yield more useful results.^{6,7} The technique of such overviews (or pooling) is simple and well described,⁶ though there are pitfalls⁷; and restriction of the analysis to published data may overestimate the size of the treatment effect since positive studies are more likely to be published.

An overview analysis of the published randomised controlled trials of glycerol in acute stroke^{1,8-14} shows that treatment reduces the odds of death within six weeks by about 36% (pooled relative odds 0.64, 95% confidence interval 0.42 to 0.96). An analysis of the results from the four trials that reported longer follow up^{1,12-14} shows that treatment is associated with a non-significant reduction in the odds of death within four months to one year of 21% (pooled relative odds 0.79, 95% confidence interval 0.49 to 1.28). The confidence intervals are wide and include the possibility that glycerol reduces the odds of early death by only 4% and increases the odds of later death by 28%. An overview analysis of the two published studies of naftidrofuryl^{2,3,15} shows that treatment is associated with a 29% reduction in the odds of death within three months but a 16% increase in the odds of remaining in hospital more than three months after the stroke. The confidence intervals were wide and naftidrofuryl could have important favourable effects on death and hospital discharge (reducing the odds by 64% and 35% respectively) or could equally have large adverse effects (increasing the odds by 40% and 107% respectively). Only one study of nimodipine in acute ischaemic stroke has been published⁴ so an overview analysis is not possible, but the study had similarly wide confidence intervals—for death within four weeks the relative odds were 0.30 (95% confidence interval 0.10 to 0.88).

Any trial of an agent designed to ameliorate acute ischaemic stroke should not include patients with haemorrhagic stroke. Two trials have performed computed tomograms to exclude intracranial haemorrhage on every patient,^{2,3,14} one on only a proportion of patients,¹ and the remainder on none or an unstated proportion. We cannot be sure that the treatment has been tested in the correct patients in trials that have not scanned all patients.

A more serious problem in all of the published trials is the quality of the data on morbidity in the survivors of acute stroke. While it is important to know whether treatment increases or reduces the chances of surviving a stroke, it is even more important to know whether treatment improves survival free of disability and dependency. None of the trials have reported their results in a way that allows assessment of this crucial measure of outcome; instead, some have used scales of neurological impairment such as the Mathew scale.⁸⁻¹⁴ Unfortunately this scale does not measure handicap or activities of daily living, and neither the original nor the subsequent modifications have been shown to be reliable, repeatable, or valid. None of the trials used a simple valid measure of activities of daily living such as the Barthel index¹⁶; nor did they attempt to measure quality of life, which is surely important for the disabled survivor of a stroke.¹⁶

The patients in these studies had all been admitted to hospital with severe strokes and were at high risk of dying: one month case fatality rates in those allocated placebo were 50%,¹ 21%,² and 21%.⁴ These results suggest that these strokes were more likely to be caused by large vessel occlusion than by small vessel disease resulting in lacunar infarction.^{17,18} Lacunar infarctions may not respond to the same treatments as large vessel occlusions, and failure to differentiate large infarcts from lacunar infarcts may obscure important treatment effects.^{17,18}

Further trials of these agents are clearly necessary. They need to be larger and confined to patients with cerebral infarction confirmed by computed tomography. The cerebral infarct should be categorised on the basis of clinical and computed tomography findings into the different subtypes of infarction. The trial results must include data on both early and late survival, on survival free of dependency, on handicap, and on quality of life measured with simple, reliable, and valid measuring scales.¹⁶ At present there is inadequate evidence to support the use of glycerol, nimodipine, or naftidrofuryl when routinely treating patients with acute ischaemic stroke.

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Mortality in congestive heart failure: effects of vasodilator therapy

Congestive heart failure is a common condition with a poor prognosis. The principal determinant of prognosis is left ventricular function, and when this is severely depressed (causing dyspnoea at rest or on minimal exertion) over half the patients are dead within a year.¹ Diuretics are the first line treatment but, although these control fluid retention, they do not improve left ventricular function. Vasodilator drugs, on the other hand, improve left ventricular function by reducing afterload and are widely used in patients who still have symptoms after treatment with diuretics.

Activation of the renin-angiotensin system is a major factor in the development of the heart failure.^{2,3} The angiotensin

converting enzyme inhibitors (including captopril and enalapril) block the conversion of angiotensin I to angiotensin II and hence cause vasodilatation and the suppression of aldosterone secretion. These separate effects improve left ventricular function and enhance the renal excretion of salt and water. The clinical benefits of these drugs have been confirmed in placebo controlled trials^{4,6} and are associated with a long term haemodynamic improvement.⁷ Although tolerance may develop,^{8,9} it occurs less frequently than with conventional vasodilators.¹⁰

Two recent trials have shown that adding vasodilators to diuretics not only improves the symptoms but also reduces the long term mortality in heart failure.^{11,12} In the first trial, by the Veterans Administration, 642 patients with moderate or severe heart failure were randomised to treatment with placebo, prazosin (20 mg daily), or a combination of hydralazine and isosorbide dinitrate (300 mg and 160 mg daily, respectively). Mortality at one year was unaffected by prazosin but was reduced by almost two fifths in the group treated with hydralazine isosorbide dinitrate. In a more recent trial from Norway 253 patients were randomised to treatment with placebo or enalapril (2.5 mg—40 mg daily). Mortality at one year was reduced by almost a third in the group treated with enalapril; this reduction was confined to patients dying of progressive heart failure, sudden death being unaffected.

Comparing these results is difficult because the patients in the Veterans Administration trial were younger and had less severe heart failure. The overall mortality, therefore, was lower and treatment with hydralazine isosorbide dinitrate produced only a marginally significant difference. Whether vasodilatation in general or converting enzyme inhibition in particular is more effective for reducing mortality must await the results of comparative studies now in progress.

How vasodilator drugs reduce mortality in congestive heart failure is not known. Sustained responsiveness to treatment must be important and the finding that prazosin did not reduce mortality may reflect the haemodynamic tolerance which frequently occurs with the drug.^{13,14} Possibly the reduction is due to the diminution in heart size and the increase in tissue oxygenation. Reductions in ventricular loading make the heart more energy efficient and help break the vicious cycle of increasing ventricular enlargement and worsening contractile function.¹⁵ Moreover, by improving cardiac output and tissue oxygenation vasodilators may delay the development of multiple organ failure, which is often seen in patients dying of heart failure.^{16,17} Unfortunately, the beneficial effects of conventional vasodilator drugs are reduced by reflex activation of the sympathetic system and stimulation of the renin-angiotensin system—which combine to increase heart rate, vascular resistance, and plasma volume.¹⁸ Converting enzyme inhibitors actively suppress these unwanted neuroendocrine responses and so may be more useful.^{18,19} They also conserve potassium and so may protect against lethal cardiac arrhythmias, although

reductions in sudden death were not seen in the Norwegian trial.

Regardless of the mechanism, the Veterans Administration and Norwegian trials have shown clearly that treatment with vasodilators can reduce mortality in congestive heart failure. Firm recommendations for the choice of drug and the selection of patients likely to benefit from treatment must await the results of further studies. At present, converting enzyme inhibitors are preferred because they are usually better tolerated than conventional vasodilators and are clinically more effective.¹⁸ A reasonable policy is to include a converting enzyme inhibitor in the treatment regimen of patients whose diuretic requirement exceeds 40 mg of frusemide daily (or equivalent doses of other diuretics). Treatment with converting enzyme inhibitors should ideally be started in hospital under cardiological supervision because profound hypotension and renal failure may occur in susceptible patients. Thus initially a low dose should be chosen (captopril 12.5 mg or enalapril 2.5 mg twice daily), which may be increased if blood pressure and renal function remain satisfactory.

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