active drug and an indistinguishable placebo.

In the Phase IIIb study, hematologic and biochemical tests were scheduled every 2 weeks for the first 8 weeks of treatment and subsequently every 12 weeks from week 12. Follow-up examinations were performed after 2, 4, 6, and 8 weeks of treatment, and subsequently every 4 weeks. Patients were followed up by telephone if they did not attend clinic visits. In the Phase IIIa study, hematologic and liver function tests were performed at screening and at weeks 2, 4, 8, 12, and 26. Other biochemical tests were performed at screening and weeks 12 and 26. Cerebral CT imaging was performed at screening to exclude hemorrhage and then again at 52 weeks in the Phase IIIb trial.

The primary objective in the Phase IIIa study was to compare the clinical safety of clopidogrel and ticlopidine among patients with cerebral infarction. The primary objective of the Phase IIIb study was to demonstrate the superiority of clopidogrel over ticlopidine in terms of safety. The secondary endpoint of both studies was to compare the clinical efficacy of clopidogrel with that of ticlopidine in the prevention of vascular events (cerebral infarction, myocardial infarction [MI], and vascular death).

The primary endpoint in this combined analysis of the two Phase III studies was to compare the safety of each medication during treatment for up to 52 weeks. In the Phase IIIa study, all adverse events that were judged by the investigator to be drug related were recorded. In the Phase IIIb study, adverse events from a predefined list of selected events were recorded regardless of relationship to the study drug. The predefined safety endpoints of particular interest were hematologic changes, hepatic dysfunction, and atraumatic serious hemorrhage (leading to or prolonging hospitalization [including all patients requiring surgery or blood transfusion] or resulting in death). Hematologic changes were defined by the investigators as leukopenia, neutropenia, and thrombocytopenia. Hepatic dysfunction was defined as increased laboratory values (above the normal range) of serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum bilirubin, γ-glutamyl transpeptidase (γ-GTP), alkaline phosphatase (AL-P), or lactate dehydrogenase (LDH), jaundice, hepatic dysfunction, or nonicteric hepatic dysfunction. Serious adverse drug reactions (ADRs) were events for which a causal relation with the investigational drug could not be ruled out by the investigator and that were life-threatening, led to or prolonged hospitalization, or resulted in irreversible impairment or death [11].

The major secondary endpoint in this combined analysis was the combined incidence of vascular events (cerebral infarction, MI, or vascular death) with up to 52 weeks' follow-up.

Rationale for combining the two studies

To determine whether it was appropriate to combine the data from the two studies, we confirmed that there was no heterogeneity between Phase IIIa and Phase IIIb on the hazard ratio of vascular events ($p = 0.767$). We have also shown that the hazard ratio between the ticlopidine and clopidogrel groups was similar despite the differences in the lengths of the follow-up periods. The methods and standards used for collecting and recording adverse events were slightly different between the two studies; however, this was based on recommendations and approval from the Pharmaceutical and Medical Devices Agency (PMDA), following the results of the Phase IIIa study.

Analyses

Safety variables

The primary safety analysis was on the combined endpoint of accessory symptoms (symptoms reported by the patient and considered by the investigator to be related to the study drug) and abnormal laboratory changes. The observation period for ADRs was from inclusion to the end of week 26 (Phase IIIa) or 52 (Phase IIIb). ADRs were categorized as (a) accessory symptoms or (b) abnormal laboratory hematologic or hepatic changes.

Efficacy variable

The primary efficacy variable was the observation of a vascular event within the 52-week maximum period of follow-up. Events were categorized as cerebral infarction, MI, vascular death, transient ischemic attack (TIA), amaurosis fugax, angina pectoris, peripheral artery occlusion, retinal artery occlusion, or other vascular event. The combined efficacy endpoint was limited to vascular events that could be definitively diagnosed (cerebral infarction, MI, and vascular death).