Stroke

Lead Article

Expert Answers to Three Key Questions

Fascinoma Cardiologica

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Primary and secondary prevention of stroke

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Stroke is the third leading cause of morbidity and mortality worldwide and a major cause of physical and intellectual disability, hence the need for clinically implementable strategies that lower stroke incidence and recurrence effectively and safely. Several studies have shown that stroke recurrence is closely and directly related to raised and even high-normal blood pressure, suggesting that blood pressure–lowering agents could exert a protective effect. This paper focuses on primary stroke prevention by examining the causes, risk factors, and current therapeutic approaches. It also reviews knowledge on secondary prevention and examines the potential of blood pressure–lowering drugs in this regard, with particular respect to a major recent intervention trial—Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS)—whose results demonstrate for the first time that angiotensin-converting enzyme inhibitor treatment markedly reduces stroke recurrence and prevents subsequent cognitive deterioration.

Keywords: cerebrovascular disease; stroke; blood pressure; primary prevention of stroke; secondary prevention of stroke; antihypertensive treatment; ACE inhibitor; PROGRESS
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Dialogues Cardiovasc Med. 2003;8:3-11

Stroke is a major public health concern for several reasons: (i) its prevalence has made it the third leading cause of death worldwide[1]; (ii) high mortality is compounded by the high rate of physical and intellectual disability in survivors[2-4]; (iii) these features make stroke a major economic burden, both socioeconomically and personally, in terms of loss of income, prolonged multiple drug therapy, and rehabilitation, in addition to impaired quality of life[4]; and (iv) population aging means that all the above will increase steadily over the next decades and absorb a substantial fraction of public health resources. This is already happening in Asian countries where stroke is much more frequent than coronary heart disease and by far the major cause of cardiovascular morbidity and mortality.[2,3] It is also happening in Western communities, where stroke has been the most common cardiovascular event in the hypertensive populations of several recent trials *(Table I).*[5]

This paper addresses three issues: (i) the causes of stroke and risk factors; (ii) primary prevention interventions; and (iii) advances in the understanding and practice of secondary prevention, aimed at reducing not only the current 20% 5-year risk of recurrence,[6,7] but also the attendant physical disability and cognitive decline.[8]

CAUSES OF STROKE

Stroke is caused by cerebral hemorrhage, but above all—in 80% to 85% of cases[2,3]—by ischemia. There are two main mechanisms of ischemic stroke: (i) formation of a thrombus in a relatively large proximal artery due either to an atherosclerotic plaque that critically reduces the arterial lumen or to plaque ulceration that triggers platelet aggregation and blood coagulation at its surface; or (ii) emboli detaching from friable plaques or from thrombi formed in the left ventricle or atrium. Several risk factors have been identified over the years *(Table II).*[9] Both in white and Asian populations, in addition to age, the incidence of stroke, whether hem-

Trial	Average age (years)	Patients randomized (n)	Strokes (n)	MI (n)
STOP-1	76	1627	82	53
SHEP	72	4736	269	165
STONE	67	1632	52	4
Syst-Eur	70	4695	124	78
Syst-China	67	2394	104	16
HOT	61	18790	294	209
CAPPP	53	10985	340	327
STOP-2	76	6614	452	293
NICS	70	414	20	4
NORDIL	60	1088	355	340
INSIGHT	67	6575	141	138

Table I. *Number of events, fatal, and nonfatal strokes, and fatal and nonfatal myocardial infarctions (MI) reported in recent prospective hypertension trials.*

Key to trial acronyms: *CAPPP: CAPtopril Prevention Project; HOT: Hypertension Optimal Treatment; INSIGHT: International Nifedipine-GITS Study: Intervention as a Goal in Hypertension Treatment; NICS: National Intervention Cooperative Study; NORDIL: NORdic DILtiazem study; SHEP: Systolic Hypertension in the Elderly Program; STOP-1 & -2: Swedish Trial in Old Patients with hypertension–1 & -2; STONE: Shanghai Trial Of Nifedipine in the Elderly; Syst-China: SYSTolic hypertension in elderly Chinese trial; Syst-Eur: Systolic hypertension in elderly in Europe trial.*

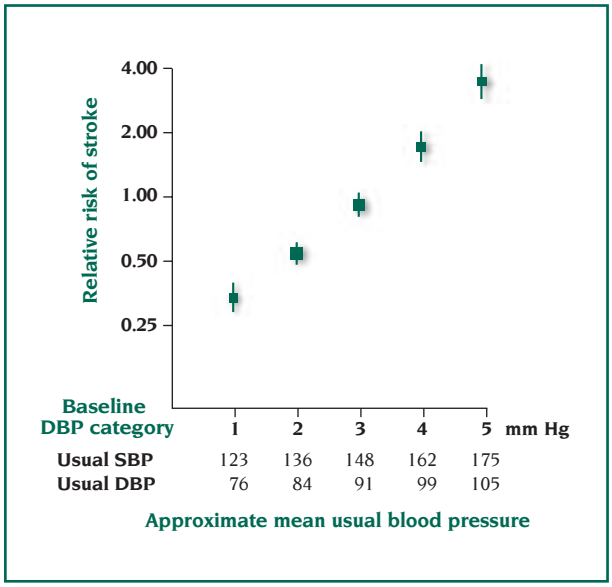

Figure 1. *Relationship between risk of stroke and systolic (SBP) and diastolic (DBP) blood pressure in 7 prospective observational studies. Solid squares: disease risk per category (square size is proportional to the number of events per blood pressure category). Vertical lines: 95% confidence intervals of relative risk estimates.*

Modified from reference 10: *MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke and coronary heart disease. Part I. Prolonged differences in blood pressure: prospective observational studies corrected for regression dilution bias.* Lancet. *1990;335:765-774. Copyright © 1990, Elsevier.*

MODIFIABLE RISK FACTORS

Well-documented risk factors

- Hypertension
- Cardiac disease
  - Atrial fibrillation
  - Infective endocarditis
  - Mitral stenosis
  - Recent extensive myocardial infarction
- Cigarette smoking
- Transient ischemic attack
- Asymptomatic carotid stenosis
- Diabetes mellitus
- Hyperhomocystinemia
- Left ventricular hypertrophy

Less well-documented risk factors

- Elevated blood cholesterol and lipids
- Cardiac disease
  - Cardiomyopathy
  - Bacterial endocarditis
  - Mitral annular calcification
  - Mitral valve prolapse
  - Valve strands
  - Spontaneous echocardiographic contrast
  - Segmental wall-motion abnormalities
  - Aortic stenosis
  - Patent foramen ovale
  - Atrial septum aneurysm
- Use of oral contraceptives
- Consumption of alcohol
- Use of illicit drugs
- Physical inactivity
- Obesity
- Migraine
- Elevated hematocrit
- Dietary factors
- Hyperinsulinemia and insulin resistance
- Acute triggers (stress)
- Hypercoagulability and inflammation
  - Fibrin formation and fibrinolysis
  - Fibrinogen
  - Anticardiolipin antibodies
  - Genetic and acquired causes
- Subclinical diseases
  - Carotid intima-media thickness
  - Aortic atheroma
  - MRI evidence of infarct-like lesions
- Socioeconomic features

NONMODIFIABLE RISK FACTORS

- Age
- Gender
- Hereditary/familial factors
- Race/ethnicity
- Geographic location

Table II. *Risk factors for ischemic stroke. MRI, magnetic resonance imaging.*

orrhagic or ischemic, is proportional to systolic and diastolic blood pressure *(Figure 1).*[10] Stroke is also more frequent in diabetes mellitus, congestive heart failure, chronic atrial fibrillation, and patients with a history of stroke or transient ischemic attack. This has clear pathophysiologic implications because: (i) high blood pressure favors arterial rupture and atherosclerotic plaque formation, also a prominent feature in diabetes; (ii) heart failure and atrial fibrillation frequently comprise thrombus formation in the left ventricle and atria; and (iii) any/all of the above are more likely to be present in patients with a cardiovascular history, thereby further increasing the risk of recurrence.

Other risk factors for stroke should also be taken into account: (i) dyslipidemia, now known to affect stroke incidence, after trials on the effects of lipid-lowering treatments contradicted the earlier negative epidemiologic data[11]; (ii) smoking, which substantially increases the risk of stroke, via the atherogenicity of tobacco and other nicotine combustion products, even when cholesterol levels are low and the lipid profile favorable, as in Asian populations[12]; and (iii) hypercoagulability states, as in heart failure, raised hematocrit, estrogen therapy, and imbalance between the factors responsible for clot formation and dissolution. Hypercoagulability may have a genetic basis. Indeed, a genetic contribution to stroke is evident from the risk factors themselves (hypertension, dyslipidemia, diabetes, etc), and the identification of stroke-prone animal strains.[13] In man, genetic factors also operate by producing structural abnormalities that weaken the resistance of cerebral vessels to pressure and precipitate hemorrhage.

PRIMARY STROKE PREVENTION

Several studies have shown that antihypertensive treatment markedly reduces the risk of stroke, thus constituting effective primary prevention.[14,15] The evidence can be summarized as follows: (i) antihypertensive treatment lowers stroke incidence in young and elderly men and women, irrespective of whether the baseline hypertension is mild or severe; (ii) benefit is marked (a 40% decrease in stroke incidence) when blood pressure is reduced by 5 to 6 mm Hg diastolic and 10 to 12 mm Hg systolic; it is also marked when treatment aims primarily at systolic blood pressure control, in patients with isolated systolic hypertension; (iii) even hypertensives with diabetes or a high cardiovascular risk profile due to previous cardiovascular disease, organ damage, or multiple additional cardiovascular risk factors[16] respond to antihypertensive treatment with a substantial reduction in stroke incidence; and (iv) benefit is unrelated to drug class: *Table III* shows both the marked decreases in stroke incidence versus placebo on conventional drugs (diuretics or β-blockers), angiotensin-converting enzyme (ACE) inhibitors, and calcium antagonists, as well as the absence of significant difference in stroke rates between the different drugs themselves.[17,18] This forces the conclusion that stroke prevention is largely due to the blood-pressure lowering per se, ie, all effective and well-tolerated antihypertensive agents are suitable for this purpose. The 1999 World Health Organization/International Society of Hypertension Guidelines[15] list six classes of antihypertensive drugs (diuretics, β-blockers, calcium antagonists, ACE inhibitors, angiotensin II–receptor antagonists, and α_1-blockers), and also recommend (again because of the belief that benefit originates from nonspecific blood pressure reduction) the combination of two or more drugs or addition to central antihypertensive agents.

Drug treatment	Relative risk (95% CI)	*P*
β-Blockers and/or diuretics vs placebo	0.64 (0.41-0.90)	<0.01
ACEIs vs placebo	0.70 (0.57-0.85)	<0.01
Calcium antagonists vs placebo	0.61 (0.44-0.85)	<0.01
ACEIs vs β-blockers and/or diuretics	1.05 (0.92-1.19)	NS
Calcium antagonists vs β-blockers and/or diuretics	0.86 (0.76-0.98)	NS
ACEIs vs calcium antagonists	1.02 (0.85-1.21)	NS

***Table III.** Stroke incidence compared between antihypertensive drug trials.*
***Abbreviations:** ACEIs, angiotensin-converting enzyme inhibitors; NS, not significant.*

Other primary prevention measures are also effective. Stroke incidence can be reduced by: (i) antidiabetic treatment in type 2 diabetes mellitus[19,20]; (ii) lipid-lowering treatment, in particular with statins, in patients not only with elevated, but also normal serum cholesterol levels[11]; and (iii) anticoagulant treatment in atrial fibrillation[21]; antiplatelet drugs[22] can also be beneficial, although much less so than anticoagulants (40% versus 70%). Use of acetylsalicylic acid at low antiplatelet doses (eg, 100 mg daily) for primary stroke prevention in the more general (and more low-risk) population is still debated.[22-24] It appears to have greater advantages in coronary prevention. In the hypertensive patients of the Hypertension Optimal Treatment (HOT)

CONTROL OF RISK FACTORS
• Smoking cessation
• Reduction of alcohol consumption
• Physical exercise
• Dietary control
MEDICAL INTERVENTIONS
• Antihypertensive drug treatment
• Antithrombotic therapy
• Hypocholesterolemic drug treatment
• Antidiabetic and lipid-lowering treatment

Table IV. *Measures for primary stroke prevention.*

study, low-dose aspirin in a setting of satisfactory blood pressure control (140/83 mm Hg) was associated with a clear-cut reduction in the incidence of myocardial infarction (-35%) with no change in that of stroke.[25] *Table IV* lists the primary stroke prevention measures. They include smoking cessation, for which evidence of benefit does not originate from controlled trials, but is nevertheless compelling because of strong observational data and a convincing pathophysiologic rationale. The specific protective properties of some drugs may also be effective in primary prevention. This could explain the greater reduction of stroke incidence observed in hypertensive patients with left ventricular hypertrophy treated with an angiotensin II antagonist versus a β-blocker, shown in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study.[26]

PRIMARY STROKE PREVENTION AND INTENSIVE ANTIHYPERTENSIVE, ANTIDIABETIC, AND LIPID-LOWERING TREATMENTS

In treated hypertensive patients in whom blood pressure is reduced to, or just above, 140/90 mm Hg, the incidence of stroke (and other cardiovascular disease) remains substantially higher than in the general population.[27] The reason may be that blood pressure in the general population is mostly well below 140/90 mm Hg, and that the relationship between blood pressure and incidence of stroke (and coronary heart disease) continues below these cutoff values *(Figure 1),* with a substantially higher risk in patients with a so-called "high-normal" blood pressure versus those with normal or optimal blood pressure (130-139/85-89 mm Hg versus 120-129/80-84 mm Hg or <120/80 mm Hg) *(Figure 2).*[28] It is thus not surprising that stroke incidence should be lower in patients undergoing more versus less intensive diastolic blood pressure reduction *(Figure 3),*[25,29,30] and further reduction of blood pressure values already below 140/90 mm Hg.[16] The evidence was collected in individuals with diabetes mellitus or a high cardiovascular risk profile, ie, in conditions in which many morbid or fa-

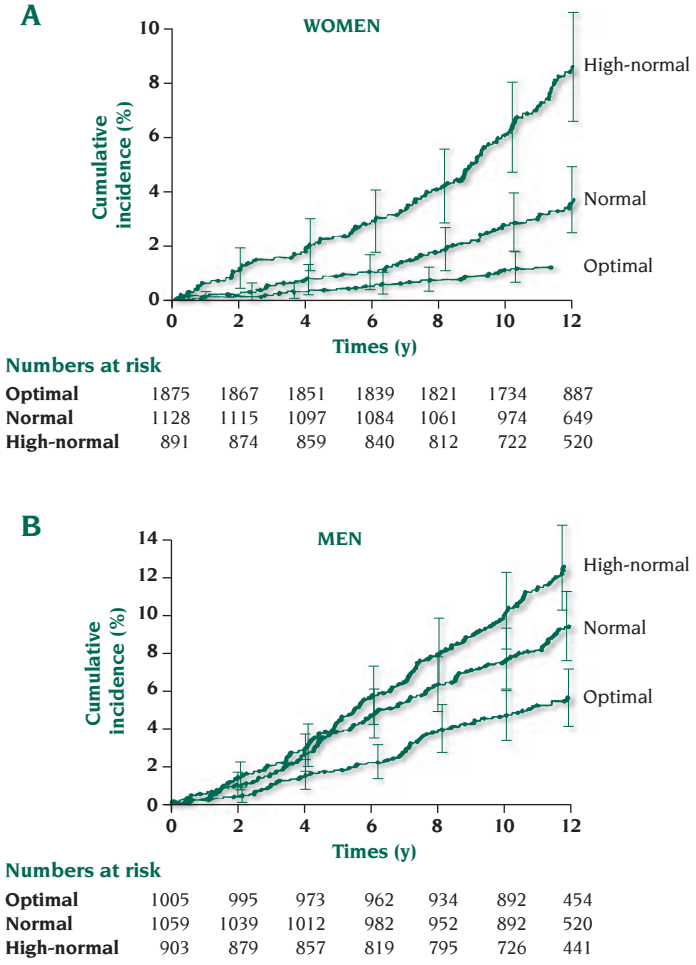

Figure 2. *Incidence of combined cerebrovascular and coronary events in women (**upper panel, A**) and men (**lower panel, B**) classified into three blood pressure groups: optimal (<120/80 mm Hg), normal (120-129/80-84 mm Hg), and high-normal (130-139/85-89 mm Hg).*

Modified from reference 28: *Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease.* N Engl J Med. *2001;345:1291-1297. Copyright © 2001, Massachusetts Medical Society.*

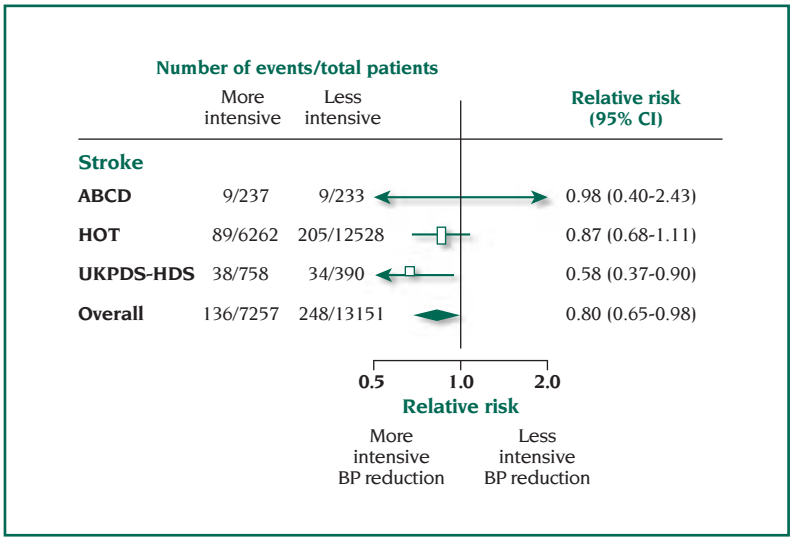

***Figure 3.** Effect of more vs less intensive blood pressure (BP) reduction in three antihypertensive drug trials.*

***Key to trial acronyms:** ABCD, Appropriate Blood pressure Control in Diabetes; HOT, Hypertension Optimal Treatment; UKPDS-HDS, United Kingdom Prospective Diabetes Study–Hypertension in Diabetes Study.*

tal cardiovascular events occur over a few years, thus giving the study sufficient statistical power. However, stroke incidence was found to be similar in the HOT study,[25] where diastolic blood pressure was reduced on average to 83 mm Hg, and in other antihypertensive treatment studies (31% vs 34%),[17] where blood pressure control was much less effective, despite an age imbalance (61 versus 53 years) that put the HOT patients at considerably greater risk. The evidence thus favors intensifying the primary prevention of cerebrovascular disease by more aggressive blood pressure–lowering treatments in diabetics, patients at high cardiovascular risk, and possibly also the hypertensive population as a whole. In the former two situations, blood pressure values regarded as abnormal and requiring treatment should no longer be ≥140/90 mm Hg, but ≥130/85 mm Hg or less.

Evidence is also growing on the benefits of intensified antidiabetic and lipid–lowering treatment in cerebrovascular prevention,[29-31] including multifactorial interventions that aim at the concomitant reduction of multiple cardiovascular risk factors. The results of concomitant correction of blood pressure elevation and dyslipidemia using antihypertensive drugs and statins will be available shortly.[32,33]

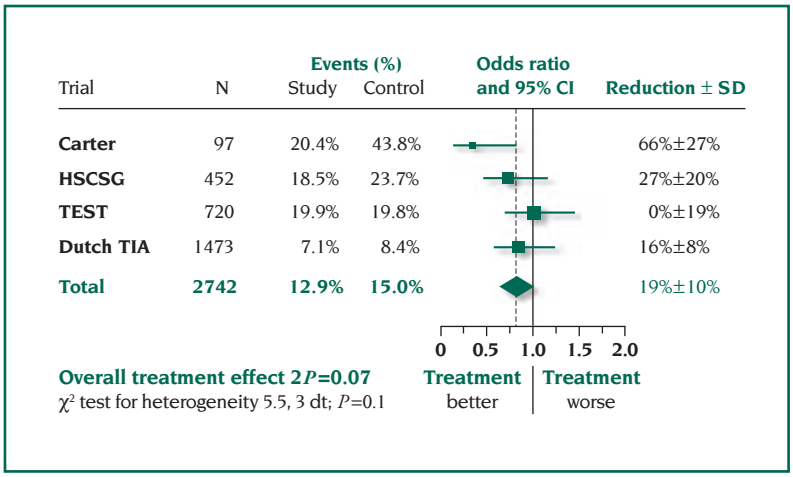

***Figure 4.** Effects of antihypertensive therapy on stroke recurrence (secondary prevention) in four randomized trials.*

***Key to trial acronyms:** Dutch TIA: Dutch Transient Ischemic Attack trial; HSCSG: Hypertension–Stroke Cooperative Study Group; TEST: Timolol, Encainide, Sotalol Trial.*

***Modified from reference 37:** MacMahon S. Blood pressure and prevention of stroke. J Hypertens. 1996;14(suppl 6):S39-S46. Copyright © 1996, Lippincott Williams & Wilkins.*

SECONDARY STROKE PREVENTION

Antiplatelet treatment lowers stroke recurrence by 30%.[34] Anticoagulant therapy is similarly or even more effective in atrial fibrillation, as is endarterectomy in tight carotid stenosis.[35,36] The benefit of blood pressure–lowering strategies, on the other hand, remained uncertain until recently because of the inconclusive data provided by the limited number of relatively small specific studies *(Figure 4)*.[37] Two studies have now shown that blood pressure reduction (using diuretics and ACE inhibitors) is also effective in secondary stroke prevention[38,39] irrespective of gender, age (≥ or <65 years), ethnicity (Asian or white), presence/absence of diabetes mellitus, and other clinical or demographic characteristics.[39]

It is worthy of special emphasis that in one of these studies, the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS),[39] the reduced risk of stroke recurrence (on average -28%, *Figure 5, page 8*) was: (i) extremely marked (-50%) in patients with a history of hemorrhagic stroke, or for hemorrhagic stroke during the treatment period; (ii) also observed in patients already under antiplatelet and antihypertensive treatment; (iii) accompanied by a reduced risk of nonfatal

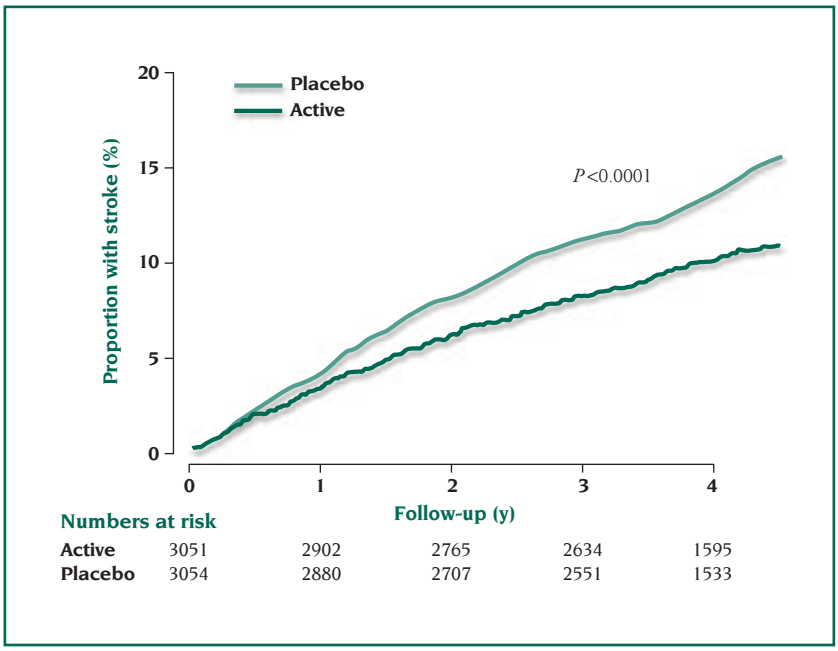

Figure 5. *PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study): incidence of stroke on perindopril (active) vs placebo.*

Modified from reference 39: *PROGRESS Collaborative Group. Randomized trial of a perindopril-based blood pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack.* Lancet. *2001;358: 1033-1041. Copyright © 2001, Elsevier.*

myocardial infarction by 38%; and (iv) not limited to hypertensive patients, but also observed in patients with no history of hypertension, and no initial blood pressure elevation, either because they were already using antihypertensive drugs or because they were normotensive. Indeed, a clear reduction in stroke was observed in patients with initial blood pressure <140/85 mm Hg in whom on-treatment values were lowered well below 130/80 mm Hg. Two major advances in the study were the demonstration of marked protection against the recurrence of hemorrhagic stroke (all previous interventions in this regard having proved unsuccessful), and the substantial risk reduction in virtually all subgroups, presumably in addition to the benefit already provided by standard interventions such as antiplatelet therapy. These findings suggest that blood pressure reduction should be pursued in the great majority of individuals with cerebrovascular disease without fear of inducing cerebral underperfusion, even if the initial blood pressure is normal and on-treatment values are relatively low. The proportion of PROGRESS patients who discontinued treatment due to symptomatic hypotension was only 1% greater than on placebo in both normotensive and hypertensive subjects, and was no more than 2% in those aged 70 or more.[39]

BLOOD PRESSURE, COGNITIVE DYSFUNCTION, AND DEMENTIA

Observational data show an association between blood pressure and cognitive dysfunction[40,41] and a higher frequency of dementia in hypertensive versus normotensive individuals.[42] The two studies investigating the benefits of antihypertensive treatment in this regard were inconclusive: one showed a clear reduction in dementia,[43] the other found no significant effect *(Table V).*[44] However, PROGRESS has shifted the balance clearly towards a favorable effect by avoiding the major limitation of the two previous studies, ie, the limited number of dementia cases. Over 400 of the PROGRESS patients with cerebrovascular disease developed dementia.[39] Although this incidence was similar in the placebo and treated groups, the subsequent incidence of dementia in patients with recurrent stroke was reduced by over 30%. Thus, blood pressure reduction remains vasculoprotective even if it fails to prevent stroke and it effectively prevents the cognitive deterioration that so often follows repeated vascular trauma to the gray and white matter.

Study	Placebo	Patients randomized (n)	*P*
SHEP	44 (1.9%)	37 (1.6%)	NS
Syst-Eur	21 (1.7%)	11 (0.9%)	<0.05

Table V. *Dementia rates [n (%)] on antihypertensive therapy vs placebo in the SHEP (Systolic Hypertension in the Elderly Program) and Syst-Eur (Systolic Hypertension in elderly in Europe) trials; NS, not significant.*

THREE KEY QUESTIONS

Although recent studies (most noteworthy among which is PROGRESS [Perindopril pROtection aGainst REcurrent Stroke Study]) have shed light on the clinical relevance of various therapeutic approaches to the management of stroke and the prevention of its recurrence, several questions remain open. These include key issues in secondary prevention, such as patient selection and the time and type of intervention. Should secondary prevention be based on antiplatelet or anticoagulant therapy? Which should be the first-line antiplatelet agent? What are the current indications for anticoagulant therapy? Is treatment compliance a major problem? Before addressing specific aspects of stroke prevention, the following "Expert Answers" section of *Dialogues* starts off by setting the scene with Geoffrey A. Donnan's reply to the very fundamental question: **"What are the mechanisms of stroke?"** which stresses ischemia's overwhelming responsibility and describes in detail the subtypes of ischemic stroke. This paves the way for the contribution of Matthew R. Walters and John L. Reid, who tackle the question of thrombolysis following acute ischemic stroke in their paper: **"Should the stroke patient be reperfused, and if so, how?"** We know that recombinant tissue plasminogen activator can be effective if given to rigorously selected patients within hours of the acute event: this article weighs the benefit/risk ratio of the reperfusion approach. Lastly, in: **"Neuroprotection: what are its prospects in the stroke patient?"** Theodoros Karapanayiotides and Julien Bogousslavsky discuss the potential of a still debated therapeutic strategy: neuroprotective agents that directly prevent ischemic cell death in brain neurons, and their combination with reperfusion and nonpharmacologic interventions such as hypothermia.

REFERENCES

1. World Health Organization.
The World Health Report. 1999. Geneva, Switzerland: WHO;1999.

2. Bonita R.
Epidemiology of stroke.
Lancet. 1992;339:342-344.

3. Khaw KT.
Epidemiology of stroke.
J Neurol Neurosurg Psychiatry. 1996;61:333-338.

4. Hankey G, Warlow C.
Treatment and secondary prevention of stroke: evidence, costs and effects on individuals and populations.
Lancet. 1999;354:1457-1463.

5. Kieldsen SE, Julius S, Hedner T, Hansson L.
Stroke is more common than myocardial infarction in hypertension: analysis based on 11 major randomized intervention trials.
Blood Press. 2001;10:190-192.

6. Alter M, Sobal E, McCoy R, et al.
Stroke in the Lehigh Valley: risk factors for recurrent stroke.
Neurology. 1987;37:503-507.

7. Burn J, Tennis M, Banford J, Sandercock P, Wade D, Warlow C.
Long-term risk of recurrent stroke after a first-ever stroke: the Oxfordshire Community Stroke Project.
Stroke. 1994;25:1605-1610.

8. Tatemichi TK, Paik M, Bagiella E, et al.
Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study.
Neurology. 1999;44:1885-1891.

9. Sacco RL, Benjamin EJ, Broderick JP, et al.
American Heart Association Prevention Conference IV. Prevention and Rehabilitation of Stroke. Risk Factors.
Stroke. 1997;28:1507-1517.

10. MacMahon S, Peto R, Cutler J, et al.
Blood Pressure, stroke and coronary heart disease. Part I. Prolonged differences in blood pressure: prospective observational studies corrected for regression dilution bias.
Lancet. 1990;335:765-774.

11. Herbert PR, Graziano JH, Cham KS, Hennekens CH.
Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials.
JAMA. 1997;278:319-321.

12. Wilhelmsen L.
Epidemiology of smoking and intervention studies of smoking.
Am Heart J. 1988;115:242-249.

13. Okamoto K, Yamori Y, Nagaoka A.
Establishment of the stroke prone spontaneously hypertensive rat (SHR).
Circ Res. 1974;34:1143-1153.

14. Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.
The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI).
Arch Intern Med. 1997;157:2413-2466.

15. Guidelines Subcommittee 1999.
World Health Organization/International Society of Hypertension Guidelines for the Management of Hypertension.
J Hypertens. 1999;17:151-183.

16. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G
Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators.
N Engl J Med. 2000;342:145-153.

17. Collins R, MacMahon S.
Blood pressure, antihypertensive drug treatment and risk of stroke and of coronary heart disease.
Br Med Bull. 1994;50:272-298.

18. Blood Pressure Lowering Treatment Trialists' Collaboration.
Effects of ACE-inhibitors, calcium antagonists and other blood-pressure-lowering drugs: results of prospectively designed overview of randomized trials.
Lancet. 2000;356:1955-1964.

19. UKPDS Final Report.
34th Annual Meeting of the European Association for the Study of Diabetes. Barcelona, Spain, September 8-12, 1998.

20. UK Prospective Diabetes Study (UKPDS) Group.
Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).
Lancet. 1998;352:837-853.

21. Stroke Prevention in Atrial Fibrillation Investigators.
Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II study.
Lancet. 1994;343:687-691.

22. Thomson R, Parkin D, Eccles M, Sudlow M, Robinson A.
Decision analysis and guidelines for anticoagulation therapy to prevent stroke in patients with atrial fibrillation.
Lancet. 2000;355:956-962.

23. Hellemons BSP, Langenberg M, Lodder J, et al.
Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomized controlled trial comparing two intensities of coumarin with aspirin.
BMJ. 1999;319:958-964.

24. Lip GY.
Thromboprophylaxis for atrial fibrillation.
Lancet. 1999;354:4-6.

25. Hansson L, Zanchetti A, Carruthers SG, et al.
Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial.
Lancet. 1998;351:1755-1762.

26. Dahlof R, Devereux RB, Kieldsen S, et al.
Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint in hypertension study (LIFE): a randomized trial against atenolol.
Lancet. 2002;359:995-1003.

27. Isles CG, Walzer LM, Bewers GD, et al.
Mortality in patients of the Glasgow Blood Pressure Clinic.
J Hypertens. 1986;4:141-156.

28. Vasan RS, Larson MG, Leip EP, et al.
Impact of high-normal blood pressure on the risk of cardiovascular disease.
N Engl J Med. 2001;345:1291-1297.

29. UK Prospective Diabetes Study Group.
Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38.
BMJ. 1998;317:703-713.

30. Estacio RO, Jeffers BW, Hiatt WR, et al.
The effects of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non–insulin dependent diabetes and hypertension.
N Engl J Med. 1998;338:645-652.

31. The Diabetes Control and Complications Trial Research Group.
The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus.
N Engl J Med. 1993;329:977-986.

32. ALLHAT Collaborative Research Group.
Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT).
JAMA. 2000;283:1967-1975.

33. Sever PS, Dalhof B, Poulter NR, et al.
Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial.
J Hypertens. 2001;19:1139-1147.

34. Antiplatelet Trialists' Collaboration.
Secondary prevention of vascular disease by prolonged antiplatelet treatment.
BMJ. 1988;296:320-331.

35. Hirsh J, Fuster V.
Guide to anticoagulant therapy. Part 2: oral anticoagulants.
Circulation. 1994;89:1469-1480.

36. Barnett H, Taylor D, Eliasziw H, et al.
Benefit of carotid endoarterectomy in patients with symptomatic moderate or severe stenosis.
N Engl J Med. 1998;339:1415-1425.

37. MacMahon S.
Blood pressure and prevention of stroke.
J Hypertens. 1996;14(suppl 6):S39-S46.

38. 38. PATS Collaborating Group.
Post-stroke antihypertensive treatment: preliminary results.
Clin Med J. 1995;108:710-717.

39. PROGRESS Collaborative Group.
Randomized trial of a perindopril-based blood pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack.
Lancet. 2001;358:1033-1041.

40. Ott A, Breteler MMB, Van Harskamp F, Stijnen T, Hofman A.
Incidence and risk of dementia: the Rotterdam Study.
Am J Epidemiol. 1998;147:574-580.

41. Liao DP, Cooper L, Cai JW, et al.
Presence and severity of cerebral white matter lesions and hypertension, its treatment and its control: the ARIC Study.
Stroke. 1996;27:2262-2270.

42. Skoog I, Nilsson L, Palmertz B, Andreasson LA, Svanborg A.
A population-based study of dementia in 85-years old.
N Engl J Med. 1993;328: 153-158.

43. Forette F, Seux ML, Staessen JA, et al.
Prevention of dementia in randomized double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial.
Lancet. 1998;352:1347-1351.

44. SHEP Cooperative Research Group.
Prevention of stroke by antihypertensive drug treatment in older person with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP).
JAMA. 1991;265:3255-3264.

What are the mechanisms of stroke?

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In spite of the fact that stroke is a significant public health problem, it is still poorly recognized that it consists of a number of heterogeneous subtypes. The major subtypes are ischemic stroke (about 80%), intracerebral hemorrhage (about 10%), and subarachnoid hemorrhage (about 5%). All have different mechanisms and risk factor profiles. Ischemic stroke subtypes may be classified mechanistically, topographically, or clinically. Mechanistic subgroups include: artery-to-artery embolism, lacunar infarction, cardioembolic mechanisms, aortic arch atheroma, borderzone and hemodynamic mechanisms, and other, rarer, causes. While some commonality of risk factor and mechanistic profiles does exist between stroke subtypes, there are significant differences that have implications for stroke prevention and management.

Keywords: stroke mechanism; risk factor; ischemic stroke; intracerebral hemorrhage; subarachnoid hemorrhage

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Dialogues Cardiovasc Med. 2003;8:15-21

Stroke is a significant public health problem worldwide. It is the second most common cause of death and major cause of disability.[1] In Western societies, incidence is relatively stable, but mortality is falling—hence, overall prevalence is increasing, thus placing strain on health care resources. Further, the burden of disease will increase over the next 20 years due to an increasingly aged population and the Westernization of Asian dietary habits. To solve this problem we need to better understand the stroke process. Stroke is defined simply by the World Health Organization as a "focal (or global) disturbance of cerebral infarction lasting 24 hours or longer with no apparent cause other than vascular." However, it conceals a myriad of mechanistic subtypes, the most important of which will be discussed in this paper.[2]

The three broad subgroups include ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. By far the majority of strokes are ischemic, although there are regional differences, such as intracerebral hemorrhage, which is more common in Asian countries. A representative distribution of the incidence of the three subgroups is shown in *Figure 1 (page 16)* from the North-East MElbourne Stroke Incidence Study (NEMESIS). It can be seen that the influence of age approximately doubles the incidence each decade.[3] The overall stroke crude annual incidence rate was 206 per 100 000 population, 72.5% of which were ischemic strokes, 14.5% intracerebral hemorrhages, 4.3% subarachnoid hemorrhages, and 8.7% were of undetermined type. Each of these three broad stroke subtypes is mechanistically quite different. Ischemic stroke is gener-

SELECTED ABBREVIATIONS AND ACRONYMS

LACI	lacunar cerebral infarction
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NEMESIS	North East MElbourne Stroke Incidence Study
NVAF	nonvalvular atrial fibrillation
PACI	partial anterior cerebral infarction
POCI	posterior cerebral infarction
SPAF	Stroke Prevention in Atrial Fibrillation
TACI	total anterior cerebral infarction
TCD	transcranial Doppler
TOAST	Trial of Org 10172 in Acute Stroke Treatment

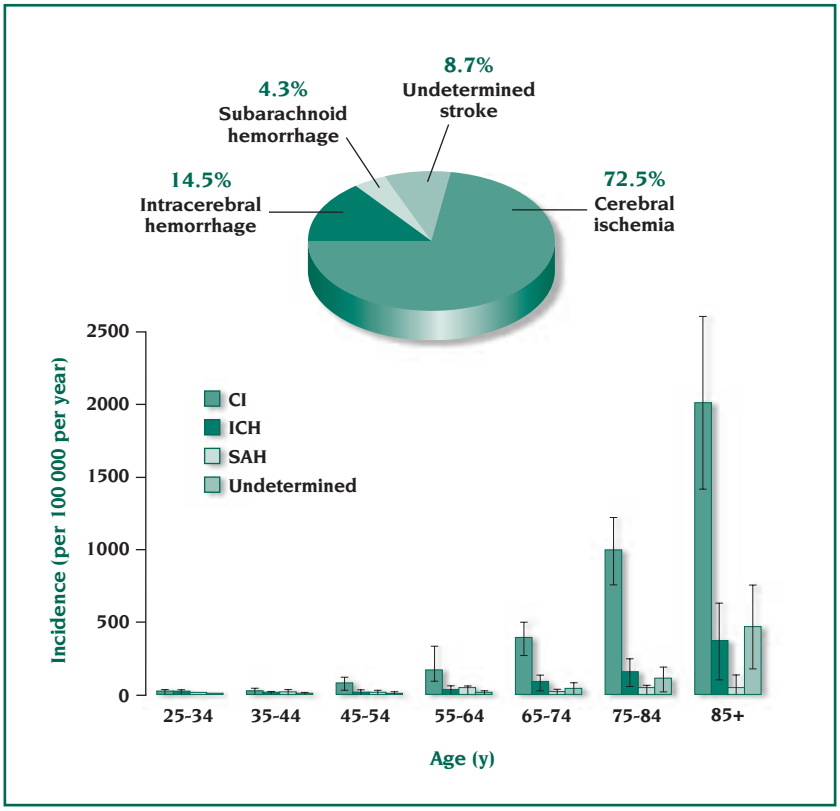

Figure 1. *The incidence of stroke and its major subtypes. From the North East MElbourne Stroke Incidence Study (NEMESIS).[3] The most common subtype is ischemic stroke (upper panel) and the incidence of stroke approximately doubles for each decade of life (lower panel).*

Abbreviations: *CI, cerebral ischemia; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.*

	Risk factor					
Stroke subtypes	**Age**	**HT**	**Smoking**	**Diabetes**	**AF**	**CHOL**
Ischemic	+++	++	++	++	++	+
Intracerebral hemorrhage	+++	+++	-	-	-	-
Subarachnoid hemorrhage	++	+	++	-	-	-

Table I. *Stroke subtypes and risk factor associations.*

Abbreviations: *AF, atrial fibrillation; CHOL, hypercholesterolemia; HT, hypertension.*

	Risk factor					
Ischemic stroke subtypes	**Age**	**HT**	**Smoking**	**Diabetes**	**AF**	**CHOL**
Artery-to-artery	+++	++	++	++	-	+
Lacunar	+++	+++	+++	++	-	±
Cardioembolic	+++	++	++	++	+++	+
Aortic arch	+++	++	++	++	-	+
Borderzone	+++	++	++	++	±	+

Table II. *Ischemic stroke subtypes and risk factor association.*

Abbreviations: *AF, atrial fibrillation; CHOL, hypercholesterolemia; HT, hypertension.*

ally caused by embolism and/or thrombosis, intracerebral hemorrhage by rupture of small penetrating vessels, and subarachnoid hemorrhage by rupture of intracranial aneurysms contained within the subarachnoid space surrounding the brain. Because stroke mechanism and risk factors are so intimately related, it is useful to compare the differing risk factor profiles for the major three subgroups shown in *Table I.* Obvious differences include atrial fibrillation as a risk factor for ischemic stroke only and smoking as a risk factor for both ischemic stroke and subarachnoid hemorrhage, but not for intracerebral hemorrhage. An elevated cholesterol level is only a weak risk factor for ischemic stroke, but is inversely related to intracerebral hemorrhage. Even within the three broad subgroups of stroke outlined above, there are further important subtypes, particularly within the ischemic and intracerebral hemorrhage groups, which will now be further discussed.

ISCHEMIC STROKE

As mentioned above, the main mechanisms of vessel occlusion that result in ischemic stroke are embolism and/or in situ thrombosis. Once the vessel is occluded, a cascade of neurochemical events follows, which may differ somewhat in gray matter (mainly neurons and supporting cells) and white matter (mainly connections between neurons with axons and other supporting cells). In gray matter, there is energy failure followed by neurotoxic glutamate release, which allows calcium entry into cells. Later, neutrophil and microglial invasion occurs, as well as apoptosis.[4] In white matter, glutamate neurotoxicity is not a major feature and a greater resistance to ischemia may exist, perhaps because of autoprotective mechanisms.[5]

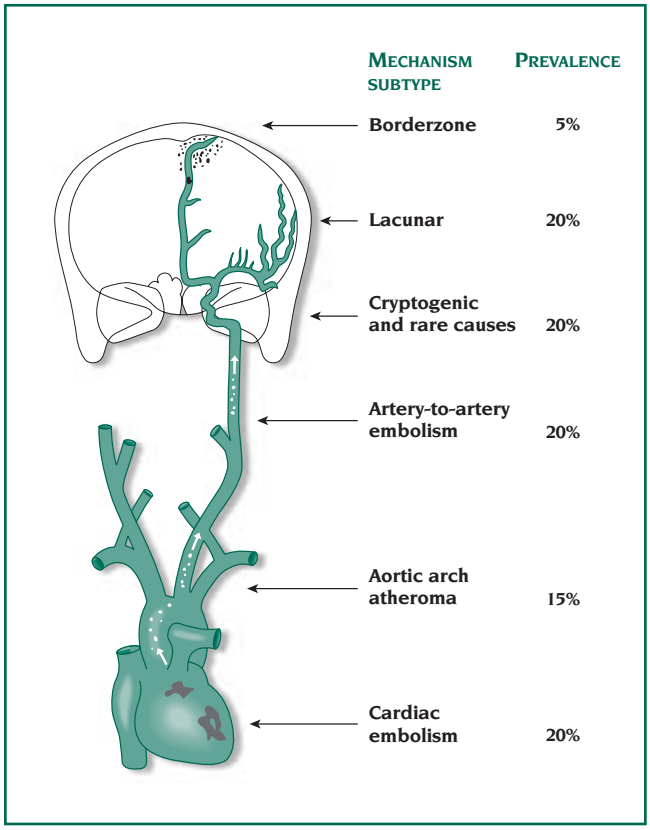

Figure 2. *Mechanistic classification of ischemic stroke. The proportions are approximate. It is of interest that at least 35% (perhaps as high as 50%) of ischemic strokes have cardiac- or aortic-associated mechanisms.*

Modified from reference 7: *Caplan LR.* Stroke: A Clinical Approach. *2nd ed. London, UK: Butterworth-Heinemann; 1993. Copyright © 1993, Elsevier Science.*

Because embolism and in situ thrombosis may occur at different sites and involve different sizes of vessels with differing consequences, several more sophisticated classifications of ischemic stroke have evolved. These are as follows:

- ***Mechanistic.*** For the Trial of Org 10172 in Acute Stroke Treatment (TOAST), a useful classification was developed where stroke mechanism was determined based on clinical signs and investigations performed *(Figure 2).*[6,7]
- ***Clinical.*** The Oxfordshire classification is a simple system developed for epidemiological studies and includes total anterior cerebral infarction (TACI), posterior cerebral infarction (POCI), partial anterior cerebral infarction (PACI), and lacunar cerebral infarction (LACI).[8]
- ***Topographic classification based on imaging.*** Here the mechanism is inferred from the topographic distribution of the infarct on computed tomography (CT) or magnetic resonance imaging (MRI) based on clinicoradiological correlations. This classification is useful for day-to-day patient management *(Figure 3).*[9] As previously established, stroke mechanism and risk factors are intimately involved and this also holds true for ischemic stroke subtypes. A mechanistic classification will be discussed here based on a modification of the TOAST system. The main mechanistic subgroups are summarized in *Figure 2* with the relative strength of risk factor association. Commonality of risk factors exists for many except for the cardioembolic subgroup. The mechanisms of ischemic stroke are also illustrated in *Table II* and will now be discussed in more detail.

Artery-to-artery embolism

This group forms about 20% of all ischemic strokes. The most common source of embolism is a stenotic region at the origin of the internal carotid artery in the neck. The development of atherosclerotic plaque appears to be similar to other parts of the body with later rupture causing cholesterol and/or platelet and clot embolism.[10,11] On traveling distally to the brain, the embolus will usually lodge in either

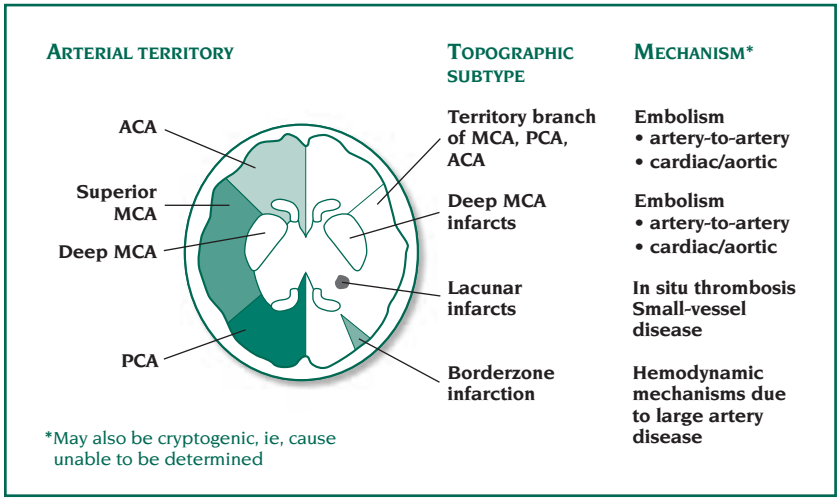

Figure 3. *Topographic classification of cerebral infarcts affecting cerebral hemispheres. Illustration shows possible CT or MRI areas of some common patterns of infarction from which mechanism can be deduced. This classification is useful for day-to-day patient management.*

Abbreviations: *ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.*

middle cerebral and/or anterior cerebral arteries and produce other transient or permanent deficits involving hemiparesis, aphasia, and sensory changes, depending upon its location. Occasionally, complete occlusion of the internal and/or common carotid arteries may occur, often producing even more pronounced clinical deficits. However, it is important to recognize that the unique collateral circulation of the brain, particularly the circle of Willis, protects it from many of these embolic and occlusive events, so that either may occur without causing clinical symptoms. Embolism may less commonly occur from the internal carotid artery higher in the carotid siphon as it enters the skull, or along the middle cerebral artery where stenoses may also occur.

Although stroke risk associated with degrees of vessel stenosis is best studied in the anterior circulation (carotid), similar principles probably apply to the vertebrobasilar system. For carotid arteries, the stroke risk remains surprisingly low if the vessel remains asymptomatic. The approximate annual fatal and nonfatal stroke risk for carotid artery stenosis of 60% or more determined by ultrasound is only about 2%.[12] Hence, for an asymptomatic carotid stenosis of this degree, the value of carotid endarterectomy is debated in spite of its efficacy.[13] Interestingly, when using transcranial Doppler (TCD) to detect emboli originating from the internal carotid artery, the rates of embolism for asymptomatic vessels are extremely low.[14] Once stenosed, carotid arteries become symptomatic, the risk of stroke appears to rise considerably. Hence, the risk of fatal or nonfatal stroke is about 10% to 18% per year[15,16] for symptomatic stenoses above 70% as defined in the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Also, the degree of ulceration detected angiographically elevates the stroke risk.[17] Hemorrhage into carotid plaque with rupture is often documented at operation (endarterectomy), although the evidence for this increasing stroke risk is less clear.[18] By using TCD, investigators have shown that rates of in vivo embolism are increased in symptomatic compared with asymptomatic carotid arteries.[14]

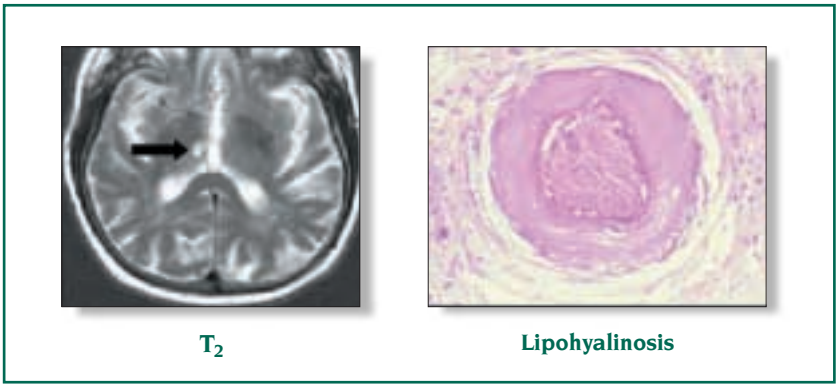

Figure 4. *Magnetic resonance imaging (MRI) showing lacunar infarct on T_2 weighted image (arrow, left panel). Lipohyalinosis of small penetrating vessel associated with lacunar infarction (right panel).*

Lacunar infarction

About 20% of ischemic strokes are caused by lacunar infarcts. This is best defined as a small infarct caused by occlusion of a single small penetrating vessel deep within the brain *(Figure 4)*.[9] These vessels stenose and occlude, much as larger vessels, although the mechanism is different.[19,20] In a remarkable series of pathological studies that have never been repeated, Fisher demonstrated that the vessel pathology associated with lacunar infarcts was most commonly microatheroma or hypertension-induced lipohyalinosis.[20] On other occasions, the vessels were found to be quite normal, consistent with the notion that microembolism could also be responsible. The lenticulostriate vessels are commonly involved in lacunar infarction. Hence, the infarcts often impinge upon the internal capsule, the large motor tract coursing through to the brain stem and spinal cord to activate contralateral face, arm, and leg. Hence the most common lacunar syndrome is pure motor hemiparesis equally involving face, arm, and leg.[21]

Logically, because of the pathological basis of lacunar infarction, hypertension is likely to be the most important risk factor. Indeed, this is the case with one study recording a relative risk of 8.9 (95% CI 4.2-18.8) compared with all other forms of ischemic stroke.[22] However, this finding is not universal and some controversy still surrounds the pathophysiology and risk factor profile of lacunar syndromes. Regardless, they are a clinically important and easily recognizable subgroup of ischemic stroke, which, because of lack of involvement of important cortical structures, tend to have a better prognosis than other forms of stroke.

Cardioembolism

Although this mechanism is recorded in most series as causing about 20% of ischemic strokes, the figure is probably higher than this because many "cryptogenic" strokes may be cardioembolic (see further down). Rheumatic valvular disease with or without atrial fibrillation is common

in the developing world and the associated stroke risk is extremely high (more than 20% per year). Nonvalvular atrial fibrillation (NVAF) is the most important source of cardioembolism for ischemic stroke in Western countries. In asymptomatic individuals, NVAF increases the risk of stroke by about five times and by about the same amount for recurrent stroke.[23,24] Based on data from the placebo arms of the Stroke Prevention in Atrial Fibrillation (SPAF) trials, a useful hierarchy of risk has been established depending on associated risk factors *(Table III).*[25]

Clinical risk group	Thromboembolism rate per year (95% CI)
No risk factors	2.5 (1.3-5.0)
One risk factor	7.2 (4.8-10.8)
Two or more risk factors	17.6 (10.5-29.9)

Table III. *Risk of thromboembolism in patients with atrial fibrillation.*[25]

The extremely high risk of embolism (mainly stroke) associated with two risk factors or more of about 18% per year represents one of the highest stroke risk profiles documented. Left ventricular failure is an underrecognized source of embolism to the brain. There is evidence provided from studies of left ventricular failure post–myocardial infarction that increasingly abnormal left ventricular function determined by echocardiography is associated with increasing stroke risk.[26] However, the overall risk from these studies is relatively low, at about 2% per year. In patients who have had a clinical stroke event, Sacco et al showed that clinically recorded congestive heart failure increased the risk of subsequent mortality about threefold.[27] Patent foramen ovale is an uncommon cause of stroke, but may be a more important mechanism and risk factor in the young. This is particularly so for the combination of patent foramen ovale and atrial septal aneurysm where the fatal and nonfatal stroke risk is about 4% per year.[28]

Aortic arch atheroma

This has more recently been demonstrated to be an important risk factor for stroke with a low relative risk of about 4% and a prevalence of about 15% of ischemic strokes. It was first established by pathological study[29] and then by two studies using transesophageal echocardiography in vivo.[30,31] It seems to be an independent risk factor and the risk increases quite significantly once the aortic arch atheroma thickness exceeds 4 mm, or the elements are mobile.

The actual mechanism associated with aortic arch atheroma is uncertain. Possibilities include stenoses of major vessels to the brain (left common carotid artery, left vertebral artery via the left subclavian artery, right common carotid, and vertebral arteries via the innominate artery). This may result in occlusion of vessels, hemodynamic effects, or embolism to the brain. Alternatively, the degree of atheroma may be a marker of atheroma elsewhere, including brain blood vessels. The recognition of this new mechanism for ischemic stroke is important, since it now may be diagnosed in vivo using transesophageal echocardiography. The best form of therapy (usually combination antiplatelet therapy or warfarin) remains uncertain.

Borderzone infarction and hemodynamic mechanisms

These mechanisms are much less common and may be as low as 5% of all ischemic strokes. The mechanism depends on the theory of most distant field vulnerability between adjacent fields of arterial supply.[32] The topographic evidence for this is that the infarcts do occur between major arterial territories of supply such as anterior, posterior, and middle cerebral arteries as well as superficial and deep branches of the middle cerebral arteries (internal borderzone infarcts) *(Figure 3).*[33]

Cryptogenic stroke and rarer causes

In a significant proportion of cases (about 15% to 20% in most series), the cause of stroke is unable to be determined, in spite of adequate investigation, and is usually classified as cryptogenic. As mentioned earlier, many of these probably have a cardiac or aortic source of embolism given the absence of stenotic vessels either intra- or extracranially shown on ultrasound or angiography. Rarer causes of stroke include carotid and vertebral artery dissection, arteritis, thrombophilic disorders, and other hematological conditions that are beyond the scope of this article.[34] Spontaneous arterial dissection is probably the most important of these and usually occurs in younger people due to a poorly understood arterial media weakness. Associated risk factors have been difficult to establish, so there are no known prevention strategies.

HEMORRHAGIC STROKE

Primary intracerebral hemorrhage

The majority of these are thought to be related to hypertension and due to the rupture of the same small penetrating vessels causing lacunar infarction. Uncertainty exists concerning the precise mechanism, since, understandably, the evidence is usually destroyed by the hemorrhage itself. Interestingly, small microbleeds shown on MRI may be a risk factor for intracerebral hemor-

rhage.[35] Also, small microaneurysms have been demonstrated to exist adjacent to and associated with intracerebral hemorrhage similar to those created by lipohyalinotic hypertensive change.[36] However, a significant proportion of cases of primary intracerebral hemorrhage are not associated with hypertension and the mechanism here remains speculative.[37] Possibilities include small vascular malformations or even microinfarcts into which bleeding has subsequently occurred on a larger scale.[38] A well-recognized subset of primary intracerebral hemorrhage is caused by amyloid angiopathy.[39] The hemorrhage in these cases is more common in the elderly and not necessarily associated with hypertension. The intracerebral hemorrhages may be small, multiple, and more peripherally located than the larger deep basal ganglionic and lobar hemorrhages associated with hypertensive hemorrhage.

Secondary intracerebral hemorrhage

This is a smaller group and may be due to a variety of pathologies including hematological abnormalities (anticoagulant), vascular malformations such as arteriovenous malformations, cavernous hamartomas, and drug-induced factors (for example, anticoagulants or drugs elevating blood pressure).[40]

CONCLUSIONS

From the preceding discussion it can be seen that the broad clinical syndrome of "stroke" is due to a multiplicity of complex and often still poorly understood mechanisms. With the gradual introduction of modern neuroimaging techniques, particularly magnetic resonance imaging and angiography, together with more sophisticated epidemiological approaches, these mechanisms are likely to be better understood over the next decade or so. While there are broad overlaps of mechanism and associated risk factors for many stroke subtypes, which allow a commonality of approach to prevention and treatment, more specific approaches are often required.

REFERENCES

1. Murray CJ, Lopez AD.

Mortality by cause for eight regions of the world: Global Burden of Disease Study.

Lancet. 1997;349:1269-1276.

---

2. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease).

A major international collaboration. WHO MONICA Project Principal Investigators.

J Clin Epidemiol. 1988;41:105-114.

---

3. Thrift AG, Dewey HM, Macdonell RA, McNeil JJ, Donnan GA.

Incidence of the major stroke subtypes: initial findings from the North East Melbourne stroke incidence study (NEMESIS).

Stroke. 2001;32:1732-1738.

---

4. Turski L, Huth A, Sheardown M, et al.

ZK200775: a phosphonate quinoxalinedione AMPA antagonist for neuroprotection in stroke and trauma.

Proc Natl Acad Sci U S A. 1998;95: 10960-10965.

---

5. Ransom BR, Stys PK, Waxman SG.

The pathophysiology of anoxic injury in central nervous system white matter.

Stroke. 1990;21(11 suppl):III52-III57.

---

6. Adams HP Jr, Bendixen BH, Kappelle LJ, et al.

Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment.

Stroke. 1993;24:35-41.

---

7. Caplan LR.

Stroke: A Clinical Approach. 2nd ed. London, UK: Butterworth-Heinemann; 1993.

---

8. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C.

Classification and natural history of clinically identifiable subtypes of cerebral infarction.

Lancet. 1991;337:1521-1526.

---

9. Donnan G, Norrving B, Bamford J, Bogousslavsky J.

Subcortical infarction: classification and terminology.

Cerebrovasc Dis. 1993;3:248-251.

---

10. Siebler M, Kleinschmidt A, Sitzer M, Steinmetz H, Freund HJ.

Cerebral microembolism in symptomatic and asymptomatic high-grade internal carotid artery stenosis.

Neurology. 1994;44:615-618.

---

11. Fisher CM, Ojemann RG.

A clinico-pathologic study of carotid endarterectomy plaques.

Rev Neurol (Paris). 1986;142:573-589.

---

12. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study.

Endarterectomy for asymptomatic carotid artery stenosis.

JAMA. 1995:1421-1428.

---

13. Chambers BR, You RX, Donnan GA.

Carotid endarterectomy for asymptomatic carotid stenosis.

Cochrane Database Syst Rev. 2000;2: CD001923. Review.

---

14. Molloy J, Markus HS.

Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis.

Stroke. 1999;30:1440-1443.

---

15. European Carotid Surgery Trialists' Collaborative Group.

MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis.

Lancet. 1991;337:1235-1243.

16. North American Symptomatic Carotid Endarterectomy Trial Collaborators.

Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis.

N Engl J Med. 1991;325:445-453.

17. Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJ.

Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial.

Stroke. 1994;25:304-348.

18. Imparato AM, Riles TS, Gorstein F.

The carotid bifurcation plaque: pathologic findings associated with cerebral ischemia.

Stroke. 1979;10:238-245.

19. Lammie GA, Brannan F, Slattery J, Warlow C.

Nonhypertensive cerebral small-vessel disease. An autopsy study.

Stroke. 1997;28:2222-2229.

20. Fisher CM.

Capsular infarcts: the underlying vascular lesions.

Arch Neurol. 1979;36:65-73.

21. Donnan G, Yasaka M.

Lacunes and lacunar syndromes. In: Ginsberg M, Bogousslavsky J, eds.

Cerebrovascular Disease Pathology Diagnosis and Management. Oxford, UK: Blackwell Science; 1998:1090-1102.

22. You R, McNeil JJ, O'Malley HM, Davis SM, Donnan GA.

Risk factors for lacunar infarction syndromes [see comments].

Neurology. 1995;45:1483-1487.

23. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB.

Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study.

Neurology. 1978;28:973-977.

24. EAFT (European Atrial Fibrillation Trial) Study Group.

Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke.

Lancet. 1993;342:1255-1262.

25. No authors listed.

Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials.

Arch Intern Med. 1994;154:1449-1457.

26. Dries DL, Rosenberg YD, Waclawiw MA, Domanski MJ.

Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence for gender differences in the studies of left ventricular dysfunction trials.

J Am Coll Cardiol. 1997;29:1074-1080.

27. Sacco RL, Shi T, Zamanillo MC, Kargman DE.

Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study.

Neurology. 1994;44:626-634.

28. Mas JL, Arquizan C, Lamy C, et al.

Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both.

N Engl J Med. 2001;345:1740-1746.

29. Amarenco P, Duyckaerts C, Tzourio C, Henin D, Bousser MG, Hauw JJ.

The prevalence of ulcerated plaques in the aortic arch in patients with stroke.

N Engl J Med. 1992;326:221-225.

30. Jones EF, Kalman JM, Calafiore P, Tonkin AM, Donnan GA.

Proximal aortic atheroma. An independent risk factor for cerebral ischemia.

Stroke. 1995;26:218-224.

31. Amarenco P, Cohen A, Tzourio C, et al.

Atherosclerotic disease of the aortic arch and the risk of ischemic stroke.

N Engl J Med. 1994;331:1474-1479.

32. Ringelstein EB, Zunker P.

Low-flow infarction. In: Ginsberg MD, Bogousslavsky J, eds.

Cerebrovascular Disease—Pathophysiology, Diagnosis, and Management. 2nd ed. Oxford, UK: Blackwell Science, 1998: 1075-1089.

33. Bogousslavsky J, Regli F.

Borderzone infarctions distal to internal carotid artery occlusion: prognostic implications.

Ann Neurol. 1986;20:346-350.

34. Caplan LR.

Specific Stroke Etiologies—Overview. In: Ginsberg MD, Bogousslavsky J, eds.

Cerebrovascular Disease—Pathophysiology, Diagnosis, and Management. 2nd ed. Oxford, UK: Blackwell Science, 1998:1587-1588.

35. Fazekas F, Roob G.

MRI changes as a risk factor for intracerebral haemorrhage. In: Donnan GA, Norrving B, Bamford J, Bogousslavsky J, eds.

Subcortical Stroke. 2nd ed: Oxford, UK: Oxford University Press; 2002:337-345.

36. Wakai S, Nagai M.

Histological verification of microaneurysms as a cause of cerebral haemorrhage in surgical specimens.

J Neurol Neurosurg Psychiatry. 1989;52:595-599.

37. Thrift AG, Donnan GA, McNeil JJ.

Epidemiology of intracerebral hemorrhage.

Epidemiol Rev. 1995;17:361-381.

38. Bogousslavsky J, Regli F, Uske A, Maeder P.

Early spontaneous hematoma in cerebral infarct: is primary cerebral hemorrhage overdiagnosed?

Neurology. 1991;41:837-840.

39. Vinters HV.

Cerebral amyloid angiopathy. A critical review.

Stroke. 1987;18:311-324.

40. Norrving B.

Cerebral hemorrhage. In: Ginsberg MD, Bogousslavsky J, eds.

Cerebrovascular Disease—Pathophysiology, Diagnosis and Management. 2nd ed. Oxford, UK: Blackwell Science; 1998:1447-1473.

Should the stroke patient be reperfused, and if so, how?

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Most strokes (85%) are ischemic. The central core of densely ischemic tissue is surrounded by a potentially salvageable "penumbral" zone amenable to thrombolytic therapy. Four major studies with recombinant tissue plasminogen activator (rt-PA) have shown that intravenous rt-PA is beneficial if used within a 3-hour timeframe by experienced centers in selected patients: 43% of patients are functionally independent at 30 days, early mortality is 13%, and the intracerebral hemorrhage rate is 3.3%. In a less evaluated procedure, intra-arterial thrombolysis, a thrombolytic drug is released directly into the occluded artery. The two methods can be combined. Backed by the hugely informative input of multimodal magnetic resonance imaging, thrombolysis now represents the most exciting challenge in vascular neurology, despite the formidable logistic constraints of the 3-hour treatment window.

Keywords: stroke; ceerebrovascular disease; clinical study; treatment; thrombolytic; streptokinase; rt-PA; prourokinase; multimodal magnetic resonance imaging

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Dialogues Cardiovasc Med. 2003;8:22-27

Stroke is the leading cause of disability in the Western world and is responsible for more deaths than any other disease with the exceptions of heart disease and cancer. The burden of cerebrovascular disease is immense; care and rehabilitation of stroke patients consume approximately 6% of all health care resources in developed countries.[1] A wide variety of strategies to treat this common and devastating condition have been investigated in recent years; undoubtedly the most successful to date has been the provision of thrombolytic therapy. In North America and a number of European countries, thrombolysis is now an established intervention for selected patients with acute ischemic stroke presenting within 3 hours of onset of symptoms. A variety of thrombolytic agents and modes of delivery have been evaluated. This article reviews the evidence that addresses the question "Should the stroke patient be reperfused, and, if so, how?"

BACKGROUND

Thrombolysis has been used for a number of years in the management for patients with myocardial infarction and its efficacy has been demonstrated by a series of large randomized, placebo-controlled trials.[2,3] Thrombolysis leads to reper-

SELECTED ABBREVIATIONS AND ACRONYMS

ASK	Australian StreptoKinase trial in stroke
ATLANTIS	Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke
dwMRI	diffusion-weighted magnetic resonance imaging
ECASS	European Cooperative Acute Stroke Study
MAST-E	Multicenter Acute STroke study–Europe
MAST-I	Multicenter Acute STroke study–Italy
MCA	middle cerebral artery
mmMRI	multimodal magnetic resonance imaging
NINDS-TPAST	National Institute of Neurological Diseases and Stroke—Tissue Plasminogen Activator Stroke Trial
PROACT	PROlyse in Acute Cerebral Thromboembolism
pwMRI	perfusion-weighted magnetic resonance imaging
rt-PA	recombinant tissue plasminogen activator
STARS	Standard Treatment with Alteplase to Reverse Stroke

fusion of vessels occluded by coronary atherothrombosis, which in turn reduces mortality and preserves left ventricular function.

Most strokes are atherothrombotic or embolic (85%), while the remainder are hemorrhagic. It was hoped that the same "open artery hypothesis" would hold true for patients with ischemic or nonhemorrhagic stroke, and that intervention to accelerate reperfusion would improve both mortality and functional outcome. In patients with stroke, it appears that a central core of densely ischemic tissue is surrounded by a "penumbral" zone of potentially salvageable tissue that is amenable to either neuroprotective or reperfusion therapy *(Figure 1).* The potential risks of thrombolysis are predictable from what is known of the pathophysiology of cerebral ischemia; reperfusion injury may occur when toxic free radicals and inflammatory cells enter an ischemic area following spontaneous reperfusion, and hemorrhagic transformation is commonly seen in patients with large infarcts. Certain groups of patients could be thought of as at higher risk of secondary intracerebral hemorrhage as a result of thrombolysis. Elderly patients already have a higher risk of spontaneous intracerebral hemorrhage, as have hypertensives and patients with embolic rather than simple occlusive atherothrombotic strokes. Delayed thrombolysis may simply lead to reperfusion of already irreversibly infarcted tissue and increase the risk of hemorrhage. When trials of thrombolytics were devised, these issues were considered and are reflected in the design, entry, and exclusion criteria of the studies. All studies incorporated a variable "time window" out of which patients were ineligible, all patients underwent brain imaging with x-ray computed tomography (CT) to exclude intracerebral hemorrhage as the primary pathology, and some studies excluded large infarcts and hypertensive patients. The analysis of treatment efficacy is crucial in the design and interpretation of any trial of stroke therapy. Most studies incorporated a validated functional outcome score such as the Barthel score.[4] These scores describe the patients' ability to perform activities of daily living. More detailed assessments of neurological function were also made, using, for example, the Scandinavian Stroke Scale.[5]

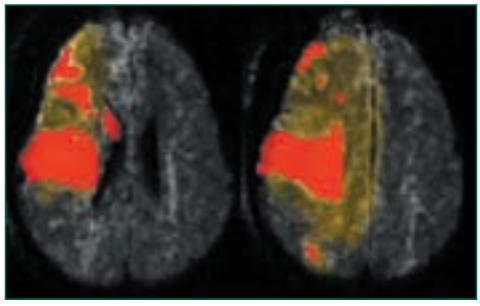

Figure 1. *Composite diffusion and perfusion images of acute stroke. The ischemic core of dead and dying brain tissue is highlighted in red; the surrounding hypoperfused area is shown in yellow. This yellow area is thought to represent the "penumbra," which may be spared by timely reperfusion.*

A variety of thrombolytic agents and means of drug delivery have been investigated in the context of acute ischemic stroke. The first group of studies to be considered will be those that used systemic intravenous administration of a thrombolytic agent.

INTRAVENOUS STREPTOKINASE STUDIES

The MAST-E (Multicenter Acute Stroke Study–Europe)[6] and ASK (Australian StreptoKinase trial in stroke)[7] treated patients with streptokinase (1.5 M units over 1 hour) or placebo within 6 and 4 hours, respectively. In both studies, there was an increase in early mortality sufficient to result in the safety committees abandoning both studies prior to completion. This correlated with a high incidence of complicating intracerebral hemorrhage. In the MAST-E study, 36% (n=156) patients treated with streptokinase vs 3% (n=154) placebo patients suffered a fatal hemorrhagic transformation of infarct.

The MAST-I (MAST-Italy) study evaluated treatment with streptokinase and aspirin compared with streptokinase or aspirin alone or placebo.[8] Again the results suggested an increase in early mortality which was more marked in patients receiving both streptokinase and aspirin, while aspirin alone appeared to be safe, but of no clear benefit. Meta-analysis of all streptokinase results failed to reveal factors that predisposed to early mortality. Streptokinase significantly increased early mortality, while there may have been a trend towards improved outcome in survivors. To date, no randomized controlled trial has supported the use of intravenous streptokinase as therapy for acute ischemic stroke. Further studies of streptokinase using different patient selection criteria, lower doses of thrombolytic, and prohibition of antiplatelet or anticoagulant coadministration have been proposed, however, at present, no such trial is under way. Although there remains some debate,[9] it is unlikely that streptokinase will have any role in the management of acute ischemic stroke.

INTRAVENOUS RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR STUDIES

Four major trials have evaluated the role of recombinant tissue plasminogen activator (rt-PA) in patients with acute stroke. There

are theoretical reasons why rt-PA may be more effective:

- First, rt-PA is known to be more "clot-specific," that is, it causes less generalized activation of plasminogen, instead having a more selective action at the site of the clot itself; this may make hemorrhagic complications less likely.
- Second, rt-PA is less antigenic than streptokinase and is not associated with a fall in blood pressure during the infusion. This may be of significance, as reducing blood pressure immediately after ischemic stroke has been associated with worse outcome.[10]
- Finally, angiographic studies in patients with acute myocardial infarction suggest rt-PA is more effective than streptokinase in reperfusing occluded coronary vessels.

ECASS 1 and 2 (European Cooperative Acute Stroke Study [first and second])[11,12] and NINDS-TPAST (National Institute of Neurological Diseases and Stroke—Tissue Plasminogen Activator Stroke Trial)[13] evaluated rt-PA at doses of 1.1 mg/kg, 0.9 mg/kg, and 0.9 mg/kg, respectively. Patients were treated within 6 hours in the ECASS studies and 3 hours in the NINDS-TPAST study. The Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study[14] used a dosage of 0.9 mg/kg administered within an initial time window of 6 hours. The time window was altered twice during the study and the results were rather less encouraging.

ECASS 1. The higher dose of rt-PA used in the ECASS 1 study is equivalent to that used in the treatment of patients with myocardial infarction. Dose-ranging studies have shown an increasing incidence of complicating hematoma formation in patients receiving doses greater than 0.85 mg/kg, and this could have contributed to the increased incidence of hemorrhages seen in the ECASS 1 study. The results of ECASS 1 are also notable for the large proportion of patients excluded from the target population analysis (109 out of 620 randomized). The protocol intended to exclude patients with greater than one-third middle cerebral artery (MCA) territory stroke on CT, ie, those with large infarcts. Sixty-six such patients were randomized, constituting the largest group of protocol violators. Survival in protocol violators was significantly worse than for those meeting the entry criteria. While analysis of the target population results suggested an improvement in functional outcome at 3 months (P=0.03), the more rigorous intention-to-treat (ITT) analysis was negative. Mortality was nonsignificantly higher in the rt-PA group in both ITT and target population (TP) analysis. In summary, the ECASS study did not show enough benefit to justify thrombolysis with rt-PA up to 6 hours after stroke onset although an improvement in functional outcome (Barthel[4] and Rankin[15] scores) was seen in the target population analysis of the rt-PA–receiving patients.

NINDS-TPAST. The National Institute of Neurological Disorders and Stroke—Tissue Plasminogen Activator Stroke Study Group assessed a lower dose of rt-PA (0.9 mg/kg) given within 3 hours of onset of CT-confirmed ischemic stroke. The results suggest an improvement in functional outcome at 3 months, with those in the treated group 30% more likely to have negligible disability at this time point. There was no difference in mortality in the actively treated patients, although there was an increase in symptomatic intracerebral hemorrhage (7% vs 1%; rt-PA vs placebo). Mortality ascribed to intracerebral hemorrhage was 3% vs 0.3%.

ECASS 2. The aim of the ECASS 2 study was to investigate the safety and efficacy of rt-PA given in a dose of 0.9 mg/kg within 6 hours of onset of ischemic stroke. Strenuous efforts to improve the quality of CT interpretation were made, and significantly fewer intracranial hemorrhages were seen in comparison with the original ECASS study. The primary outcome measure was the proportion of patients reaching modified Rankin[15] scores (mRS) of 0 or 1 (ie, little or no disability) at 3 months. The study failed to demonstrate a statistically significant difference between treated and placebo groups; however when the outcome measure was redichotomized to define good outcome as mRS of 0 to 2, a beneficial effect of rt-PA was seen. The authors concluded that rt-PA treatment leads to a clinically relevant improvement in outcome without increased morbidity and mortality despite increased symptomatic hemorrhage. However, the failure of the trial to demonstrate efficacy using predetermined end points has led to the widespread interpretation of the trial as neutral. Incorporation of the ECASS 2 data into a meta-analysis of trials of rt-PA in acute stroke reveals a favorable odds ratio of 0.67 (95% confidence interval [CI] 0.56-0.80) with respect to death and disability.

ATLANTIS. The ATLANTIS study was designed to assess the safety and efficacy of intravenous rt-PA 0.9 mg/kg within 6 hours of ischemic stroke. Two years after recruitment commenced, the time window was changed to 0 to 5 hours due to adverse interim safety analysis in the 5-to-6–hour group. After a further 3 years, the time window was further modified (3 to 5 hours) due to the results of NINDS-TPAST. With the exception of the time window, entry criteria were very similar to those

employed by the NINDS-TPAST investigators. The ATLANTIS study was terminated prematurely in July 1998 following further interim safety analysis, which concluded that "treatment was unlikely to prove beneficial." The 90-day results in the placebo and rt-PA groups did not differ with regard to the primary outcome measure, and the use of intravenous rt-PA beyond 3 hours after stroke onset is not supported by the ATLANTIS study.

TRANSLATION OF TRIAL RESULTS INTO CLINICAL PRACTICE: THE STARS STUDY

Following publication of the NINDS-TPAST study, rt-PA was approved for use in acute ischemic stroke within 3 hours of onset of symptoms. Concerns were raised that the clinical benefit observed in the NINDS-TPAST patients would not be reproduced outside of the highly controlled atmosphere of a clinical trial. The Standard Treatment with Alteplase to Reverse Stroke (STARS) trial[16] investigators addressed these concerns in a prospective, monitored, multicenter trial that evaluated outcome of patients thrombolysed in 57 hospitals in the USA. The results of this trial were reassuring—43% of treated patients were functionally independent at 30 days, early mortality was low (13%), and the overall rate of symptomatic intracerebral hemorrhage was comparable to that observed in NINDS-TPAST at 3.3%.

SUMMARY OF SYSTEMIC THROMBOLYTIC THERAPY FOR ISCHEMIC STROKE

NINDS-TPAST was the first trial to demonstrate that early intervention can improve the outcome for patients with acute ischemic stroke. The ECASS 2 study failed to reproduce the convincingly positive results of NINDS-TPAST; however, meta-analysis suggests a beneficial effect of intervention with rt-PA. The benefit of thrombolysis with intravenous rt-PA in patients with acute ischemic stroke has been demonstrated and the trial results appear to be reproducible when the treatment is implemented outside of the context of a clinical trial in the USA. Use of rt-PA can be justified when used judiciously within an experienced center. An application for use of rt-PA in acute stroke in the European Community is currently under consideration. It is likely that approval will be granted for use within 3 hours of ictus in patients with similar characteristics to those in NINDS-TPAST.

In contrast to the rt-PA trials, all studies that used streptokinase in stroke patients have yielded resoundingly negative results. Although it has been argued that the potential benefit of streptokinase has yet to be fully investigated,[9] on the basis of current evidence its use cannot be justified in the context of acute ischemic stroke.

INTRA-ARTERIAL STUDIES

Intra-arterial thrombolysis involves administration of thrombolytic drugs distal to, directly within, and proximal to luminal thrombus within an occluded cerebral artery. The technique has a number of potential advantages over systemic administration, which may enable provision of treatment to a larger group of patients. Cerebral angiography can be performed immediately prior to instillation of a thrombolytic, hence precise characterization of the arterial occlusion is possible with documentation of the degree and extent of posttreatment reperfusion. Targeted delivery of thrombolytic enables attainment of high concentrations of thrombolytic drug at its site of action and reduction in systemic exposure, hence bleeding complications are minimized and patients deemed unsuitable for systemic thrombolysis due to bleeding risk may still receive treatment.

Although no randomized comparative data exist, open clinical series[17,18] have suggested a higher recanalization rate with intra-arterial (60% to 80%) than intravenous (20% to 60%) delivery of thrombolytics. Differences in recanalization rates are particularly marked in the context of internal carotid or proximal middle cerebral artery (MCA) occlusion; these vessels seem particularly resistant to intravenous thrombolysis.

The PROACT studies

A number of clinical trials have helped clarify the role of intra-arterial thrombolysis in the management of ischemic stroke. The first PROlyse in Acute Cerebral Thromboembolism trial (PROACT I)[19] examined the effect of intra-arterial delivery of 6 mg of recombinant prourokinase upon arterial patency in 40 patients with MCA occlusion of less than 6 hours' duration. Recanalization rate was 57.7% in the actively treated group and 14.4% in the placebo recipients. Although the study was not designed to detect an effect of intra-arterial thrombolysis upon outcome, a trend towards benefit of prourokinase was observed. The second PROACT trial[20] followed up the suggestion of benefit obtained in the first study. In PROACT II, 180 patients with MCA occlusion of less than 6 hours' duration were randomized to receive 9 mg of intra-arterial prourokinase plus low-dose heparin or heparin alone. A 15% absolute benefit in the number of patients with minimal or no disabil-

ity at 90 days was seen, associated with similar rates of recanalization to those seen in PROACT I. The PROACT studies suggest a role for intra-arterial thrombolysis in the future management of acute stroke; however, that role is yet to be fully defined. Intra-arterial thrombolysis is an invasive procedure that is not without its drawbacks. Manipulation of catheters within the cerebral vessels confers risk of vasospasm or thrombus formation with potentially serious clinical sequelae; although the PROACT studies reported relatively low procedure-related complication rates, adverse events occurring outside of the context of a clinical trial may impinge upon the observed benefit of the intervention. Specialist facilities and expertise are required; at present, these are not widely available outside tertiary stroke centers in either the US or Europe, and hence, at present, relatively few patients will benefit from its use. The necessary preoperative preparation may extend "door-to-needle" time and reduce the benefit of reperfusion. These problems have prompted further investigation of combined thrombolytic strategies that aim to confer the advantages of the intra-arterial technique, but also enable provision of very rapid treatment.

The potential benefit of combined intravenous and intra-arterial thrombolysis has recently been explored in a small pilot study,[21] in which low-dose intravenous rt-PA was administered prior to cerebral angiography and intra-arterial thrombolysis. The technique appeared safe and feasible, with high rates of arterial recanalization. The promising results of this small study will doubtless stimulate further work in the evolution of future acute strategies, including combination of thrombolytic agents with future neuroprotective drugs.

THE FUTURE

Improved patient selection

The trials discussed all used CT to exclude intracerebral hemorrhage prior to administration of thrombolytic agent. This technique is notoriously insensitive in the context of acute ischemic stroke, and will eventually be replaced by multimodal magnetic resonance imaging (mmMRI).[22] This modality allows reliable identification, localization, and quantification of ischemic core of the infarct early after stroke using diffusion-weighted sequences (dwMRI), and in addition allows evaluation of cerebral perfusion with perfusion weighting (pwMRI).

Examination of the "mismatch" between diffusion and perfusion deficit *(Figure 1)* allows quantification of salvageable brain tissue, and serial imaging can assess the effect of reperfusion or neuroprotective strategies upon infarct maturation. Multimodal MRI may therefore reduce heterogeneity of stroke recruited into future efficacy studies and may provide useful surrogate end points for these trials.

Improved arterial recanalization

The combination of intra-arterial thrombolysis with other nonpharmacologic revascularization techniques is being studied and undoubtedly holds promise for the future. Acute balloon angioplasty of the cerebral vessels is already being used in some centers, although there are insufficient data to justify its widespread use.

A variety of newer mechanical clot disruption techniques such as umbrella and coil devices have been developed and may be employed as adjunctive strategies in the future.

Practical aspects

There is evidence supporting the benefits of rt-PA in selected stroke patients if administered within 3 hours of the onset of symptoms. Translation of these clinical trial findings into routine practice will not be easy. There are major challenges in educating patients, relatives, and doctors in primary care and hospitals to make all aware of the opportunities and urgency of referral of patients with focal neurological symptoms of cerebrovascular disease within the 3-hour time window. In addition, there are considerable logistic and resource issues in providing brain imaging (usually CT) 24 hours a day, 7 days a week, to exclude cerebral hemorrhage (or more rarely, noncerebrovascular diagnoses) within the 3-hour treatment window. Finally, there needs to be available clinical expertise to assess the scans and the patient's clinical state and to deliver thrombolysis in the time window and ongoing care of the patient.

New models of care, together with community education programs, need to be developed if the potential benefits of thrombolysis and stroke are to be realized in practice.

CONCLUSION

Thrombolytic therapy is the only proven treatment for acute ischemic stroke. Intravenous administration of rt-PA has been extensively evaluated in clinical trials and there is general agreement that this intervention is beneficial when used within 3 hours of onset of symptoms. Intra-arterial thrombolysis has been less thoroughly evaluated, but may be appropriate in the context of major arterial occlusion in a patient who will tolerate angiography, assuming the requisite facilities and expertise are available.

The advent of mmMRI, neuroprotective agents, and nonpharmacologic means of arterial reperfusion have the potential to improve current acute strategies. The evaluation and implementation of these novel techniques are the most important and exciting challenges in vascular neurology today.

REFERENCES

1. Woo J, Cockram C.

Cost estimates for chronic diseases.

Dis Manage Health Outcomes. 2000;8: 29-41.

2. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI).

Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction.

Lancet. 1986;1:397-402.

3. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group.

Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2.

Lancet. 1988;2:349-360.

4. Mahoney F, Barthel D.

Functional evaluation: the Barthel Index.

Md Med J. 1965;14:61-65.

5. Lindstrom E, Boysen G, Christiansen LV, aRogvi-Hansen B, Nielsen BW.

Reliability of Scandinavian Neurological Stroke Scale.

Cerebrovasc Dis. 1991;1:103-107.

6. The Multicenter Acute Stroke Trial—Europe Study Group.

Thrombolytic therapy with streptokinase in acute ischemic stroke.

N Engl J Med. 1996;335:145-150.

7. Donnan GA, Hommel M, Davis SM, McNeil JJ.

Streptokinase in acute ischaemic stroke.

Lancet. 1995;345:578-579.

8. Candelise L, Aritzu E, Ciccone A, Ricci S, Wardlaw J.

Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke.

Lancet. 1995;346:1509-1514.

9. Bath P.

Alteplase not yet proven for acute ischaemic stroke.

Lancet. 1998;352:1238-1239.

10. Wahlgren NG, McMahon DG, De Keyser J, Indredavik B, Ryman T.

Intravenous Nimodipine West European Stroke Trial (INWEST) of Nimodipine in the treatment of Acute Ischaemic Stroke.

Cerebrovasc Dis. 1994;4:204-210.

11. Hacke W, Kaste M, Fieschi C, et al.

Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS).

JAMA. 1995;274:1017-1025.

12. The Second European Acute Stroke Study (ECASS II).

Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke.

Lancet. 1998;352:1245-1251.

13. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.

Tissue plasminogen activator for acute ischemic stroke.

N Engl J Med. 1995;333:1581-1587.

14. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S.

Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke.

JAMA. 1999;282:2019-2026.

15. Rankin J.

Cerebral vascular accidents in patients over the age of 60: prognosis.

Scott Med J. 1957;2:200-215.

16. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA.

Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study.

JAMA. 2000;283:1145-1150.

17. del Zoppo GJ.

Thrombolytic therapy in the treatment of stroke.

Drugs. 1997;54(suppl 3):90-98.

18. Jahan R, Duckwiler GR, Kidwell CS, et al.

Intra-arterial thrombolysis for treatment of acute stroke: experience in 26 patients with long-term follow-up.

Am J Neuroradiol. 1999;20:1291-1299.

19. del Zoppo GJ, Higashida RT, Wechsler L, et al.

PROACT: a phase II randomised trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism.

Stroke. 1998;29:4-11.

20. Furlan A, Higashida R, Wechsler L, et al.

Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized, controlled trial. Prolyse in Acute Cerebral Thromboembolism.

JAMA 1999;282:2003-2011.

21. Lewandowski CA, Frankel M, Tomsick TA, et al, and the EMS Bridging Trial Investigators.

Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial.

Stroke. 1999;30:2598-2605.

22. Warach S.

New imaging strategies for patient selection for thrombolytic and neuroprotective therapies.

Neurology. 2001;57:S48-S52.

Neuroprotection: what are its prospects in the stroke patient?

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Neuroprotective drugs aimed at limiting infarct size, prolonging the therapeutic window for thrombolysis, or minimizing postischemic reperfusion injury and inflammation, have demonstrated excellent results in experimental models of ischemia, but lack of efficacy in clinical trials and were often associated with serious side effects. Criticism has been leveled at each stage in the development progress from preclinical testing to trial analysis. However, by elaborating guidelines for assessing the adequacy of preclinical testing and by optimizing eligibility criteria, dose selection, control of confounding factors, and end points in clinical trials, the prospects of success will increase. Combination of reperfusion strategies with neuroprotection, combination of agents targeting different mechanisms of the ischemic cascade, and nonpharmacologic neuroprotection, such as hypothermia, all seem quite promising.

Keywords: stroke; neuroprotection; brain ischemia; clinical trial; stroke model

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Dialogues Cardiovasc Med. 2003;8:28-34

The concept of neuroprotection relies on the principle that delayed neuronal injury occurs after ischemia. Because the ischemic cascade is clearly a process and not an instantaneous event, the potential exists for modifying the process after the clinical ictus and altering the final outcome.[1,2] If we consider that a stroke occurs every 53 seconds in North America, then we realize that "lost" time in developing effective stroke treatments equals "lost" brain.

A plethora of neuroprotective agents targeting diverse cellular and molecular mechanisms *(Table I)* have been extensively tested in randomized trials of acute ischemic stroke, and no agent has been proven effective, despite promising results in animal models.[3,4]

DO PAST FAILURES PRECLUDE FUTURE SUCCESS?

After the failure of so many trials, it would be reasonable to wonder, "Will neuroprotectants ever work in humans?" We do not know the answer. However, we should keep in mind that, in science, lack of evidence of efficacy does not obligatorily equal lack of efficacy. Is it possible that basic methodological flaws allow preclinical studies to provide inadequate or even overoptimistic data? The small, lissencephalic rodent brain has rheological and metabolic properties vastly different from the comparatively enormous gyrencephalic human brain. Conversely, if neuroprotectants work in the laboratory, but not at the bedside, which methodological flaws in

SELECTED ABBREVIATIONS AND ACRONYMS

ASTIN	Acute Stroke Therapy by Inhibition of Neutrophils
GAIN	Glycine Antagonist In Neuroprotection
IMAGES	Intravenous MAGnesium Efficacy in Stroke
NIHSS	National Institutes of Health Stroke Scale
NINDS-TPAST	National Institute of Neurological Diseases and Stroke—Tissue Plasminogen Activator Stroke Trial
NOS	nitric oxide synthase
POST	Potassium channel Opener Stroke Trial
PROACT II	PROlyse in Acute Cerebral Thromboembolism II
rt-PA	recombinant tissue plasminogen activator
TIA	transient ischemic attack

Neuroprotective agent	Comments	Results
Voltage-gated Ca^{2+} channel antagonists		
Nimodipine, Flunarizine, Darodipine (PY 108-068), Isradipine		No efficacy, IV nimodipine is associated with a poorer outcome due to blood pressure lowering
Inhibitors of presynaptic glutamate release		
BW619C89	Pyrimidine derivative	Trial discontinued
Lubeluzole	Na^+ channel blocker, NOS modulator	No efficacy, safe when combined with rt-PA
Fosphenytoin	Na^+ channel blocker	No efficacy
Propentophylline	Adenosine transport inhibitor	No efficacy
Lifaricine	Na^+,Ca^{2+} channel blocker, D_2 agonist	Trial discontinued
NMDA antagonists		
Dextrorfan	Noncompetitive inhibition	Trial discontinued
Aptiganel	Noncompetitive inhibition	Trial discontinued
Dizolcipine (MK-801)	Noncompetitive inhibition	Trial discontinued
Magnesium	Noncompetitive inhibition, voltage-gated, Ca^{2+} channel antagonist	Ongoing trial (IMAGES)
Selfotel	Competitive inhibition	Trial discontinued
Eliprodil	Polyamine site antagonist, slow Ca^{2+} channel blocker	No efficacy
Gavestinel	Glycine site inhibitor	No efficacy
Agents acting on other receptors		
NBQX	AMPA antagonist	Trial discontinued
BAY 3102	1A serotonin agonist	Ongoing trial
BMS-204352	K^+ channel agonist	Ongoing trial (POST)
Nalmefene	Opiate κ-receptor antagonist	No efficacy
Clomethiazole	GABA-A, Cl^- channel modulator	No overall efficacy, safe when combined with IV rt-PA, possible benefit in total anterior cerebral infarction
Antioxidants		
Tirilazad	21-amino steroid, lipid peroxidation inhibitor	No efficacy
Ebselen	Glutathione peroxidase-like action	No efficacy
Citicoline	Phosphatidylcholine synthesis	Possible benefit in medium-sized infarcts
Other agents		
GM-1	Exogenous ganglioside, non-NMDA antagonist, membrane stabilizator	No efficacy
Piracetam	Membrane modulator	No overall efficacy, possible benefit in patients with moderate-to-severe deficiency treated <7 hours
DCL Hb	Hemoglobin-based oxygen carrier	Trial discontinued
bFGF	Basic fibroblast growth factor, neurotrophin	Trial discontinued
Enlimomab	Murine monoclonal antibodies against ICAM-1	No efficacy, worse outcome
Hu23F2G	CD11/CD18 human monoclonal antibodies to integrins	Trial discontinued
r-NIF	Recombinant neutrophil inhibitory factor	Ongoing trial (ASTIN)
Nonpharmacologic (physiologic) neuroprotection		
Hypothermia	Moderate hypothermia (32°C-34°C) within 3 hours after cardiac arrest. Moderate hypothermia (33°C-35°C) in patients with severe middle cerebral artery infarction	Improved neurologic outcome at discharge or at 6 months Nonrandomized, small trial, possible benefit in this group of patients

Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate; bFGF, basic fibroblast growth factor; D_2, dopamine receptor 2; GABA, gamma-aminobutyric acid; ICAM-1, intercellular adhesion molecule–1; NMDA, *N*-methyl-D-aspartate; NOS, nitric oxide synthase; r-NIF, recombinant neutrophil inhibitory factor; rt-PA, recombinant tissue plasminogen activator. ***Trial acronyms:*** ASTIN; Acute Stroke Therapy by Inhibition of Neutrophils; IMAGES, Intravenous Magnesium Efficacy in Stroke; POST, Potassium channel Opener Stroke Trial.

Table I. *Neuroprotective agents tested in clinical trials.*

clinical trial design precluded replication of the positive results? As Grotta[5] suggests, do we need to do the "rat experiment" in man? In an attempt to address these issues, guidelines for assessing the adequacy of preclinical testing *(Table II)* and clinical trials have been elaborated.[6,7] The following points should be considered.

Drug dose	Generate dose-response curves in several species; assess likelihood of drug penetration of tissue at risk
Therapeutic time window	Assess carefully the time interval after the onset of ischemia or reperfusion when the drug can be successfully administered
Animal models	Study permanent and transient ischemia models initially in rats/mice, then possibly in cats or primates in a randomized and blinded fashion; results should be replicated by independent laboratories; consider influence of sex
Physiological monitoring	Monitor blood pressure, blood gases, hemoglobin, glucose, brain temperature, and cerebral blood flow for as long as possible
Outcome measures	Evaluate acute and long-term outcome (typically reduced infarct volume). Assess functional recovery in multiple animal species
Target populations	It is uncertain if benefit in young, healthy animals can be extrapolated to elderly, sick humans
Combination therapy	Consider using agents that affect multiple mechanisms of neuronal injury after ischemia, simultaneously or in succession (the "cocktail" approach)

Table II. *Recommendations for preclinical evaluation of neuroprotectants in experimental brain ischemia (STAIR, Stroke Therapy Academic Industry Roundtable).*[6]

Target population

In animal studies, most neuroprotectants are ineffective if started more than 2 to 4 hours after the onset of ischemia.[1,2] Hitherto, no clinical trial has yet included enough patients within that 4-hour window to reach any conclusions about efficacy. Moreover, future clinical trials should be more selective in targeting patients with a sufficient volume of "penumbra" as evidenced by magnetic resonance imaging (MRI) (perfusion-diffusion mismatch) or by perfusion computed tomography (CT).[8] If there is too little potentially salvageable brain tissue at the beginning of treatment, then neuroprotectants obviously do not have much to "protect!" Additionally, the efficacy of most neuroprotectants on white matter ischemia is largely unknown, whereas clinical trials commonly include patients without specifying lesion location. Therefore, if an agent does not protect against white matter ischemic injury, then patients with lacunae or subcortical white matter infarcts are not likely to benefit.

There is little reason to believe that a single neuroprotective agent will be as effective as intravenous (therapeutic gain of 11% to 13%) or intra-arterial (therapeutic gain of 15%) thrombolysis.[9,10] Nevertheless, typically, neuroprotective trials were powered for an unrealistic 10% to 12% absolute benefit. Using the most optimistic assumptions about treatment effect based on available data, one study[11] estimated that neuroprotection trials would require about 4000 total patients. However, enhancing the proportion of patients with tissue substrate for neuroprotection by applying the measures mentioned above could reduce sample size to 400 patients per treatment arm. Current trials are targeting smaller benefits: the Intravenous MAGnesium Efficacy in Stroke (IMAGES) trial seeks a 5.5% improvement in 2700 patients (though even that may be optimistic).[12]

Dose selection and optimal duration of administration

The difficulties encountered in assessing efficacy in phase 2 trials lead many researchers to suggest the maximum tolerated dose for efficacy trials.[5] However, if the dose-response relationship is nonlinear, eg, bell-shaped, high doses lead to a reduction in efficacy.[12] For this reason, the adaptive randomization design, first applied in cancer trials and currently in the ongoing Acute Stroke therapy by Inhibition of Neutrophils (ASTIN) trial (neutrophil inhibitory factor), seems particularly promising: a computer algorithm randomly allocates doses chosen to fall within a prespecified range of known safety; patient responses are reported back to the randomization computer, which will gradually "learn" which doses have apparent benefit and will decide on the most informative dose to employ at the next randomization opportunity.[9] The choice for the optimal duration of administration of the neuroprotective agent seems even more complicated since certain drugs may exert different or even opposite actions, depending on the timing of administration. For instance, gamma-aminobutyric acid (GABA) agonists may be neuroprotective in the hyperacute phase of brain ischemia, but may worsen outcome when administered subacutely. The phase of locally reduced flow, present in

100% of patients within 9 hours, drops to 30% within 4 days after stroke onset, but viable tissue may be demonstrated up to 48 hours.[13] Perhaps neuroprotection should be administered for several days or weeks after stroke, when the risk of recurrence is the highest.[14]

Pathophysiological homogeneity and choice of outcome measures

The problem of stroke heterogeneity has been considerably underestimated in clinical trial design.[11] Population heterogeneity alone may be sufficient to explain failure of neuroprotection trials, since, even in the largest trials, the sample size was inadequate to detect an effect size equivalent to that in trials with thrombolysis. It comes as no surprise that clinical efficacy has been difficult to demonstrate in underpowered trials where infarcts of all shapes, sizes, times, severities, and arterial territories, due to various vascular pathologies, have been lumped together. Instead of viewing ischemic stroke as a single disease entity, future trials should more appropriately target specific homogeneous stroke subtypes. We should keep in mind that the PROlyse in Acute Cerebral Thromboembolism II (PROACT II) trial, the only acute stroke trial that was designed to randomize patients with a single type of vascular lesion (middle cerebral artery [MCA] occlusion), thus simulating the "rat experiment," was positive with only a small sample size. Standardization of stroke severity is also of paramount importance. Patients with mild baseline deficits (National Institutes of Health Stroke Scale [NIHSS] scores <6 to 7) have a high rate of spontaneous improvement to normal or near-normal by 3 months. On the other hand, patients with severe strokes (NIHSS >20 to 22) are unlikely to have a full recovery. Therefore, the chances of detecting clinical efficacy would be increased by using low and high NIHSS cutoffs and ensuring that treatment groups are matched in distribution of NIHSS scores.[4,7]

Choosing the most appropriate end point and when it should be measured is crucial both for preclinical testing and clinical trials. Histological end points (typically infarct volume reduction) do not provide evidence on the functional status of neurons and are less predictive of long-term histology than early behavioral assessments. Therefore, both histological and functional measures of motor, sensory, or cognitive deficits should be evaluated at early and extended time points after ischemia to produce evidence of sustained neuroprotection of a drug. Certainly, mortality is an inappropriate end point for clinical neuroprotection trials. It is generally considered undesirable to reduce mortality at the expense of an increased proportion of patients with vegetative survival, but, more importantly, active treatment may involve a small "cost" in terms of mortality and yet may be considerably effective in survivors. In prior trials, measures of impairment (stroke recovery), disability (activity limitations), and handicap (participation restrictions) have been used. All three types of end points have advantages and disadvantages. For instance, if disability scales are used (Barthel index, modified Rankin scale), more patients will be considered recovered; instead, if impairment scales are used (NIHSS), fewer patients will be considered recovered.[4] Choosing how to define a positive outcome within a specific rating scale can also be crucial. With unselected populations showing a U-shaped distribution of Barthel outcomes, even a marked improvement across the board leads to few patients crossing any arbitrary boundary set in the range between 60 and 90 Barthel points.[9] Potential ways of avoiding reliance on a single outcome measure include use of a trichotomous instead of a dichotomous analysis (as in the recent Glycine Antagonist In Neuroprotection [GAIN] trials), use of the global statistic approach by performing simultaneous testing of treatment effect on various scales (as in the National Institutes of Neurological Diseases and Stroke—Tissue Plasminogen Activator Stroke Trial [NINDS-TPAST] with recombinant tissue plasminogen activator [rt-PA]), or use of variable outcome thresholds according to initial stroke severity.[7] In addition to clinical scoring scales, neuroimaging end points could be included among the outcome measures used in the global test. As the therapeutic efficacy of neuroprotectants will likely be inferior to that of reperfusion treatments, it may be documented only by using less strict criteria for recovery (eg, NIHSS <7 or Rankin score 0-2).

NONPHARMACOLOGIC (PHYSIOLOGIC) NEUROPROTECTION: ARE YOU HAVING A BRAIN ATTACK? JUST COOL DOWN!

It has been known for years that hypothermia reduces ischemic neuronal injury. Accidental hypothermia can protect a drowning victim from otherwise fatal hypoxic ischemic brain damage. Animal studies suggest that: (i) hypothermia is clearly effective not only in global, but also in focal ischemia; (ii) the earlier hypothermia is instituted, the better the neuroprotection; (iii) lower temperatures afford more neuroprotection; and (iv) the duration of hypothermia is critical, since neurons may die if hypothermia is aborted too soon.[15] The principle of neuroprotection after global brain is-

chemia was recently demonstrated in two trials of rapidly applied hypothermia in patients who had been resuscitated after cardiac arrest *(Table III).*[16,17] A small nonrandomized trial of patients with large cerebral infarctions showed that mild hypothermia with a brain temperature between 33°C and 35°C may be safe and reduce mortality rate in this group of patients.[18] Several methods of inducing hypothermia are currently being investigated in feasibility trials, such as external cooling devices and transvascular cooling methods. Phase 1 studies are under way. If hypothermia is to be a successful strategy in stroke patients, it will likely need to be initiated within 2 hours of stroke onset. Even then, hypothermia may still prove to be ineffective unless circulation is restored to the ischemic brain spontaneously or by reperfusion therapy. Concerning the latter, in preclinical studies it has been demonstrated that although the rate of clot dissolution with tissue plasminogen activator (t-PA) is slowed by hypothermia, the beneficial effect of tissue neuroprotection due to the cooling seems to outweigh any delay in clot dissolution, producing a net benefit.

Study	Method	Favorable outcome (OR, 95 CI)
N Engl J Med 2002;346:549-556[16]	N=77; 33°C <2 hours after the return of spontaneous circulation for 12 hours	5.25 (1.47-18.76), *P*=0.011
N Engl J Med 2002;346:557-563[17]	N=275; 32°C-34°C for 24 hours; median interval between restoration of circulation and initiation of cooling: 105 min	1.4 (1.08-1.81), *P*=0.009

Table III. *Studies of moderate hypothermia after cardiac arrest. CI, confidence interval; OR, odds ratio.*

NEUROPROTECTION WITH INSULIN

Like hypothermia, insulin has been more extensively studied in global than in focal ischemia. Hypoglycemia is not necessary for the neuroprotective effect of insulin in global ischemia, suggesting a direct effect of insulin. Studies in cats suggest that normoglycemia is optimal, implying a U-shaped dose-response curve.[15] We believe that a clinical neuroprotection trial of insulin should be undertaken in focal ischemic stroke.

OTHER PARAMETERS AFFECTING NEUROPROTECTION

In most trials, management of simple physiological variable such as blood pressure, blood sugar, and temperature is left entirely at the discretion of the physician. There is clear evidence that lowering the blood pressure may worsen the outcome after stroke: intravenous nimodipine administration was associated with worse outcome due to blood pressure reduction. While in preclinical studies physiologic variables are maintained at a constant level, the opposite seems to be the case for clinical neuroprotection trials. As the optimal approach to the management of these variables is not yet known, small variations of them could easily outweigh any potential neuroprotective effect of a drug.

THE FUTURE OF NEUROPROTECTION

We know from the laboratory that neuroprotectants are generally more effective if given to animals with reversible rather than permanent arterial occlusion. Questions remain concerning the effective level of a drug reaching the ischemic tissue if the artery supplying this territory is occluded. The feasibility and safety of IV rt-PA followed by the administration of clomethiazole or lubeluzole has been demonstrated.[5] While past approaches precluded prior treatment with thrombolysis, current trials such as Potassium channel Opener Stroke Trial (POST), IMAGES, and ASTIN allow thrombolysis according to local guidelines.

Neuroprotective agents with potential clinical interest include nitric oxide synthase (NOS) inhibitors, protease inhibitors (particularly calpain inhibitors), antiapoptotic agents, and neurotrophins. Aminoguanidine is a relatively selective inhibitor of inducible NOS, which appears to be safe and well tolerated in humans. Although excitotoxic necrosis is considered the main mechanism of ischemic cell death in most cases, apoptosis may occur in penumbral regions that escape excitotoxic death. Antiapoptotic agents as cycloheximide and caspase inhibitors have been effective in preclinical studies, and the therapeutic window for antiapoptotic therapy may be longer than that of most other neuroprotective agents. However, the importance of apoptosis in human stroke and the clinical relevance of antiapoptotic therapy are not yet known and merit further investigation. We now possess blood-brain barrier drug-targeting

Combination	Model of ischemia	Species	References
NMDA antagonist + caspase inhibitor	focal transient	mouse	*Br J Pharmacol.* 1998;124:756-62
NMDA antagonist + AMPA antagonist	hippocampal slice	rat	*Brain Res.* 1999;23:299-308
NMDA antagonist + NOS inhibitor	global	gerbil	*Eur J Pharmacol.* 1999;381:113-119
AMPA antagonist + NOS inhibitor	global	gerbil	*Eur J Pharmacol.* 1999;381:113-119
Tirilazad + $MgCl_2$	focal transient	rat	*Neurosurgery.* 1999;44:163-171
Caffeine + ethanol	focal transient	rat	*Neuropharmacology.* 2000;39:515-522
bFGF + caspase inhibitor	focal transient	mouse	*Br J Pharmacol.* 2001;133:345-350
Antioxidant + antioxidant	thromboembolic	rat	*Neurosci Lett.* 2002;321:100-104

Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate; bFGF, basic fibroblast growth factor; NOS, nitric oxide synthase; NMDA, *N*-methyl-D-aspartate.

Table IV. *Examples of successful combinations of neuroprotectants in experimental models of brain ischemia.*

technology, which will enable us to study in human stroke large-molecule drugs such as neurotrophins (eg, brain-derived neurotrophic factor, BNDF).[19]

Given the complexity of events in the ischemic cascade and the disappointing results from single-agent trials, effective neuroprotection may require rational multiple drug therapy that combines drugs targeting different mechanisms of ischemic cell damage.[20] The synergistic effect of a number of agents has been demonstrated in animal studies *(Table IV).* Currently, the concept of "drug cocktail" is that drugs would better be administered sequentially rather than as mixtures. The initial treatment might be a "clot buster" followed by a safe alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) or noncompetitive *N*-methly-D-aspartate (NMDA) antagonist or possibly even a sodium channel antagonist that would prevent further release of glutamate. The second treatment, to follow within a day or so, might be a free radical scavenger. The third one, after 72 to 96 hours, could be an anti-inflammatory or antiapoptotic agent. The final treatment could target the restoration of function of injured neurons (eg, neuroimmunophillins).

A recently emerged concept is that of prophylactic neuroprotection,[12,14] according to which a neuroprotective agent would be taken daily by high-risk individuals to limit ischemic damage, should a stroke occur, as well as to facilitate other interventions, such as thrombolytic therapy by prolonging the therapeutic window. Short-term prophylactic neuroprotection would be indicated, for instance, in patients undergoing coronary surgery, carotid endarterectomy, or techniques involving intravascular manipulation. Long-term prophylactic neuroprotection would be suitable for patients with multiple risk factors, elderly patients with chronic atrial fibrillation, or patients with transient ischemic attacks (TIAs) not eligible for carotid endarterectomy. Preliminary observations suggest that therapy with statins may remodel endothelium in a manner that may become clinically important in the face of a proximate ischemic insult.[21] This is mediated by the preservation of the endothelial NOS activity and putative anti-inflammatory and antioxidant properties. In preclinical studies, statins have been show to reduce brain infarct size in a cholesterol-independent manner. Further investigation of the role of statins in human neuroprotection is warranted.

Despite the plethora of negative neuroprotection trials, several agents have been extremely effective in animal models. It seems quite implausible that these preclinical data should not be translated to humans, given a potent agent, adequate drug levels in the ischemic brain, a "reasonable" time window, no significant side effects, and well-designed phase 3 trials.[22] Learning from our mistakes is wisdom that even lower forms of life possess. As Gorelick[23] states, "it is too early for the death knell for neuroprotectants to toll."

REFERENCES

1. Ginsberg MD.
Neuroprotection in brain ischemia: an update (part I).
Neuroscientist. 1995;1:95-103.

2. Ginsberg MD.
Neuroprotection in brain ischemia: an update (part II).
Neuroscientist. 1995;1:164-175.

3. Martinez-Vila E, Sieira PI.
Current status and perspectives of neuroprotection in ischemic stroke treatment.
Cerebrovasc Dis. 2001;11(suppl 1):60-70.

4. Gladstone DJ, Black SE, Hakim AM.
Toward wisdom from failure. Lessons from neuroprotective stroke trials and new therapeutic directions.
Stroke. 2002;33:2123-2136.

5. Grotta J.
Neuroprotection is unlikely to be effective in humans using current trial designs.
Stroke. 2001;33:306-307.

6. Stroke Therapy Academic Industry Roundtable (STAIR).
Recommendations for standards regarding preclinical neuroprotective and restorative drug development.
Stroke. 1999;30:2752-2758.

7. Stroke Therapy Academic Industry Roundtable III (STAIR-II).
Recommendations for clinical trial evaluation of acute stroke therapies.
Stroke. 2001;32:1598-1606.

8. Wintermark M, Reichhart M, Cuisenaire O, et al.
Comparison of admission perfusion computed tomography and qualitative diffusion- and perfusion-weighted magnetic resonance imaging in acute stroke patients.
Stroke. 2002;33:2025-2031.

9. Lees KR.
Neuroprotection is unlikely to be effective in humans using current trial designs: an opposing view.
Stroke. 2002;33:308-309.

10. Furlan AJ.
Acute stroke trials: strengthening the underpowered.
Stroke. 2002;33:1450-1451.

11. Muir KW.
Heterogeneity of stroke pathophysiology and neuroprotective clinical trial design.
Stroke. 2002;33:1545-1550.

12. Lees KR.
Advances in neuroprotection trials.
Eur Neurol. 2001;45:6-10.

13. Devuyst G, Bogousslavsky J.
Recent progress in drug treatment for acute ischemic stroke.
Cerebrovasc Dis. 2001;11(suppl 1):71-79.

14. Devuyst G, Bogousslavsky J.
Clinical trial update: neuroprotection against acute ischemic stroke.
Curr Opin Neurol. 1999;12:73-79.

15. Auer RN.
Non-pharmacologic (physiologic) neuroprotection in the treatment of brain ischemia.
Ann N Y Acad Sci. 2001;939:271-282.

16. The Hypothermia After Cardiac Arrest Study Group.
Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest.
N Engl J Med. 2002;346:549-556.

17. Bernard SA, Gray TW, Buist MD, et al.
Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.
N Engl J Med. 2002;346:557-563.

18. Schwab S, Schwartz S, Spranger M, Keller E, Bertram M, Hacke W.
Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction.
Stroke. 1998;29:2461-2466.

19. Pardridge WM.
Neuroprotection in stroke: is it time to consider large-molecule drugs?
Drug Discov Today. 2001;6:751-753.

20. Slikker W, Youdim M, Palmer GC, Hall E, Williams C, Trembly B.
The future of neuroprotection.
Ann N Y Acad Sci. 1999;890:529-533.

21. Vaughan CJ, Delanty N.
Neuroprotective properties of statins in cerebral ischemia and stroke.
Stroke. 1999;30:1969-1973.

22. Davis SM, Donnan GA.
Neuroprotection: establishing proof of concept in human stroke.
Stroke. 2002;33;309-310.

23. Gorelick PB.
Neuroprotection in acute ischemic stroke: a tale of for whom the bell tolls?
Lancet. 2000;355:1925-1926.

Surfing the Heart

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Cardiofind

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Cardiofind provides clinicians and basic scientists in the cardiovascular sciences a one-stop search engine for heart research by offering screened, rated links to a wide variety of topics, varying from professional organizations to libraries. The site is useful, in particular, for the database of meetings and of publications on cardiology. The "Home" subsection provides a quick list of the screened links.
The site Editors state that support for Cardiofind is indicated when and where appropriate.

SkillStat Learning Inc

http://www.skillstat.com

SkillStat provides dynamic learning tools for health care professionals.
The site was created by SkillStat Learning Inc, a company aspiring to become a leader in creating dynamic and effective on-line learning tools: the approach utilized is indeed strikingly different from the more conventional approaches to the concept of e-learning.
SkillStat Learning Inc outlines its ambitious project of developing, over the next few months, several multilingual and multimedia learning modules and interactive on-line simulators in acute cardiac intervention, as well as on-line games. A taste of the kind of "experience" SkillStat is developing is available in the form of a cardiac life support testing and assessment tool, an ECG simulator, and various games.
This site is an interesting experiment in the wide and heterogeneous field of e-learning, so far characterized by very classic teaching.

Heart and Metabolism

http://www.heartandmetabolism.org

This is a new web site dedicated to the on-line edition of the journal *Heart & Metabolism*.
Heart & Metabolism is a scientific journal provided by Servier as a medical service to specialists. It aims to increase cardiologists' awareness of the important role of cardiac metabolism and its alterations during ischemic conditions, both from a pathophysiological and clinical standpoint. Each issue of the journal focuses on a specific topic (eg, refractory angina; obesity; gene and cell therapy, etc), which is addressed by experts in the field.

- The Homepage features an introduction to the journal, indicating the aims and scope of the journal and its contents. There is also a link to Servier, the sponsor of the journal.
- The Editorial Board section provides the names of the chief editor (Frans Visser, Netherlands), of the editorial board, and of the publisher (with an e-mail link to the latter).
- The Latest Issue section, currently No. 17 (is self-explanatory!) In this section, as in the following, the abstracts of all articles cited in the journal's articles are provided in full, with a direct link to PubMed.
- The Back Issues section is a practical tool to find an article published on a specific topic. It provides access to No. 5 to 16. The first 4 issues, brought out by another publisher, are no longer available.
- The E-mail the Editor section enables readers to pose questions to the Editor-in-Chief in connection with a published article, and welcomes suggestions of new topics or specific articles.

All sites accessed March 1st, 2003

Dialogues Cardiovasc Med. 2003;8:35

Icons of Cardiology

Claude Bernard and experimental physiology

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Physiology at the beginning of the 19th century was dominated by *vitalistic* theories, which postulated that life is governed by mysterious, nonquantifiable "vital forces." In spite of the late 18th-century discovery of oxygen by Lavoisier, Priestly, and others, and of the essential role that oxygen plays in sustaining animal life, few efforts had been made to identify the laws that govern physiological behavior. Claude Bernard, a *determinist* who used the experimental method to identify and quantify physicochemical laws that operate in living animals, is generally viewed as one of the pioneers who built the foundation for modern physiology.

BIOGRAPHY

Claude Bernard was born in 1813, the son of a wine maker in Saint-Julien, in the Rhône region of France.[1-5] At age 18, while apprenticed to a pharmacist, he produced a comic play and began work on a historical tragedy. In 1834, he went to Paris to show the latter to the professor of French poetry at the Sorbonne and was advised that he would be better off studying medicine. He followed this advice and enrolled at the Sorbonne, where as a medical student he came under the influence of François Magendie, an innovative investigator who "brought physiology in France back to the experimental method in which it had been established in England by Harvey."[1] In 1841, Bernard's skill at dissection led to a collaboration with Magendie that ended with the latter's death in 1855. Bernard succeeded Magendie as professor of physiology at the Sorbonne, where he remained active in research until he died in 1878. Bernard's last studies included work on fermentation; his notes, which were published posthumously, included the statement that alcohol could be produced by a "soluble ferment outside of life" (cited by 3). This led to a controversy with Pasteur, who believed that only living organisms could carry out fermentation. The dispute was resolved in Bernard's favor in 1895, when a yeast extract was shown to produce alcohol and carbon dioxide from sugar.

Claude Bernard *(1813-1878).*

Reproduced from reference 2: *Heymans CJF, Folkow B. Vasomotor control and the regulation of blood pressure. In: Fishman AP, Richards DW, eds.* Circulation of the Blood: Men and Ideas. *New York, NY: Oxford University Press; 1964 (chap 7). Copyright © 1964, Alfred P. Fishman.*

EARLY DISCOVERIES

Working between 1846 and 1851 in a laboratory that Olmsted and Olmsted liken to a three-ring circus,[1] Claude Bernard showed that pancreatic secretions aid fat absorption from the gut, convert starch to sugar, and digest proteins. He also found that sugar is stored in the liver as glycogen and that curare, by preventing frog muscle from responding to motor nerve stimulation without inhibiting the response to direct stimulation, interferes with signal transmission from nerve to muscle. In 1851, Bernard made his major contribution to cardiology when he demonstrated the vasoconstrictor response to sympathetic stimulation.

Bernard observed that severing the cervical sympathetic nerves in the rabbit increases the temperature of the ipsilateral ear. Because of his earlier finding that stimulation of these nerves causes sugar to appear in the blood and urine, he had initially postulated that sympathetic activation would produce heat. For this reason, according to Walter Cannon, Bernard expected that:

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Dialogues Cardiovasc Med. 2003;8:36-38

> … the ear deprived of nerve impulses would be cooler than its mate on the other side. To his great surprise, it was considerably warmer. Without at first knowing the import of what he had done, he had disconnected the blood vessels of the ear from the nervous influences that normally hold them moderately contracted; thereupon [warm blood] was flushed through the expanded vessels in a faster flow and the ear temperature rose. Thus by accident appeared the first intimation that the passage of blood into different parts of the body is under the government of nerves—one of the most significant advances in our knowledge of the circulation since Harvey's proof… that the blood does indeed circulate in the vessels.[6]

Bernard confirmed the vasoconstrictor effect of sympathetic stimulation in 1858 when he showed that galvanic stimulation of the cut ends of the sympathetic nerves reduces venous outflow from the submaxillary salivary gland.[1]

DETERMINISM AND VITALISM

Claude Bernard was among the first of the determinists who believed that life is controlled by quantifiable physical and chemical laws. He wrote:

> It matters little whether or not we admit that [the force that governs life] differs essentially from the forces presiding over the phenomena of inorganic bodies, the vital phenomena which it governs must still be determinable; for the force would otherwise be blind and lawless, and that is impossible.[7]

He condemned those who "believe that the study of the phenomena of living matter can have no relation to study of the phenomena of inorganic matter," concluding:

> [vitalists] look on life as a mysterious supernatural influence which acts arbitrarily by freeing itself wholly from determinism… [These] vitalistic ideas, taken in the sense which we have just indicated, are just a kind of medical superstition, a belief in the supernatural [that] encourages ignorance and gives birth to a sort of unintentional quackery; that is to say, the belief in an inborn, indefinable science.[7]

Bernard's pioneering—and effective—use of the experimental method to identify laws that determined the behavior of living organisms helped lay the foundation of modern medicine. Writing in the latter quarter of the 19th century, he recognized that physiological laws could not "be wholly elucidated by the physicochemical phenomena known in inorganic nature"[7] that were known at the time; however, he insisted:

> …the sciences of life [are not set apart from the other sciences] by scientific method. Biology must borrow the experimental method of physicochemical sciences, but keep its special phenomena and its own laws [which are] immutable, and the phenomena governed by these laws are bound to the conditions on which they exist, by a necessary and absolute determinism.[7]

Bernard supported these arguments with data that, by describing the operation of natural forces, document the role of experiment in defining physiological laws.

THE MILIEU INTÉRIEUR

Claude Bernard's greatest intellectual contribution to physiology was his concept of the *milieu intérieur,* which he viewed as a highly regulated internal environment that surrounds the tissues of warm-blooded animals. In contrast to the "cosmic" *milieu extérieur* that is common to both inorganic and living bodies, and which is subject to wide variations (eg, in temperature and composition), the fixed internal environment essential to the *vie constante* is normally maintained by a number of physiological mechanisms. According to Bernard:

> The *vie constante,* where life manifests itself independently of the external environment [is] characterized by freedom and independence… Here life is never suspended, but flows steadily on apparently indifferent to alterations in its cosmic environment or changes in its material surroundings. Organs, structural mechanisms, and tissues all function uniformly… [Because] the *milieu intérieur* surrounding the organs, the tissues, and their elements never varies, atmospheric changes cannot penetrate beyond… we have an organism which has enclosed itself in a kind of a hothouse. The perpetual changes of external conditions cannot reach it; it is not subject to them, but is free and independent.[8]

Bernard's recognition of the highly regulated environment within the human body led to Walter Cannon's later concept of *homeostatic* mechanisms that maintain the constancy of the *milieu intérieur.*

HEALTH, DISEASE, AND THERAPY

Claude Bernard divided the medical sciences into three "basic parts": *physiology,* the phenomena of life in the normal state; *health,* the normal conditions of life; and *pathology,* diseases and their determining causes.[7] He viewed sickness and death as resulting from disturbances of the mechanisms that regulate the internal environment, while therapy uses medical agents to cure disease by reversing the pathological mechanisms caused by physiological abnormalities.

Bernard understood that he was working at a time when medicine was largely empirical. He noted that during his lifetime therapeutics advanced separately from physiology because "as neither of them was well established, they were not called upon to support each other in medical practice."[7] Understanding these limitations, Bernard was able to look forward to a time when medicine would become scientific, when "it must then be founded on physiology." He recognized that:

knowledge of pathological or abnormal conditions cannot be gained without previous knowledge of normal states [so that] the therapeutic action of abnormal agents, or medicines, on the organism cannot be scientifically understood without first studying the physiological action of the normal agents which maintain the phenomena of life.[7]

He concluded:

…scientific medicine can be established only by experimental means, ie, by direct and rigorous application of reasoning to the facts furnished us by observations and experiment. Considered in itself, the experimental method is nothing but reasoning by whose help we methodically submit our ideas to experience, the experience of facts.[7]

One can only imagine how Bernard, were he to be alive today, would be gratified to observe the dependence of modern cardiology not only on physiology and biochemistry, but also on molecular biology.

CONCLUSION

Claude Bernard's use of the experimental method to identify the physical and chemical processes responsible for life challenged the a priori reasoning of the vitalists who had previously dominated physiology. In this way, he provided the foundation for modern physiology. By emphasizing the data obtained from carefully conducted experiments, however, he did not deny the role of hypotheses and a fertile imagination, both of which he recognized as essential for scientific progress. Bernard used a simple analogy to contrast the roles of experiment and imagination:

Put off your imagination, as you take off your overcoat, when you enter the laboratory; but put it on again. as you do your overcoat, when you leave the laboratory. Before the experiment and between whiles, let your imagination wrap you round; put it right away from you during the experiment lest it hinder your powers of observation. (cited by 3 and 4).

REFERENCES

1. Olmsted JMD, Olmsted EH.

Claude Bernard and the Experimental Method in Medicine. New York, NY: Schuman; 1952.

---

2. Heymans CJF, Folkow B.

Vasomotor control and the regulation of blood pressure. In: Fishman AP, Richards DW, eds.

Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964(chap 7).

---

3. Major RH.

A History of Medicine. Springfield, Ill: Thomas; 1954.

---

4. Garrison FH.

An Introduction to the History of Medicine. Philadelphia, Pa: Saunders; 1929.

---

5. Mettler CC.

History of Medicine. Philadelphia, Pa: Blakiston; 1947.

---

6. Cannon WB.

The Way of an Investigator. New York, NY: Norton; 1945.

---

7. Bernard C.

An Introduction to the Study of Experimental Medicine. Greene HC, trans. New York, NY: Dover; 1957.

---

8. Bernard C.

Leçons sur les Phénomènes de la Vie Communs aux Animaux et aux Végétaux. (Citation translated by Fulton J. F.) Paris, France: Ballière; 1878.

Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias

S. MacMahon, R. Peto, J. Cutler, R. Collins, P. Sorlie, J. Neaton, R. Abbott, J. Godwin, A. Dyer, J. Stamler

Lancet. 1990;335:765-774

This is where the simple concept of "blood pressure (BP) levels" as a direct and continuous risk exposure, rather than the conventional "hypertension" versus "normotension" categorical disease-risk paradigm, was first, most powerfully, presented. Pooling data from several prospective cohort studies and using advanced meta-analysis techniques, MacMahon together with colleagues Peto, Collins, and others in Oxford showed a strongly positive and continuous association between the risk of stroke (and coronary artery disease) and usual levels of diastolic blood pressure (DBP). Moreover, they demonstrated that there was no detectable lower level of DBP below which the risk of stroke does not continue to decline. This highly cited landmark paper went on to form the basis of subsequent pivotal outcome clinical trials of BP-lowering therapies in various high-risk patient groups, including in the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) (see page 49), while further similar meta-analyses better clarified the effects of prolonged BP differences in specific population groups.

A major limitation of previous analyses of the association between vascular disease rates and BP had been the use of single baseline values, which are prone to bias, due in part to the measurement process itself and in part to random variation in an individual's usual level of BP. Such error underestimates the real association between usual (ie, long-term average) BP and disease. In correcting for "regression dilution bias," MacMahon et al showed that prolonged differences in usual DBP of 5, 7.5, and 10 mm Hg, were associated with at least a 34%, 46%, and 56% reduction in stroke incidence, respectively. These estimates were much larger than previously recognized, and emphasize the opportunities for reducing the burden of vascular disease from even modest BP-lowering strategies.

A controversial issue at this time related to how far BP levels should be lowered, and at what point lowering BP is no longer beneficial, and possibly even harmful. Much of the debate about a potential J-shaped rather than linear association of BP had been focused on coronary artery disease, but was also relevant to stroke. Proponents of the J-curve claimed that lowering BP too far would result in blood flow being compromised, leading to cardiac or cerebral ischemia. This paper showed no evidence of a lower threshold level below which DBP was no longer associated with lower stroke risk, and, conversely, there was no upper threshold level above which stroke risk increased much more rapidly.

The small numbers of events in the individual studies, and subsequent wide confidence intervals around the relative risk estimates in each of the categories of DBP, did not permit a reliable assessment the association of DBP and stroke, particularly at extreme levels of DBP. The increased power provided by the pooled analysis and subsequent narrow confidence intervals around the estimates allowed a reliable demonstration of an approximate, log-linear relation of mean usual DBP and stroke incidence. This finding of consistent proportional risk reductions associated with a given DBP reduction across all DBP levels was of enormous importance. Since most strokes, and other vascular events, occur in individuals who would usually be considered as having "normal BP levels," even modest reductions in BP from population-wide public health measures, such as salt reduction, could confer major absolute benefits on the incidence of disease. In addition, the concept is applicable to extending the benefits of BP-lowering treatment to a wide variety of high-risk patient groups defined on the basis of established vascular disease or diabetes.

1990

After 105 years of colonial rule, Namibia becomes independent, with Sam Nujoma as its first president; President Bush awards Jesse Owens the Congressional Gold Medal; and Lithuania declares it's independence

Probability of acute stroke: a risk profile from the Framingham Study

P. A. Wolf, R. B. D'Agostino, A. J. Belanger, W. B. Kannel

Stroke. 1991;22:312-318

Key modifiable risk factors for stroke have been identified in many epidemiological studies, but they have generally been assessed in terms of relative impact in order to understand the etiology of disease. In this analysis, using data from the Framingham study cohort, Wolf and colleagues clearly show that risk factors for disease should not be considered in isolation. They also provide a simple method of assessing stroke risk and the likely benefits of blood pressure–lowering treatment in different individuals.

The importance of a particular risk factor in an individual can be expressed in terms of relative risk (ie, the risk of occurrence of disease in a group of individuals exposed to the factor versus the incidence in individuals not exposed) and absolute risk (ie, the incidence of disease in those exposed to the risk factor minus the incidence in those not exposed). As shown in this paper, many risk factors are interrelated and the presence of more than one risk factor in an individual can have an additive effect on the overall risk of stroke. For example, the probability of stroke in a 70-year-old man or woman with isolated mild hypertension (defined herein as a systolic blood pressure greater than 160 mm Hg) is only slightly increased above the average annual risk of 1% to 2% at this age. However, in the presence of diabetes mellitus, cigarette smoking, associated symptomatic vascular disease, atrial fibrillation, and ECG changes, the annual stroke risk may increase upwards of eightfold to about 10%. Thus, while the proportional reduction in the incidence of stroke commensurate with the lowering of blood pressure is similar, whether treatment is undertaken in a 70-year-old with isolated hypertension or in another person of similar age, but with an associated sea of other vascular risk factors, the absolute reduction in the incidence of stroke is much greater in the latter individual because he or she has a much higher absolute risk of stroke.

The paper was intended to provide clinicians with a simple health risk appraisal function to help them identify persons at substantially increased overall risk relative to that for an individual of comparable age and sex, resulting from the interaction of multiple risk factors. Contrary to widely held opinion at the time, the paper also showed that elderly patients have potentially more to gain from antihypertensive therapy than younger patients. However, it was hoped that this appraisal function would facilitate better health care and the simultaneous modification of multiple risk factors. Unfortunately, many subsequent studies have shown that it is hard work for clinicians to modify unhealthy lifestyles in their patients, while many high-risk individuals who have the most to gain from therapy are undetected or undertreated. Even so, much effort has gone into extending this work, with several national and international organizations publishing blood pressure guidelines that incorporate simple color risk tables, and, more recently, computer software programs have been developed to work "in real time" during the doctor-patient consultation. All these simple quantitative vascular risk profiles and treatment guidelines aim to guide the physician and educate his or her patients to modify their risk factors.

1991

At the 63rd Academy Awards
"Dance with Wolves" wins the Oscar for
Best Film; Latvia and Estonia vote to
become independent from the USSR; and
Leo Fender, inventor of the Fender guitar, dies

A population-based study of dementia in 85-year-olds

I. Skoog, L. Nilsson, B. Palmertz, L. A. Andreasson, A. Svanborg

N Engl J Med. 1993;328:153-158

Dementia is a clinical syndrome characterized by global impairment of cognitive functioning of sufficient severity to result in the loss of previously acquired skills, leading to the disturbance of physical and social function, often with abnormal behavior. As an aged-related chronic disease with significant burdensome effects on patients, family carers, and health services, the aging of populations worldwide is further intensifying the impact of dementia on societies. At the time of this publication, few population-based studies had examined the prevalence of dementia, and of its subtypes, particularly in the very elderly (ie, those aged ≥85 years), who are the fastest-growing segment of the population in developed countries. Such epidemiological information is essential for the planning of services, both in size and scope, and for elucidating age-specific risk factors for the condition.

Population-based studies of dementia are complex undertakings, as exemplified in this study, which involved a representative sample of 494, or approximately 60%, of all residents aged 85 years of Gothenberg, Sweden. People were invited to participate in a 3-stage diagnostic assessment process that involved an initial visit by a nurse in their own home followed by attendance at two sequential outpatient clinics. The first clinic visit with a geriatrician included a neuropsychological evaluation and other tests, while the other visit was with a psychiatrist who characterized the clinical features, potential etiological factors, and the results of a computed tomography (CT) head scan, to derive a final diagnosis.

An insidious onset and a progressive decline of symptoms has been regarded as the hallmark of Alzheimer's disease (AD), as compared with vascular dementia (VaD) in which there is more likely to be an abrupt deterioration in cognitive function, or a fluctuating, stepwise progression of cognitive deficits. In order to facilitate research, several standardized diagnostic criteria for AD, VaD, and other subtypes of dementia, have been developed and tested, but, unfortunately, the criteria for each overlap, and there is still no general consensus on which is the most appropriate to use, particularly within a population-based setting. In this study, "probable VaD" and "mixed dementia" were diagnosed on the basis of a history of acute focal neurological symptoms and signs without any clear temporal connection with the evolution of the dementia syndrome over at least several months. Combining these diagnostic groups in the analyses may have led to an over-reporting of the frequency of vascular dementia.

1993

The 12-member European Economic Community sets up a vast free-trade zone; Czechoslovakia splits into the Czech Republic and Slovakia; and Van Morrison, The Doors, Cream, and Creedence Clearwater Revival are inducted into the Rock and Roll hall of fame

Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial

F. Forette, M. L. Seux, J. A. Staessen, L. Thijs, W. H. Birkenhager, M. R. Babarskiene, S. Babeanu, A. Bossini, B. Gil-Extremera, X. Girerd, T. Laks, E. Lilov, V. Moisseyev, J. Tuomilehto, H. Vanhanen, J. Webster, Y. Yodfat, R. Fagard

Lancet. 1998;352:1347-1351

For most of last century, Alzheimer's disease (AD) was considered to be the main cause of dementia and it had a distinct clinical and neuropathological profile. In the 1990s, though, converging lines of evidence from basic science and epidemiological studies shifted thinking towards cerebrovascular disease and vascular risk factors, in particular hypertension, as being of key importance in triggering the onset, or influencing the progression of dementia, both AD and vascular dementia (VaD). The Systolic Hypertension in Elderly in Europe (Syst-Eur) trial, undertaken to investigate the effects of antihypertensive therapy with a calcium antagonist (nitrendipine) in over 3000 elderly patients with isolated systolic hypertension, included a substudy to test the hypothesis that this treatment could also prevent the onset of dementia. Considerable excitement was understandably generated by this primary publication of the substudy results, showing that the treatment reduced the risk of dementia by a large 50%, and that the majority of dementia cases prevented were of the AD type rather than being due to VaD.

Closer examination of the paper, however, reveals a number of methodological irregularities in the substudy, which call into question the reliability of the data and some of the conclusions that were drawn. To begin with, the substudy was grossly underpowered to test the prespecified hypothesis of a 30% reduction in the incidence of dementia from treatment, as the required length of follow-up was not achieved. This was due to the trial being stopped early (mean follow-up 1.2 years) because of clear evidence of benefit on the primary vascular end point. Consequently, the confidence interval around the point estimate of the treatment effect was wide, ranging from no effect to a massive 70% reduction in incidence of dementia. Moreover, given that these estimates were made on only 30 dementia end points, it is really not possible to draw any reliable inference regarding the differential effect of treatment on the subtypes of dementia.

Another factor of concern was that the analyses were not intention-to-treat, as several hundred randomized patients were excluded because they failed to complete an assessment for dementia at the first annual follow-up visit due to the early termination of the trial. Furthermore, the lack of an effect on the Mini-Mental State Examination (MMSE), an accepted brief measure of cognitive ability that yields a continuous score from 0 to 30, is confusing. Although the MMSE covers only a narrow domain of cognitive functions and is confounded by physical impairments, education, and language ability, there is a considerable body of evidence to confirm its reliability and validity as a measure of cognitive impairment and as a screening tool for the detection of dementia. Given the large effect of treatment on dementia, it is surprising that there was no corresponding differential decline in MMSE scores between the groups. Of course, this could be explained by the insensitivity of the MMSE for detecting mild cognitive impairment, and the highly skewed distribution of scores towards the higher level of functioning in this population.

Despite these concerns, though, the Syst-Eur trial was an important study that adds strength to the argument about the potential for the prevention of dementia through the modification of vascular risk factors, and supports the need to include cognitive measures in cardiovascular trials, as has been the case in subsequent trials including the Study of COgnition and Prognosis in the Elderly (SCOPE) and the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) (see page 49).

1998

Former Chilean dictator Pinochet is arrested in London pending an extradition order to Spain to face charges on murder and torture; death at the age of 68 of British Poet Laurate Ted Hughes; and 60 teenagers are killed in a disco fire in Gothenburg, Sweden

Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group

L. Hansson, A. Zanchetti, S. G. Carruthers, B. Dahlof, D. Elmfeldt, S. Julius, J. Menard, K. H. Rahn, H. Wedel, S. Westerling

Lancet. 1998;351:1755-1762

The HOT trial was an ambitious study designed to investigate the optimal target diastolic blood pressure (DBP) level and the potential benefit of low-dose aspirin in older patients with hypertension. While it is well established that antihypertensive treatment can reduce the incidence of the various manifestations of cardiovascular disease, many patients on treatment remain at high risk, due in part to inadequate control of blood pressure, but also potentially due to an increase in risk at low levels of blood pressure. In addition, there was continued uncertainty about the balance of benefit and risk of aspirin in patients at "intermediate risk" of vascular disease, such as in those with isolated hypertension.

Overall, nearly 20 000 patients (mean age 61.5 years; range 50 to 80 years) with hypertension and DBP levels of between 100 and 115 mm Hg, from 26 countries, were randomly assigned to one of three target BP levels (≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg) and low-dose, 75-mg daily aspirin or placebo. Open label antihypertensive therapy with the long-acting calcium antagonist felodipine 5 mg daily was given to all patients, and clinicians were provided with the option of using a stepwise incremental therapy schedule to reduce BP to within the target range. The trial was well designed and had a high level of follow-up and a high number of outcome events.

Unfortunately, while the reduction in BP achieved was large in all three groups, in which a high proportion of patients achieved their BP targets, the small differences in BP levels and the lower than expected event rates across the three target groups did not produce significant differences in the effects of treatment, except on myocardial infarction. Although there did not appear to be any additional benefit of treatment at lower BP levels, the confidence intervals were wide around the point estimates for event rates associated with the extremes of BP levels. In addition, though, there was no clear evidence of a J-shaped curve in relation to major vascular events with the achieved BP reductions, including the subgroup of 3000 patients with evidence of coronary artery disease at randomization.

An important unexpected finding was that BP-lowering therapy seemed particularly beneficial in the 1500 patients with diabetes mellitus at randomization. While all patients with diabetes in each of the three groups showed a reduction in cardiovascular event rates, the greatest benefit was seen in the ≤80 mm Hg group. Stroke rates, for example, were 30% lower in the ≤80 mm Hg group compared with the ≤90 mm Hg group. These results must be interpreted with caution, however, as they were derived from a post-hoc subgroup analysis, with small numbers of events and wide confidence intervals.

The effect of aspirin as a primary prevention strategy in patients with hypertension had not been previously investigated, and there was concern that the potential benefits could be offset by an increased risk of intracerebral hemorrhage in such patients. The Hypertension Optimal Treatment (HOT) trial showed that the relative benefit of aspirin in the prevention of myocardial infarction of 36% (confidence interval 15% to 51%) was similar to that seen in high-risk patients, such as those with coronary artery disease. Moreover, the benefit was achieved with no substantial increase in the risk of stroke.

1998

Terry Nichols is sentenced to life imprisonment for his involvement in the Oklahoma City bombing in which 168 died;
Chinese paleontologists discover the fossils of two feathered dinosaurs, supporting the theory that birds evolved from dinosaurs; and
Japan, the world's second largest economy, is officially in recession

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)

UK Prospective Diabetes Study (UKPDS) Group

Lancet. 1998;352:837-853

It is well recognized that patients with diabetes mellitus are at high risk of cardiovascular disease including stroke, as well as retinopathy and renal failure. While tight control of blood glucose levels has been shown to decrease the progression of microvascular disease, less certain are the benefits of such treatment on the prevention of macrovascular complications, which are the main cause of morbidity and mortality in patients with diabetes mellitus. The United Kingdom Prospective Diabetes Study (UKPDS) is an amazing study, since it was based on a large primary care–based inception cohort of nearly 4000 patients, who as well as undergoing extensive investigations had been followed up intensively and rigorously since the mid-1970s. The study was designed to establish whether, in patients with type 2 diabetes, intensive blood glucose control can reduce the incidence of macrovascular or microvascular complications, and whether any particular therapy was more advantageous than another.

This paper shows, as most clinicians and patients well realize, that even with the best of efforts, intensive therapy results in only modest reductions in blood glucose levels over conventional therapy (0.9% absolute and 11% relative difference in HbA_{1c} levels between intensive [7.0%] and conventional [7.9%] groups). Moreover, the best control of blood glucose levels is achieved in the few years of initiating such treatment. Despite these limitations, though, intensive therapy translated into a substantial 25% reduction in the risk of microvascular end points, most of which was due to the prevention of retinopathy as evident by fewer patients requiring photocoagulation in the study. Unfortunately, the study did not have sufficient power for the observed trends of reduced macrovascular end points, in particular the 16% reduction in the incidence of myocardial infarction, to reach the standard level of significance. Yet, these results do allay previous concerns about the sulfonylureas and/or insulin therapy and an increased risk of cardiovascular events due to the promotion of atheroma. Unfortunately, the benefits of intensive blood glucose control are not without a price, the most obvious of which are weight gain and an increase in hypoglycemic episodes. One assumes that these effects translate into reduced quality of life, lower self-esteem, and impaired work capacity for patients. It also means that the benefits of intensive blood glucose control may be offset by adverse effects on an individual's vascular risk factor profile, including an elevation of blood pressure levels and alterations in lipids.

Given the multiple challenges faced by patients and their families in achieving ideal blood glucose control from intensive therapy, together with the lack of definitive evidence for these observations to indicate that reductions in microvascular disease translate into the prevention of macrovascular disease, a more practical, acceptable, and cost-effective strategy to improve long-term outcome in patients with diabetes mellitus is probably the modification of vascular risk factors, in particularly blood pressure–lowering therapy. Additional observational data from the UKPDS and other studies suggest that improved blood pressure control can reduce the risk of cardiovascular disease in patients with diabetes, but definitive end point data subsequently became available from recent trials, such as the Heart Outcomes Prevention Evaluation (HOPE) study.

1998

Mark McGwire of the St Louis Cardinals
hits his 62nd home run of the baseball season
to break the all-time record;
Iran lifts the fatwa against Salman Rushdie,
author of the "Satanic Verses";
and German chancellor Helmut Kohl is defeated
by Gerhard Schröder in the German elections

Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations

G. J. Hankey, C. P. Warlow

Lancet. 1999;354:1457-1463

In this paper, which was based on his talk at the first Lancet Forum on Stroke, Hankey, together with his mentor and the doyen of evidence-based stroke medicine, Warlow, provides an overview of the effectiveness and costs of strategies for the various stroke management strategies available at the end of the 1990s. Although the costing analyses used were rather crude, the standardized approach and extrapolation of the estimates to a large, albeit urban Western population, and use of the major measures of effect—relative risk reduction (RRR), absolute risk reduction (ARR), and number-needed-to-treat (NNT)—provide a comprehensive and balanced comparison of strategies.

Arguably the single most important therapeutic advance in stroke treatment was the availability of strong evidence from pooled clinical trial data showing that well-coordinated multidisciplinary inpatient stroke unit care can significantly improve the likelihood of returning home and retaining independence after stroke. Compared with conventional care in a general medical ward, stroke units are associated with an RRR of 9% and an ARR of 5.6%. Thus, the NNT in a stroke unit to prevent one patient from dying or becoming dependent is an impressive 18. In fact, of all the treatments available for stroke patients, stroke units seem to be associated with the greatest absolute benefit, as the benefits of stroke unit care apply across all subgroups of patients, including those who are old, severely disabled, or admitted late to hospital.

Another major therapeutic advance is the use of thrombolytic therapy for acute ischemic stroke. In 1996, the United States Food and Drug Adminstration (FDA) approved the use of intravenous recombinant tissue plasminogen activator (rt-PA) in selected patients with acute ischemic stroke, provided treatment can be given within 3 hours of the onset of symptoms. The approval was based largely on the results of two combined, National Institute of Neurologic Disease and Stroke (NINDS) acute stroke studies, where all patients were treated within 3 hours, and showed an overall benefit of therapy despite a risk of intracerebral hemorrhage of about 5%. Although subsequent individual trials of rt-PA (and streptokinase) with time windows extending beyond 3 hours after the onset of stroke have failed to show a definite positive benefit, Hankey and Warlow went on to estimate that use of thrombolysis with a 6-hour time window from stroke onset results in a 10% RRR in death or disability from stroke, and the benefits (NNT of 63 patients per 1000 avoiding "death or long-term dependence") are several times greater than for aspirin, but only applicable to about 10% of all patients with stroke in the population.

Apart from rt-PA, the only other proven effective treatment is aspirin 300 mg, administered within the first 48 hours after the onset of ischemic stroke, shown to reduce the ARR of death or dependency at 6 months by 1.2%, mainly by reducing early recurrent ischemic stroke.

Therapies of proven benefit in the prevention of stroke include blood pressure–lowering therapy, antiplatelet therapy, cholesterol-lowering therapy, anticoagulation, and carotid endarterectomy. The absolute benefits of these interventions appear to be greater in subjects in whom the absolute risk is particularly high, notably older people and those with existing vascular disease. Among these strategies, blood pressure reduction appears to be the most cost-effective strategy, resulting in the largest number of strokes avoided in the target population for a modest cost.

1999

The Pakistani government is overthrown
in the midst of economic strife and intensified
fighting with India over Kashmir,
and General Pervez Musharraf takes control;
the medical charity "Médecins sans Frontières"
wins the Nobel Peace Prize; and
France defeats New Zealand 43-31 to win
the semifinal in the rugby World Cup

Which targets are relevant for therapy of acute ischemic stroke?

W. D. Heiss, A. Thiel, M. Grond, R. Graf

Stroke. 1999;30:1486-1489

With the advent of modern neuroimaging (ie, computed tomography [CT] and magnetic resonance imaging [MRI]), clinicians were able to confirm the bedside diagnosis of stroke, differentiate accurately cerebral hemorrhage from infarction, and identify cerebral lesions for stroke syndromes in life. Functional neuroimaging extends this ability by providing researchers with an understanding of the pathophysiological process underlying cerebral infarction that follows acute focal ischemia due mainly to occlusion of cerebral arterial blood vessels. The work of Heiss and colleagues, using positron emission tomography (PET), was instrumental in advancing knowledge in this area. In this paper, they characterize the different processes underlying acute cerebral ischemia and provide a basis for estimating the opportunities for benefit offered by the different treatment approaches.

Ten patients with acute hemisphere stroke were studied, initially with PET within 3 hours of the onset of symptoms, and then with MRI a few weeks later. By comparing the patterns of cerebral blood flow and metabolism on PET with the size of the matured infarcts shown on MRI, three distinct areas of cerebral ischemia were identified: a dense necrotic core of primary neuronal death; a surrounding area of reversible ischemia, known as the "penumbra"; and an outer area of tissue without major ischemia. Although there was considerable variation in the size of the infarcts among the individuals, the largest area (51% to 92% of final infarcts) was the core, followed by the penumbra (8% to 34%), while the outer area of sufficient perfusion was quite small (2% to 25%). They concluded that the final cerebral infarct is caused mainly by the initial severe ischemia, while evolution of ischemia within the penumbra either occurs very rapidly or has only a minor role in determining final outcome. The authors go on to suggest that the findings explain why neuroprotective drugs to date have failed as a treatment for acute stroke.

The seminal finding from research in the last decade is recognition of the ischemic penumbra, which has focussed attention on therapies to minimize, or even reverse, the damaging effects of cerebral ischemia, provided treatment can be initiated within a short time period from onset. This "therapeutic window" may be divided into two partly overlapping components: the "reperfusion window" related to the restoration of blood flow, and the "neuroprotective window" related to the cascade of biochemical, programmed cell death and other damaging effects that occur in neurons within the penumbra. Clinical trials have shown that the reperfusion window is very short, perhaps only a few hours, whereas the neuroprotective time window may extend up to 48 hours and beyond. Unfortunately, the success of various neuroprotective agents in animals has not been replicated in man. There are many potential explanations for this, including the appropriateness of animal models of human brain ischemia, the dose and speed of delivery of agents, and inadequate sample size, outcome measures and other design issues of trials.

While an effective neuroprotective agent for acute stroke has yet to be identified, considerable progress has been made in thrombolytic therapy, which aims to restore blood flow to prevent or lessen the spreading ischemia within the penumbra. However, as outlined by Hankey and Warlow (see previous summary), thrombolysis is only applicable to a very small proportion of all stroke patients in the community. Thus, the best approach to reducing the burden of stroke is through effective prevention strategies.

1999

The women's US soccer team defeats China to win the World Cup; John F. Kennedy Jr and his wife Carolyn Bessette Kennedy are killed in plane crash off the coast of Martha's Vineyard; and US cyclist Lance Armstrong wins the Tour de France after overcoming cancer

Effects of ACE inhibitors, calcium antagonists, and other blood-pressure–lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration

B. Neal, S. MacMahon, N. Chapman, for the Blood Pressure Lowering Treatment Trialists' Collaboration

Lancet. 2000;356:1955-1964

Systematic reviews, with their strict and explicit methods for identifying, selecting, and synthesizing data, reduce bias (error) and improve the reliability of the conclusions drawn about the effectiveness of therapies and of the recommendations for practice that may follow. Thus, systematic reviews including meta-analyses are now well accepted as a fundamental activity of epidemiological research and the backbone of evidence-based health care.

A large number of individual blood pressure (BP)-lowering trials, mainly of diuretics and/or β-blockers compared with placebo undertaken up to the mid-1990s have established beyond doubt the benefits of such therapy, albeit in mainly middle-aged or older people with hypertension. Moreover, subsequent meta-analyses of these trials have demonstrated that BP reductions of about 10 to 12 mm Hg systolic and 5 to 6 mm Hg diastolic are associated with relative reductions in stroke risk of 30% to 40%, and of coronary artery disease of about 15%. However, there have been few direct comparisons of newer agents, such as angiotensin-converting enzyme (ACE) inhibitors or calcium antagonists, against these older drugs, or evaluations of therapy in other high-risk patient groups, on different vascular-specific outcomes, and across different levels of BP, to allow firm conclusions to be draw to guide therapy.

The program of prospective systematic overviews of randomized trials that are being undertaken by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC), chaired by MacMahon, includes investigations of the effects of different classes of BP-lowering agents on mortality and major cardiovascular morbidity in different patient populations. In this, the first of the analyses, ACE inhibitors were shown to decrease the risks of stroke, coronary artery disease, and major cardiovascular events by 20% to 30% in various high-risk patient groups (eg, history of cardiovascular disease or diabetes) in association with only modest reductions in BP. Moreover, the benefits of treatment were consistent for patients with and without a history of hypertension. The calcium antagonists, on the other hand, showed reductions in the risks of stroke and major cardiovascular events by about 30% to 40%, but there was no clear evidence of reductions in the risks of coronary artery disease or heart failure, despite most of the trials being undertaken in patients with hypertension.

The overviews that compared the effects of more intensive and less intensive BP-lowering therapies provided some evidence of potentially important differences between treatment regimens of differing intensity, and confirm the results of observational studies indicating greater benefits conferred from greater reductions in BP throughout the range of BP levels. The overviews comparing different classes of BP therapies suggest that there may be modest, but potentially important differences among the different drug classes in their effects on cause-specific outcomes. For example, the results of the overview comparing calcium antagonists with diuretics or β-blockers suggest a lower risk of stroke, but a greater risk of coronary artery disease with calcium antagonists.

Although considerable efforts were made to reduce random error and other bias in these data, the small number of events in some of the analyses and the problem of nonadherence to therapy in many long-term studies made it difficult to draw reliable conclusions on the cause-specific effects of different classes of BP-lowering agents. Resolution of these uncertainties is likely to be forthcoming from subsequent overviews with even more published randomized trials by the BPLTTC.

2000

Israeli Prime Minister Ehud Barak's resigns to force an early election; Serbs elect Zoran Djindjic as their new prime minister, sweeping away last remnants of Slobodan Milosevic's regime; and Ethiopia and Eritrea sign a peace deal ending their border war

Randomised trial of a perindopril-based blood-pressure–lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack

PROGRESS Collaborative Group

Lancet. 2001;358:1033-1041

In providing an overview of this important paper, the reviewer first wishes to declare his link to the study as a member of the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) Management Committee. While this may suggest a certain degree of bias in favor of the results, it also means that he has had to think carefully about their significance and applicability.

In the early 1990s, it was well established that stroke risk is strongly and continuously related to the usual level of both SBP and DBP. The relationship holds true for both primary and secondary stroke, and for the main subtypes, ischemic and hemorrhagic stroke. While antihypertensive trials have demonstrated unequivocal benefits with regard to cardiovascular morbidity and mortality, with decreases of 10 to 12 mm Hg in SBP and 5 to 6 mm Hg in DBP being associated with a reduction of approximately 35% to 40% in the incidence of primary stroke, trials of BP-lowering therapy in patients with preexisting cerebrovascular disease had not been able to demonstrate clear reductions in the incidence of secondary stroke. This lack of direct evidence, together with concerns about the potential hazards of such therapy worsening brain ischemia and/or precipitating stroke, has meant that the approach to BP lowering among neurologists and other clinicians involved in the care of stroke patients has been particularly conservative, with far greater attention being focused on antithrombotic therapy and carotid endarterectomy for the secondary prevention of stroke and other vascular events. PROGRESS now resolves much of the uncertainty of BP-lowering therapy in patients with a history of cerebrovascular disease, particularly in those with normal or lower BP levels.

PROGRESS was a meticulously designed and organized multicenter trial, undertaken independently of the industry sponsor, in over 6100 individuals from 172 collaborating centers in 10 countries from 1995 to 2001. The aim was to determine the balance of benefits and risks of perindopril (an angiotensin-converting enzyme [ACE] inhibitor) with or without the diuretic indapamide on recurrent stroke in patients with a history of stroke or transient ischemic attack (TIA). Importantly, there were no prespecified blood pressure entry criteria, with the inclusion of both "hypertensive" and "nonhypertensive" patients. The study shows that the treatment reduced the incidence of stroke, major coronary events, and major vascular events by 28%, 26%, and 26%, respectively. These benefits were associated with an average reduction in SBP/DBP of 9/4 mm Hg. Active treatment also reduced the incidence of ischemic stroke by approximately one quarter and hemorrhagic stroke by one half, and was equally effective in important patient subgroups, Asian and non-Asian, old and young, across different stroke subtypes, and in patients with and without hypertension. The benefits were even greater among patients treated with the combination of perindopril and indapamide (in whom BP was lowered by a mean of 12/5 mm Hg), which reduced the risk of stroke by 43%, major coronary events by 35%, and major vascular events by 40%.

The results indicate that treatment with the combination therapy for 5 years equates to the avoidance of 1 fatal or major nonfatal vascular event among every 11 patients assigned to active treatment. Moreover, the absolute benefits of such treatment may be even greater in Asian populations where there is a higher incidence of hemorrhagic stroke and steeper stroke risk and BP associations. Taken together with the results of other trials, including the Heart Outcomes Prevention Evaluation (HOPE) trial of ramipril in patients with mainly coronary artery disease, PROGRESS confirms the benefits, safety, and tolerability of ACE inhibitor–based therapy in a broad range of high-risk patient groups, irrespective of initial levels of BP levels.

2001

Violinist Isaac Stern dies at 81; pioneering heart surgeon Christiaan Barnard dies aged 78; and Hijackers crash jetliners into the Twin Towers of the New York World Trade Center and the Pentagon, causing thousands of casualties

Stroke

Bibliography of One Hundred Key Papers

selected by **Giuseppe Mancia, MD and Guido Grassi, MD**
Clinica Medica – Ospedale S. Gerardo – Monza (Milano) - ITALY

Algra A, van Gijn J.
Aspirin at any dose above 30 mg offers only modest protection after cerebral ischaemia.
J Neurol Neurosurg Psychiatry. 1996;60:197-199.

ALLHAT Collaborative Research Group.
Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone.
JAMA. 2000;283:1967-1975.

Alter M, Sobal E, McCoy R, et al.
Stroke in the Lehigh Valley: risk factors for recurrent stroke.
Neurology. 1987;37:503-507.

American Heart Association.
AHA Practice guidelines for the use of imaging in transient ischaemic attacks and acute stroke.
Stroke. 1997;28:1480-1497.

Antiplatelet Trialists' Collaboration.
Secondary prevention of vascular disease by prolonged antiplatelet tretment.
BMJ. 1988;296:320-331.

Bamford J, Sandercock P, Dennis M, et al.
A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project—1981-1986: methodology, demography and incident cases of first-ever stroke.
J Neurol Neurosurg Psychiatry. 1988;51:1373-1380.

Barnett H, Taylor D, Eliasziw H, et al.
Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis.
N Engl J Med. 1998;339:1415-1425.

Blauw GJ, Lagaay AM, Smelt AH, et al.
Stroke, statins and cholesterol: a meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors.
Stroke. 1997;28:946-950.

Blood Pressure Lowering Treatment Trialists' Collaboration.
Effects of ACE-inhibitors, calcium antagonists and other blood-pressure-lowering drugs: results of prospectively designed overview of randomized trials.
Lancet. 2000;356:1955-1964.

Bonita R.
Epidemiology of stroke
Lancet. 1992;339:342-344.

Borhani NO, Mercuri M, Borhani PA, et al.
Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial.
JAMA. 1996;276:785-791.

Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE.

Common carotid intima-media thickness and risk of stroke and myocardial infarction—the Rotterdam study.
Circulation. 1997;96:1432-1437.

Brott T, Bogousslavsky J.

Treatment of acute ischaemic stroke.
N Engl J Med. 2000;343:710-722.

Burn J, Tennis M, Banford J, Sandercock P, Wade D, Warlow C.

Long-term risk of recurrent stroke after a first-ever stroke: the Oxfordshire Community Stroke Project.
Stroke. 1994;25:1605-1610.

CAPRIE Steering Committee.

A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE).
Lancet. 1996;348:1329-1339.

Collins R, MacMahon S.

Blood pressure, antihypertensive drug treatment and risk of stroke and of coronary heart disease.
Br Med Bull. 1994;50:272-298.

Dahlof B, Devereux RB, Kjeldsen SE, et al.

Cardiovascular morbidity and mortality in the Losartan Intervention For the Endpoint reduction in hypertension study (LIFE).
Lancet. 2002;359:995-1003.

Diener HC, Cunha L, Forbes C, Silvenius J, Smets P, Lowenthal A.

European Stroke Prevention study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke.
J Neurol Sci. 1996;143:1-13.

Estacio RO, Jeffers BW, Hiatt WR, et al.

The effects of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non–insulin dependent diabetes and hypertension.
N Engl J Med. 1998;338:645-652.

European Carotid Surgery Trialists' Collaborative Group.

Randomized trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST).
Lancet. 1998;351:1379-1387.

Forette F, Seux ML, Staessen JA, et al.

Prevention of dementia in randomized double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) Trial.
Lancet. 1998;352:1347-1351.

Gent M, Blakely JA, Easton JD, et al.

The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke.
Lancet. 1989;1:1215-1220.

Gillum LA, Mamidipudi SK, Johnston SC.

Ischaemic stroke risk with oral contraceptives: a meta-analysis.
JAMA. 2000;284:72-78.

Goldstein LB, Adams R, Becker K, et al.

Primary prevention of ischaemic stroke.
Stroke. 2001;32:280-299.

Golledge J, Greenhalgh RM, Davies AH.

The symptomatic carotid plaque.
Stroke. 2000;31:774-781.

Gueyffier F, Boissel JP, Boutitie F, et al.

Effect of antihypertensive treatment in patients having already suffered from stroke. Gathering the evidence.
Stroke. 1997;28:2557-2562.

Guidelines Subcommittee 1999 World Health Organization / International Society of Hypertension.

Guidelines for the management of hypertension.
J Hypertens. 1999;17:151-183.

Hacke W, Kaste M, Fieschi C, et al, for the ECASS Study Group.

Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS).
JAMA. 1995;274:1017-1025.

Hademenos GJ, Massoud TF.

Biophysical mechanisms of stroke.
Stroke. 1997;28:2067-2077.

Hankey GJ, Warlow CP.

Treatment and secondary prevention of stroke: evidence, costs and effects on individual populations.
Lancet. 1999;354:1457-1463.

Hansson L, Zanchetti A, Carruthers SG, et al.

Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial.
Lancet. 1998;351:1755-1762.

Hass WK, Easton JD, Adams HP, et al.

A randomized trial comparing ticlopidine hydrocloride with aspirin for the prevention of stroke in high-risk patients: Ticlopidine Aspirin Stroke Study Group.
N Engl J Med. 1989;321:501-507.

Heart Outcomes Prevention Evaluation Study Investigators.

Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients.
N Engl J Med. 2000;342:145-153.

Heiss WD, Thiel A, Grond M, Graf R.

Which targets are relevant for therapy of acute ischaemic stroke?
Stroke. 1999;30:1486-1489.

Hellemons BSP, Langenberg M, Lodder J, et al.

Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomized controlled trial comparing two intensities of coumarin with aspirin.
BMJ. 1999;319:958-964.

Herbert PR, Graziano JH, Cham KS, Hennekens CH.

Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials.
JAMA. 1997;278:319-321.

Hirsh J, Fuster V.

Guide to anticoagulant therapy. Part 2: oral anticoagulants.
Circulation. 1994;89:1469-1480.

Hobson RWI, Weiss DG, Fields WS, et al, for the VA Cooperative Study Group.

Efficacy of carotid endarterectomy for asymptomatic carotid stenosis: the Veterans Affairs Cooperative Study Group.
N Engl J Med. 1993;328:221-227.

Inzitari D, Eliasziw M, Gates P, et al.

The causes and risk of stroke in patients with asymptomatic internal carotid artery stenosis.
N Engl J Med. 2000;342:1693-1700.

Isles CG, Walzer LM, Bewers GD, et al.

Mortality in patients of the Glasgow Blood Pressure Clinic.
J Hypertens. 1986;4:141-156.

Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA.
Statins and the risk of dementia.
Lancet. 2000;356:1627-1631.

Johnston KC, Li JY, Lyden PD, Candhal S, et al.
Medical and neurological complications of ischaemic stroke: experience from the RANTTAS trial.
Stroke. 1998;29:447-453.

Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.
The sixth report of the Joint National Committee on Prevention, detection, evaluation and treatment of high blood pressure. (JNC VI).
J Hypertens. 2000;18:1795-1800.

Kaira L, Evans A, Perez I, Knapp M, Donaldson N, Swift CG.
Alternative strategies for stroke care: a prospective randomized controlled trial.
Lancet. 2000;356:894-899.

Kannel WB, McGee DL.
Diabetes and cardiovascular disease: the Framingham Study.
JAMA. 1979;241:2035-2038.

Khaw KT.
Epidemiology of stroke.
J Neurol Neurosurg Psychiatry. 1996;61:333-338.

Kieldsen SE, Julius S, Hedner T, Hansson L.
Stroke is more common than myocardial infarction in hypertension: analysis based on 11 major randomized intervention trials.
Blood Pressure. 2001;10:190-192.

Kiely DK, Wolf PA, Cupples LA, et al.
Familial aggregation of stroke: the Framingham study.
Stroke. 1993;24:1366-1371.

Kitamura A, Iso H, Iida H, et al.
Trends in incidence of coronary heart disease and stroke and the prevalence of cardiovascular risk factors among Japanese men from 1963 to 1994.
Am J Med. 2002;112:104-109.

Kjeldsen SE, Erdine S, Farsang C, Sleight P, Mancia G.
1999 WHO/ISH Hypertension Guidelines: highlights and European Society of Hypertension update.
J Hypertens. 2002;20:153-155.

Liao DP, Cooper L, Cai JW, et al.
Presence and severity of cerebral white matter lesions and hypertension, its treatment and its control: the ARIC Study.
Stroke. 1996;27:2262-2270.

Lip GY.
Thromboprophylaxis for atrial fibrillation.
Lancet. 1999;354:4-6.

MacMahon S.
Blood pressure and prevention of stroke.
J Hypertens. 1996;14(suppl 6):539-546.

MacMahon S, Peto R, Cutler J, et al.
Blood pressure, stroke and coronary heart disease. Part I. Prolonged differences in blood pressure: prospective observational studies corrected for regression dilution bias.
Lancet. 1990;335:765-774.

MacMahon S, Rogers A.
The epidemiological association between blood pressure and stroke: implications for primary and secondary prevention.
Hypertens Res. 1994;17(suppl 1):S23-S32.

Mancia G, Giannattasio C, Grassi G.
Current antihypertensive treatment: can we do better?
Am J Hypertens. 1999;12:1315-1385.

Mancia G, Grassi G.
Antihypertensive treatment: past, present and future.
J Hypertens. 1998;16(suppl 1):51-57.

Mancia G, Grassi G.
Rationale for the use of fixed combination in the treatment of hypertension.
Eur Heart J. 1999;20(suppl 2):214-219.

Mancia G, Grassi G.
World Health Organization / International Society of Hypertension Guidelines and the role of ongoing trials.
Eur Heart J. 2000;21(suppl D):D7-D10.

Mancia G, Grassi G.
Blood pressure reduction as part of the multifactorial approach to treatment of cardiovascular disease.
Eur Heart J. 2001;22(suppl B):B32-B36.

Mancia G, Groppelli A, Casadei R, Omboni S, Mutti E, Parati G.
Cardiovascular effects of smoking.
Clin Exp Hypertens. 1990;A12: 917-929.

Marks MP, Marcellus M, Norbash AM, Steinberg GK, Tong DC, Albers GW.
Outcome of angioplasty for atherosclerotic intracranial stenosis.
Stroke. 1999;30:1065-1069.

Okamoto K, Yamori Y, Nagaoka A.
Establishment of the stroke-prone spontaneously hypertensive rat (SHR).
Circ Res. 1974;34:1143-1153.

Ott A, Breteler MMB, Van Harskamp F, Stijnen T, Hofman A.
Incidence and risk of dementia: the Rotterdam Study.
Am J Epidemiol. 1998;147:574-580.

Park JB, Schiffrin EL.
Effects of antihypertensive therapy on hypertensive vascular disease.
Curr Hypertens Rep. 2000;2:280-288.

PATS Collaborating Group.
Post-stroke antihypertensive treatment. A preliminary result.
Clin Med J. 1995;108:710-717.

PROGRESS Collaborative Group.
Randomized trial of a perindopril-based blood pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack.
Lancet. 2001;358:1033-1041.

Qizilbash N, Lewington S, Duffy S, et al.
Cholesterol, diastolic blood pressure and stroke. 13 000 strokes in 45 0000 people in 45 prospective cohorts: Prospective Studies Collaboration.
Lancet. 1995;346:1647-1653.

Sacco RL, Benjamin EJ, Broderick JP, et al.
American Heart Association Prevention Conference IV. Prevention and rehabilitation of stroke. Risk factors.
Stroke. 1997;28:1507-1517.

Sacco RL, Boden-Albala B, Gan R, et al.
Stroke incidence among white, black and Hispanic residents of an urban community: the Northern Manhattan Stroke Study.
Am J Epidemiol. 1998;147:259-1268.

Safar ME.
Pulse pressure, arterial stiffness and cardiovascular risk.
Curr Opin Cardiol. 2000;15:258-263.

Safar ME, Blacher J, Mourad JJ, London GM.

Stiffness of carotid artery wall material and blood pressure in humans. Application to antihypertensive therapy and stroke prevention.

Stroke. 2000;31:782-790.

Scandinavian Simvastatin Survival Study Group.

Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S).

Lancet. 1994;344:1383-1389.

Sever PS, Dalhof B, Poulter NR, et al.

Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial.

J Hypertens. 2001;19:1139-1147.

SHEP Cooperative Research Group.

Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP).

JAMA. 1991;265:3255-3264.

Shinton R, Beevers G.

Meta-analysis of relation between cigarette smoking and stroke.

BMJ. 1989;298:789-794.

Skoog I, Nilsson L, Palmertz B, Andreasson LA, Svanborg A.

A population-based study of dementia in 85-year-olds.

N Engl J Med. 1993;328:153-158.

Stroke Prevention in Atrial Fibrillation Investigators.

Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: stroke prevention in atrial fibrillation II study.

Lancet. 1994;343:687-691.

Stroke Unit Trialists' Collaboration.

Collaborative systematic review of the randomized trials of organized inpatient (stroke unit) care after stroke.

BMJ. 1997;314:1151-1159.

Sytkowski PA, D'Agostino RB, Belanger AJ, et al.

Secular trends in long-term sustained hypertension, long-term treatment, and cardiovascular mortality; the Framingham Heart Study 1950-1990.

Circulation. 1996;93:697-703.

Tatemichi TK, Paik M, Bagiella E, et al.

Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study.

Neurology. 1999;44:1885-1891.

The Diabetes Control and Complications Trial Research Group.

The effect of intensive treatment of diabetes on the development and progression of long-term complication in insulin-dependent diabetes mellitus.

N Engl J Med. 1993;329:977-986.

The INDIANA (Individual Data Analysis of Antihypertensive Intervention Trials) Project Collaborators.

Effect of antihypertensive treatment in patients having already suffered from stroke: gathering the evidence.

Stroke. 1997;28:2557-2562.

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.

Tissue plasminogen activator for acute ischaemic stroke.

N Engl J Med. 1995;346:1509-1514.

Thomson R, Parkin D, Eccles M, Sudlow M, Robinson A.

Decision analysis and guidelines for anticoagulation therapy to prevent stroke in patients with atrial fibrillation.

Lancet. 2000;355:956-962.

Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, Schroll M, for the WHO MONICA project.

Stroke incidence, case fatality and mortality in the WHO MONICA project.

Stroke. 1995;26:361-367.

UKPDS Final Report.

34th Annual Meeting of the European Association for the Study of Diabetes.

Barcelona, Spain, September 8-12, 1998. 1998.

UK Prospective Diabetes Study (UKPDS) Group.

Intensive blood-glucose control with sulphnyolureas or insulin compared with conventional treatment and risk of complications in patients with type II diabetes (UKPDS 33).

Lancet. 1998;352:837-853.

UK Prospective Diabetes Study Group.

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38.

BMJ. 1998;317:703-713.

Vasan RS, Larson MG, Leip EP, et al.

Impact of high-normal blood pressure on the risk of cardiovascular disease.

N Engl J Med. 2001;245: 1291-1297.

Walker SP, Rimm EB, Ascherio A, et al.

Body size and fat distribution as predictors of stroke among US men.

Am J Epidemiol. 1996;144:1143-1150.

Wannamethee SG, Shaper AG, Whincup PH, et al.

Smoking cessation and the risk of stroke in middle-aged men.

JAMA. 1995;274:155-160.

White HD, Simes RJ, Anderson NE, et al.

Pravastatin therapy and the risk of stroke.

Engl J Med. 2000;343:317-326.

Wilhelmsen L.

Epidemiology of smoking and intervention studies of smoking.

Am Heart J. 1988;115:242-249.

Wolf PA, Abbott RD, Kannel WB.

Atrial fibrillation as an independent risk factor of stroke: the Framingham Study.

Stroke. 1991;22:983-988.

Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB.

Probability of stroke: a risk profile from the Framingham Study.

Stroke. 1991;22:312-318.

Wolf PA, D'Agostino RB, O'Neal MA, et al.

Secular trends in stroke incidence and mortality: the Framingham study.

Stroke. 1992;23:1551-1555.

Wood D, De Backer G, Faergeman O, Graham I,

Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other societies on coronary prevention.

J Hypertens. 1988;16:1407-1414.

World Health Organization.

The World Health Report 1999. 1999. Geneva, Switzerland: WHO; 1999.