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Drug Therapy for Acute Ischaemic Stroke

Risks versus Benefits

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Contents

Abstract

Stroke is a very common medical emergency that, until recently, had no specific treatment. Following the results of several major trials (including 2 'mega-trials'), aspirin (acetylsalicylic acid) can be recommended for the majority of patients with acute ischaemic stroke. While the benefit of aspirin is only modest, i.e. an increase of 11 per 1000 long term independent survivors, the public health benefit in the world will be substantial as this treatment could be given to millions of patients with acute ischaemic stroke each year.

Heparin is associated with a reduction in early recurrent ischaemic stroke, but there is no net benefit because of a similar sized excess of recurrent haemorrhagic stroke (even for those in atrial fibrillation).

Thrombolytic therapy has not been so widely tested and the results of the small trials to date have yielded conflicting results. The only positive publication to date (comprised of 2 related trials) evaluated the recombinant tissue plasminogen activator alteplase, but such treatment is probably only indicated for highly selected patients. Further trials are almost certainly required and it would be unwise to change clinical practice based on the current evidence.

No other stroke treatments have been shown to be beneficial, and much larger trials will be required to confirm or refute possible moderate benefits of treatment. A well organised stroke service and participation in clinical trials will improve the future care of patients with acute ischaemic stroke.

Stroke is common, frequently disabling and often fatal.[1,2] Therapeutic nihilism has dominated stroke medicine for decades but this attitude can no longer be justified.[3] Recent trials have provided evidence for the balance of the risks and benefits associated with a variety of drugs. In this review, the systematic assessment of patients with suspected stroke is described, and the roles of the new drug treatments in the light of recent studies are discussed.

Often the question is asked of why we have many treatments for acute myocardial infarction (AMI) and very little to offer the patient with acute stroke. The answer to this question is complex but can probably be explained by a few simple differences between stroke medicine and short term coronary care: the stroke syndrome is far more heterogeneous; until recently stroke units were few in number; and, patients with stroke are much older than those with AMI. Until computerised tomographic (CT) scanning was widely available we were unable to reliably distinguish ischaemic stroke from primary intracerebral haemorrhage. The inability to diagnose the underlying pathology of stroke correctly severely compromised early trials of antithrombotic therapy and thrombolytic therapy for acute stroke. Finally, stroke disease is primarily a disease of the elderly and the elderly dysphasic stroke patient does not attract the attention the same sort of attention as a 40-year-old patient who survives an AMI.

The series of 'mega-trials' for AMI which emerged in the past decade have taught physicians many lessons.[4] First and foremost is the surprisingly large number of patients that need to be randomised to provide really reliable evidence of the balance of risks and benefits of treatments with only moderate effects.[5] Expert opinion, the mainstay of medical education since the time of Hippocrates, has many advantages but unfortunately is hopeless if the expert turns out to be wrong.[6,7] In practical terms there are 2 main requirements for the assessment of new treatments: first, large numbers of patients need to be randomised (to reduce random error as individuals are so different from each other); and secondly, true random allocation and blinded assessment eliminates a systematic bias.[5]

1. Short Term Stroke Treatment: a Step-Wise Approach

The best clinical units are those where attention to detail is combined with a simple but systematic approach to a clinical problem. Such an approach is vital for the rational use of drugs for patients in the acute phase of stroke. Figure 1 illustrates the simple steps to be taken when assessing a patient with suspected stroke. In the following section these simple questions illustrating the role of drug therapy at each point will be described in more detail.

1.1 Is it a Stroke?

Bedside diagnosis is surprisingly accurate if care is taken to get a third party history. The telephone is a powerful tool in obtaining diagnostic information. Key parts of the history include questioning the patient (or relative, or carer) about stroke risk factors and the onset of symptoms. Stroke is usually defined as a sudden onset of focal (or global) loss of cerebral function with symptoms lasting more than 24 hours (or leading to death) with a presumed vascular cause.[8]

Whilst this definition is useful for epidemiology it is less useful in the emergency room when 'time is brain'. If we wait 24 hours to check if it really is a stroke we miss the therapeutic window! A more pragmatic definition for acute stroke care would not include the 24-hour time limit but an acceptance that symptoms that fail to resolve within an hour or two are likely to represent a stroke if left untreated, and thus urgent assessment should proceed. A major aim of acute stroke treatment is to convert a potentially irreversible event (the stroke) into a transient event (a transient ischaemic attack; TIA).

Once we are convinced we are dealing with an acute cerebral vascular event the next step is to identify the underlying stroke pathology.

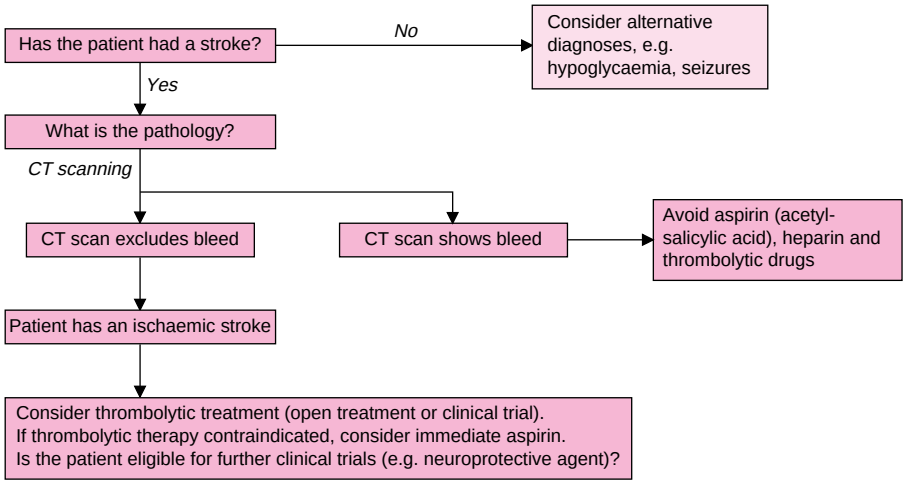

Fig. 1. A simple pathway for stroke care. **CT** = computerised tomography.

1.2 What is the Stroke Pathology?

Most strokes are due to cerebral infarction[1] and, whilst clinical scoring systems can help predict infarct from haemorrhage,[9-11] the gold standard investigation remains CT scanning. Bleeding due to primary intracerebral haemorrhage is immediately visible on the CT scan; thus, CT scanning can exclude a bleed. As subsequent treatment depends on the pathology of the stroke, an early CT scan is vital in the short term management of stroke. The longer a CT scan is delayed the less certain the initial pathology, as bleeding into a cerebral infarct can occur, mimicking a primary intracerebral haemorrhage.[12] This implies that if the CT scan is delayed (e.g. 24 hours after the onset of stroke symptoms) and the scan appearance is that of a primary intracerebral haemorrhage, there could be uncertainty about the initial stroke pathology. Such an appearance may represent a primary intracerebral haemorrhage, or massive haemorrhagic transformation of cerebral infarction. It is also illogical to delay CT scanning until such time that the cerebral infarct is visible as the main rationale of treatment is to prevent such infarction. The main message must be to perform CT scanning as early as possible after stroke onset to determine stroke pathological sub-type.

1.3 What Should be Done Immediately?

After diagnosing the stroke and excluding a primary intracerebral haemorrhage we are now in a position to consider urgent treatment. At this stage patients (and their relatives and carers) need information and explanation, so they should be told the likely diagnosis. During the preceding clinical assessment a bedside swallow assessment should be performed to assess whether swallowing is safe. Not only is this good practice but it allows sensible prescribing of subsequent treatment.

1.4 The Drug Treatment of Ischaemic Stroke

1.4.1 Thrombolytic Therapy

Ischaemic stroke is due to occluded cerebral (or extracranial) arteries and a rational treatment is one which recanalises the occluded vessels and protects the ischaemic brain until full revascularisation can occur.

Thrombolytic therapy, which revolutionised AMI treatment, has now been evaluated in patients with acute ischaemic stroke. As the trials have been rather small, the results from individual studies are prone to false positive and false negative results.

To try and reduce the effects of random error the risks and benefits of treatment derived from a recent meta-analysis published electronically in the

Cochrane library, and in a recent paper, will be discussed.[13,14]

The totality of the evidence suggests that whilst very early treatment can improve long term outcome, there are substantial early risks of cerebral haemorrhage. Only 12 trials, including a total of 3435 patients, were identified. Brain imaging prior to randomisation was mandatory in all these studies to exclude strokes due to primary intracerebral haemorrhage and drug treatment was given using the intravenous route. Three trials used urokinase, 4 trials used streptokinase and 5 trials used a tissue plasminogen activator (t-PA). All but the Multicentre Acute Stroke Trial – Italy Group[15] trial were placebo controlled. Although 5 trials had no age limit, 6 trials excluded those over 80 years of age and 1 study excluded those over 85 years.

One interesting point to note was the very large difference in case-fatality between some of trials (as observed in the placebo group). This suggests that the studies included rather different types of populations and as a consequence the results of the overview may not be generalisable.

Overall, allocation to thrombolytic therapy was associated with a statistically significant absolute reduction of 6.5% in longer term poor outcome (i.e. dead or dependent 3 to 6 months after stroke). This absolute reduction can be stated as about 65 extra patients alive and independent, per 1000 treated with thrombolytic therapy (95% confidence interval 28 to 107). This substantial treatment effect can be compared with the effect of streptokinase in AMI which had a treatment effect of 28 deaths prevented per 1000 patients treated in the ISIS-2[4] trial.

However, this substantial benefit with drug treatment was associated with significant risks.[14] There was an early excess of deaths (about 90 extra early deaths per 1000 treated). In addition, there was a substantial early hazard due to cerebral haemorrhage. There were an extra 70 symptomatic cerebral bleeds, of which about 50 were fatal per 1000 treated. Interestingly, the excess of deaths in the thrombolytic treatment groups was less marked at the end of the trial follow-up suggesting that thrombolytic therapy tends to have a net effect of accelerating death due to stroke. Of course, we simply do not know whether the patients who die because of complications of thrombolytic therapy were the ones who would have died if untreated.

Other important data to emerge from this overview included the evidence that the delay in treatment is important. The excess of deaths seemed to disappear if analysis was restricted to those randomised within 3 hours of stroke onset. Unfortunately, the systematic review included too few patients to provide reliable evidence of statistically significant differences in the treatment effects of the different types of thrombolytic agent, especially if very early treatment alone was considered (within 3 hours of onset of symptoms).

A word of caution is needed in the interpretation of these data as there was significant heterogeneity between the studies. This implies that the studies were very different from each other and can indicate that some of the trials were unusually optimistic or pessimistic in the individual estimates of treatment effects.

Alternatively, the heterogeneity may be the result of significant methodological differences and thus the one positive publication that was significant in its own right needs particular scrutiny. This publication, from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS), reported the combined results from 2 very similar studies of very early administration of the recombinant t-PA alteplase.[16] Close inspection of the NINDS paper will help guide clinicians in their decision to use a t-PA (table I), but the decision to license alteplase for this indication has been controversial.[18]

The possibility that the positive results from these two trials were due to chance have been dismissed by some[18] but cannot be excluded, especially in view of the other less promising results. To help get around these difficulties, well organised stroke centres should have very strict protocols for the emergency use of alteplase for highly selected patients. Participation in further

Table I. Suggested checklist for hospital units wishing to offer emergency treatment with tissue plasminogen activator (t-PA) for patients with acute ischaemic stroke

Have you a well organised hospital stroke service?
Have you a mechanism to quickly identify patients with stroke in the emergency room?
Can you 'fast-track' patients to the computerised tomographic scanner?
Have you got intensive care back up facilities?
Patient selection for emergency treatment with t-PA
Patient (or appropriate delegate) consents to treatment?
Clear history of the time of onset of symptoms of acute stroke?
Computerised tomographic scan has excluded intracerebral haemorrhage?
Treatment can be started within 3 hours of onset of stroke symptoms?
Stroke symptoms not improving rapidly (i.e. unlikely to be a transient ischaemic attack?)
No contraindications to thrombolytic therapy such as:
No recent head trauma?
No surgery within previous 14 days?
No evidence of gastrointestinal haemorrhage or haematuria in previous 21 days?
Systolic blood pressure <185mm Hg; diastolic pressure <110mm Hg?
No arterial puncture at a noncompressible site within previous 7 days?
No coagulopathy, e.g. advanced liver disease
No concurrent warfarin or heparin treatment (unless normal clotting studies)?
Mimics of severe stroke excluded (seizures[17] and hypoglycaemia)?

randomised trials of thrombolytic therapy versus placebo should also be encouraged.

It must be noted that evidence from randomised controlled trials involving over 17 000 patients was required to convince doctors that thrombolytic therapy was effective for patients with AMI.[4,19] It is likely that a larger study than the NINDS trial will be needed to convince doctors that the risks of thrombolytic therapy are worth the later benefits for acute ischaemic stroke. Meta-analysis may convince some but not all. The results of the thrombolytic trials to date raise more questions (table II) than answers and these uncertainties will only be resolved by further trials. Urgent research is needed to develop safer thrombolytic agents (or more focused use of available agents). Many thousands more patients may need to be randomised to provide really reliable data on the balance of risks and benefits, but this is not an unreasonable request. Do we really want to base our treatment of the next few million strokes on a trial of a few hundred patients?

1.4.2 Antithrombotic Therapy

Following the publication of the International Stroke Trial[20] and the Chinese Acute Stroke Study,[21] we now have evidence from randomised controlled trials of the balance of risks and benefits of immediate antithrombotic therapy from about 20 000 patients for heparin and 40 000 patients for aspirin (acetylsalicylic acid). *In summary,* immediate aspirin can be safely recommended for most patients with ischaemic stroke but as yet there are no convincing data that immediate heparin has any net benefit.

1.4.3 Aspirin (Acetylsalicylic Acid)

Aspirin is a proven treatment for AMI and is now well established for the secondary prevention of vascular events for a wide variety of patients at high risk of vascular death.[4,22] In addition, meta-analysis has shown that aspirin can prevent deep vein thrombosis (a recognised complication of stroke).[23] It was therefore considered a promising treatment for acute ischaemic stroke.

The International Stroke Trial was a pragmatic, open randomised controlled trial that aimed to include a wide variety of patients with acute ischaemic stroke from a wide variety of hospitals in many countries. Trial procedures were simplified

Table II. Remaining uncertainties about thrombolytic therapy for acute ischaemic stroke

What is the precise time window?
Which thrombolytic agent is most beneficial?
What is the optimal dose?
Is the treatment of severe hypertension mandatory?
Are there any age limits to treatment?
Are very early computerised tomographic scan changes of ischaemia an absolute contraindication to treatment?
Who is at particular risk of intracerebral haemorrhage?
How precise are the treatment effects?
Should we avoid heparin treatment?
When is it safe/appropriate to start aspirin (acetylsalicylic acid)?

to facilitate participation in the study. The entry criteria were straightforward:

- a clinical diagnosis of stroke with onset of symptoms first noted within previous 48 hours
- no clear indication or contraindication for immediate aspirin or heparin
- uncertainty of the benefit of early antithrombotic treatment
- no evidence of intracerebral haemorrhage (CT scanning was strongly advised but not mandatory prior to randomisation).

Those allocated to immediate aspirin were prescribed aspirin in a dose of 300 mg/day and rectal aspirin was recommended if the patient was unable to swallow. Treatment was continued for 14 days (or hospital discharge if sooner). Treatment was not blinded, but efforts were made to blind the 6-month assessment of dependency for stroke survivors.

The entry criteria were identical in the Chinese Acute Stroke Study but the dose of aspirin was somewhat lower at 160mg/day and treatment was given in double-blind fashion for 1 month.

The results from these 2 very large studies were very similar (and support the notion that the blinded assessment of outcome in the International Stroke Trial was successful at reducing systematic bias). Individually, neither study was large enough in its own right to provide statistically significant results of the pre-specified analyses, due to the very modest benefit of aspirin.

However, in combining the aspirin results from both studies (and the small Multicentre Acute Stroke Trial – Italy Group trial[15]) there was a significant reduction in the rate of recurrent stroke and death in hospital of about 9 (SD = 3) per 1000 patients treated. About 11 (SD = 3) recurrent ischaemic strokes and deaths were prevented and there were about 2 (SD = 1) extra intracranial bleeds per 1000 patients treated. In addition, there was a significant reduction in those patients who died or were dependent at the end of trial follow-up with a benefit of about 11 (SD = 6) extra independent patients per 1000 treated. It should, however, be noted that there were some differences between the trials: patients in the Chinese Acute Stroke Study were more likely to have had a pre-randomisation CT scan and were of lower risk and younger in age.

There was no clear evidence of a relationship between the delay in starting treatment and treatment effect of aspirin; one explanation is that aspirin is merely acting as a secondary preventative agent with little influence on the initial area of infarction.

Treatment effects appeared similar across a large number of clinically identifiable subgroups. The concordance of the results suggests that aspirin is widely practicable but with a modest treatment effect. The paradox is that immediate aspirin may well prevent many more patients dying or becoming disabled following an acute stroke than thrombolytic therapy. This is because aspirin can be given to the vast majority of patients with ischaemic stroke while thrombolytic therapy is currently only applicable to highly selected patients. Hospital services need to be organised to ensure that this very cheap and simple treatment is not forgotten.

1.4.4 Heparin

Heparin has been used for decades for the treatment of stroke,[24-26] but despite a promising meta-analysis of earlier trials[27] the results of the International Stroke Trial do not support the routine use of heparin.[20] In the International Stroke Trial (see section 1.4.3) two doses of subcutaneous unfractionated heparin were tested: 5000U twice daily and 12 500U twice daily. Monitoring of the activated partial thromboplastin times was not mandatory and left to the discretion of the attending physician (treatment was not blinded). The rationale of using a fixed subcutaneous dose was to simplify the treatment, avoid the inevitable stop/start problems of intravenous treatment and not interfere with early rehabilitation.

The pre-specified analyses for the heparin groups of the International Stroke Trial were early mortality (deaths within 14 days of randomisation) and 6-month poor outcome (dead or dependency). At 14 days there were non-significantly fewer deaths in the heparin allocated patients (9 *vs* 9.3%). More deaths in the heparin group were due to intra-

and extracranial bleeding (40 *vs* 18). At 6 months the proportion of dead or dependent patients were identical for the heparin and 'avoid heparin' groups at 62.9%.

These disappointing results hide a fascinating mix of risks and benefits as heparin significantly reduced the chance of early recurrent ischaemic stroke (2.9% for the heparin group versus 3.8% for the control) which was offset by an increase in haemorrhagic recurrent stroke (1.2 *vs* 0.4%). Both results were highly significant. In addition, heparin was associated with a significant excess of transfused or fatal extracranial bleeds mainly attributable to the 12 500U twice daily heparin regimen. Many clinicians are convinced that patients in atrial fibrillation must be anticoagulated immediately after the onset of ischaemic stroke yet the International Stroke Trial has shown that the reduction in recurrent ischaemic stroke is still offset by the increase in recurrent haemorrhagic stroke (table III).

Are there any data from the International Stroke Trial to suggest that certain subgroups may benefit form treatment? Unfortunately, close inspection of the many published subgroup analyses is not encouraging. In fact, there is evidence that those with severe strokes (e.g. those patients with a large cortical infarct or depressed consciousness level or a poor prognostic stroke) do particularly badly. This finding is consistent with the view that the larger the infarct, the greater the risk of haemorrhagic transformation of infarction. As only 5000 patients were randomised to the smaller heparin dose (5000U twice daily), there are insufficient data to reliably detect an additional small benefit of adding low dose subcutaneous heparin to aspirin for the early treatment of ischaemic stroke.

What does all this mean in routine clinical practice? Patients with no clear contraindication to aspirin should be given aspirin immediately after a CT scan has excluded a primary intracerebral haemorrhage. Routine use of heparin should be avoided unless required for another specific indication (e.g. pulmonary embolism or deep vein thrombosis). Patients in atrial fibrillation should be given aspirin for the first 2 weeks. At the end of 2 weeks of treatment clinicians should consider starting warfarin and stopping the aspirin if there are no contraindications to oral anticoagulation.

Table III. Heparin is not beneficial for patients in atrial fibrillation and recent ischaemic stroke[a]

	Heparin (%) [n = 9716]	No heparin (%) [n = 9717]
Patients in sinus rhythm		
Recurrent ischaemic stroke	2.9	3.6*
Recurrent haemorrhagic stroke	1.1	0.4**
Total recurrent stroke	4.0	4
Death or nonfatal stroke	10.3	10.3
Patients in atrial fibrillation		
Recurrent ischaemic stroke	2.8	4.9***
Recurrent haemorrhagic stroke	2.1	0.4****
Total recurrent stroke	4.9	5.3
Death or nonfatal stroke	19.1	20.7

a This table summarises the risks and benefits of subcutaneous heparin for patients with ischaemic stroke subdivided by cardiac rhythm in the International Stroke Trial.[20] The figures refer to events within the 14-day allocated treatment period. It can be seen that patients in atrial fibrillation have a higher absolute risk of poor outcome compared to those in sinus rhythm. The significant reductions due to heparin in recurrent ischaemic strokes are offset by the risk of recurrent haemorrhagic strokes even for those in atrial fibrillation. This table is a subgroup analysis of the patients randomised in the International Stroke Trial.[20]

***** $2p < 0.05$; ****** $2p < 0.01$; ******* $2p < 0.001$; ******** $2p < 0.00001$.

Low molecular weight heparin and heparinoids have not been tested in large enough studies to provide reliable data on effectiveness. The preliminary results of the randomised trial of danaparoid sodium (ORG-10172) in acute stroke were also disappointing.[28]

1.4.5 Neuroprotective Agents

The main focus of treatment for ischaemic stroke is to restore the normal vascular anatomy. Without an adequate blood supply, the brain will undergo infarction. During the early phase of ischaemia there is a therapeutic opportunity to halt or reverse the harmful influx of calcium into the cells, as well as to reduce (or antagonise) the release of the neurotoxic excitatory amino acids.[29,30] These treatment strategies, the so-called neuroprotective agents, may extend the time window for successful

Table IV. Treatments for acute stroke

Treatment	Comment
Aspirin (acetylsalicylic acid)	Beneficial
Unfractionated heparin	Risks outweigh benefits
Low molecular weight heparin	More trials needed
Danaparoid sodium (ORG-10172)	Await final results from TOAST but likely to be similar to heparin
Thrombolytic therapy	More trials needed, some centres use tissue plasminogen activators
Lubeluzole[31]	More trials needed
Intravenous magnesium[32]	More trials needed
Glycerol[33]	More trials needed (in certain subgroups)
Corticosteroids	More trials needed (in certain subgroups)
Mannitol	More trials needed (in certain subgroups)
Benzodiazepines	More trials needed
Ancrod[33]	More trials needed
Batroxobin[33]	More trials needed
Methylxanthines[33]	More trials needed
Epoprostenol (prostacyclin)	More trials needed
Calcium antagonists	More trials needed
Clomethiazole (chlormethiazole)	More trials needed
NMDA receptor antagonists	Can adverse effects be reduced?
Gangliosides[33]	Not worthwhile
Haemodilution[34]	Not worthwhile
Enlimomab (antileucocyte)	More studies needed (septicaemic complications too great in initial clinical trials)
Blood pressure manipulation	More studies needed
Blood glucose lowering[35]	Trials needed for hyperglycaemic patients

NMDA = *N*-demethyl-D-aspartate; **TOAST** = the randomised trial of danaparoid sodium (a heparinoid also known as ORG-10172) in acute stroke.

revascularisation and add to the benefits of antithrombotic and fibrinolytic agents. A detailed discussion is beyond the scope of this review but the reviews by Muir[29] and Dorman[30] offer a useful summary.

1.4.6 Other Treatments

Many other drugs have now been evaluated in patients with acute ischaemic stroke but none have shown a significant overall benefit. With few exceptions all the randomised controlled trials have been too small to reliably exclude a moderate beneficial treatment effect. Whilst phase I trials are vital to evaluate the safety of new drugs (or new indications for older drugs), they should not used to eliminate promising drugs merely because the results are rather disappointing. The play of chance overwhelms many treatment effects, and trials sponsored by pharmaceutical companies still tend to be too small, with a major risk of false positive or negative results. In addition, there is a real risk that promising neuroprotective drugs are being discarded too early in development.

Table IV lists some promising drugs (or treatment strategies) which need to be evaluated further and also some treatments which are probably ineffective. Large phase III trials are planned for the neuroprotective agents lubeluzole, intravenous magnesium and benzodiazopines and the results are awaited with interest. Clinical classification of ischaemic stroke subtype has been shown to be feasible in the acute phase of stroke and this new methodology will enable trials to concentrate on important stroke subtypes. For example, glycerol or corticosteroids should be evaluated for patients with large hemispheric infarction as identified by the Total Anterior Circulation Infarct (TACI) subtype using the Oxfordshire Community Stroke Classification.[17]

Blood pressure lowering may be detrimental in the acute phase of stroke and more work is needed in this area.[36,37] Lowering of elevated glucose levels may be another metabolic strategy worth pursuing.[35]

2. The Future

We now have the trial methodology to test simple practicable treatments in tens of thousands of patients with acute ischaemic stroke; still, many more ‘mega-trials’ are needed to identify treatments with moderate benefits. Meta-analyses of small trials will help guide whether further trials are worthwhile and will summarise the world evidence in the absence of a single convincing study.[38] In addition, subtype classification of the

heterogeneous group of patients with cerebral infarction will allow focused treatment targeted to the presumed underlying pathology.

It is very unlikely that there is a panacea for all types of ischaemic stroke (aspirin may the best agent in this regard), and thus logical combinations of treatment should be evaluated. For example, a 2 × 2 factorial design of a neuroprotector and thrombolytic drug seems a very worthwhile design.

Stroke physicians should ensure their local hospitals provide organised stroke services.[39] There is no doubt that stroke units will facilitate further research. Efforts to reduce the delay from stroke onset to medical attention are likely to be beneficial and will allow specialised units to consider thrombolytic therapy for highly selected patients.[40]

As we currently lack an ideal stroke treatment we must all encourage participation in acute stroke trials as part of our routine clinical practice. Only data from randomised controlled trials will change clinical practice for the better.

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