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Lessons from the Past for the Near Future

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To know where we are and where we are headed in the future, we need to know where we have been in the past. My task is to critically review experience in order to suggest ways to move forward.

I. Diagnosis of acute brain ischemia and intravenous (IV) thrombolytic treatment

A. Clarification of the pathophysiology of acute brain ischemia and modern diagnosis

Myocardial and brain ischemia are dynamic processes that evolve during time. Early studies of the pathology of patients dying of myocardial infarction found a relatively low rate of occlusive coronary thrombi. These studies were performed 12 hours or more after symptom onset. Later studies performed within 4 hours of onset showed that the cause of myocardial infarction in the great majority of patients was acute thrombosis of a coronary artery [1].

Similarly, angiographic and necropsy studies of patients with acute brain ischemia during the last half of the twentieth century showed that most acute brain infarcts were caused by emboli that arose from the heart, aorta, and from atherosclerotic occlusive lesions in the carotid and vertebral arteries in the neck. The process was dynamic and emboli often blocked an intracranial artery and then became dislodged and moved distally. Small emboli were often cleared. Angiography within the first 8 hours after the onset of focal brain ischemia showed a high frequency of embolic occlusion of large intracranial arteries [2,3]. If successive films were taken during angiography emboli often could be shown to move distally [4,5].

Miller Fisher and Raymond Adams extensively studied their necropsy material and defined the pathophysiology and dynamic nature of brain embolism [6,7]. Sudden blockage of a brain-supplying artery caused ischemia to neurons and also resulted in ischemic damage to the small blood vessels within the area of ischemia. When the obstructing embolus moved distally, as it often did, the previously ischemic region was reperfused with blood. The damaged capillaries and arterioles within that region were no longer competent and blood leaked into the surrounding infarcted tissue.

Other studies during the same time described the distribution of atherosclerosis and thrombosis within brain-supplying arteries. In white men, the predominant atherosclerotic disease was at or near the origins of the internal carotid and vertebral arteries in the neck [8,9]. Thrombi that developed within the internal carotid arteries (ICAs) often propagated cranially, and emboli broke off from the top of the clot. Intracranial atherosclerosis was more common in women, African-Americans, and individuals of Asian origin [11,12]. Degenerative changes termed lipohyalinosis often developed in penetrating artery branches of the main intracranial arteries. Occlusive changes in these vessels led to small deep lacunar infarcts [13,14].

During the last decades of the twentieth century there was a dramatic improvement in technology capable of imaging the brain and the blood vessels that supplied the brain. MRI proved superior to CT scan in showing acute infarcts and hemorrhages. Diffusion-weighted images (DWI) showed brain infarcts soon after ischemia onset. CT angiography (CTA) and MR angiography (MRA) could accompany brain imaging with CT and MRI and quickly and relatively accurately showed occlusive arterial and venous lesions. CT and MR perfusion (Perfusion-weighted Images PWI) studies performed concurrently with brain and arterial imaging showed regions of brain tissue that were deprived of their normal blood supply. Duplex ultrasound non-invasively showed occlusive lesions in the neck and transcranial Doppler ultrasound could show and monitor disease in the large intracranial arteries. By the turn of the century clinicians could safely and quickly determine during life the nature and location of occlusive lesions, the extent of brain infarction, and regions of brain that were underperfused but not yet infarcted.

B. Experience with IV thrombolytic treatment

In early thrombolytic studies during the 1980s, acute stroke patients were screened clinically and by CT, and then angiography was performed. If an intracranial arterial occlusion was shown, thrombolytic drugs were given. Follow-up angiography was performed after treatment to assess recanalization. These studies were observational only since controls were not used and patients were not randomized but successive patients meeting protocol requirements were treated [15-18]. Recanalization heavily correlated with outcome. Thrombolytic agents act only by lysing clots. If arteries are not opened the drugs do not facilitate recovery. Knowing the recanalization rate of agents given IV and IA in patients with various occlusive arterial lesions is extremely helpful in choosing appropriate therapy.

In some clinical studies, the vascular lesions were defined by angiography and thrombolytic drugs were given IV [15-18]. Among 370 patients treated

with IV rt-PA, within 6 to 8 hours, one third of the arteries treated showed significant recanalization compared to only 5% of 58 control arteries. MCA branch occlusions recanalized best followed by occlusions of the superior and inferior divisions of the MCA. Mainstem MCA occlusions recanalized less often than branch and division MCA lesions. ICA occlusions rarely recanalized and there were no recanalizations when both the ICA and MCA were occluded. Embolic occlusions recanalized more often than in-situ thrombosis of atherostenotic arteries. Recanalization was better when there was angiographic evidence of good collateral circulation before administration of rt-PA.

These observational studies were followed by randomized trials. None of the IV randomized trials required or reported vascular testing before treatment and all used clinical findings and CT as entry requirements. The first reported large multicenter randomized trial of IV thrombolysis was the European Cooperative Acute Stroke Study (ECASS) which included 620 patients with acute hemispheral strokes among 75 hospitals in 14 European countries [19,20]. 313 patients were randomized to receive rt-PA and 307 to placebo. Treatment was given within 6 hours of the onset of symptoms of brain ischemia. Patients who had major early infarct signs (diffuse hemispheral swelling, parenchymal hypodensity, effacement of cerebral sulci in > 1/3 of the MCA territory) and hemorrhage on initial CT scans, which were read at local sites, were excluded. An independent blinded CT scan reading panel later retrospectively reviewed the CT scans and determined protocol violations of the CT scan entry criteria. Many patients had protocol deviations, mostly because local centers failed to recognize CT abnormalities that should have excluded patients. The study was considered negative. More patients treated with rt-PA had good outcomes but more patients did poorly and more patients died [19,20].

The next study was the National Institute of Neurological Diseases and Stroke (NINDS) study [21]. Compared to ECASS l, the NINDS used lower rt-PA dose and had earlier treatment (302 patients were treated within 90 minutes and 322 between 90 and 180 minutes) Ischemia on entry CT scans did not exclude patients. Patients treated with IV rt-PA were at least 30% more likely to have minor or no disability at 3 months. Symptomatic intracerebral hemorrhages were more common in rt-PA treated patients (6.4% vs 0.6%) and patients who had more severe neurological deficits at entry and patients 75 years or older had more hemorrhages. The mortality at 3 months was 17% in the rt-PA group vs 21% in the placebo group [22]. There was no important difference in outcome in stroke subtype groups but quick entry and absence of vascular and cardiac imaging made the clin-

ical diagnosis of stroke mechanism tentative at best. A committee that reviewed the NINDS results reported that the stroke mechanism subtype results were not valid [22].

In the ECASS ll trial, investigators treated 800 patients from Europe, Australia, and New Zealand with rt-PA or placebo within 6 hours of stroke onset [23]. They used the rt-PA dose used in the NINDS trial. Patients with major infarcts on CT scan were excluded but vascular imaging was not performed before treatment. Guidelines for control of hypertension were more explicit than in ECASS l or the NINDS trial. In ECASS ll, 36.6% of placebo-treated patients had favorable outcomes – a better result than thrombolysed patients in the ECASS l and NINDS trials. Among the rt-PA-treated group, 40.3% had favorable outcomes – not statistically significantly different from the placebo-treated group. Treatment results and hemorrhage frequencies were similar in the 0-3 hour and 3-6 hour treatment groups. In the interval between the 2 ECASS trials, stroke centers had developed widely in Europe and were manned by experienced stroke neurologists, internists, and nurses. The results in the placebo and thrombolysis groups reflect better medical care delivered in dedicated stroke centers. Later a third European study, ECASS lll, using a similar protocol to ECASS ll, showed that IV rt-PA was more effective than placebo when patients were treated in the 3-4.5 hour window [24].

Concurrent with ECASS lll, investigators began to use modern MRI and CT protocols along with clinical data to attempt to better select patients likely to benefit from thrombolysis and those at most risk of hemorrhage and other complications. Trials (EPITHET [25] DIAS [26], and DEFUSE [27]) and extensive experience [29] established the feasibility of using modern brain and vascular imaging to optimally choose patients for thrombolysis.

The Desmoteplase in Acute Ischemic Stroke (DIAS) Trial was a placebo-controlled double-blind randomized dose finding Phase ll trial of Desmoteplase [27], a plasminogen activator fibrinolytic enzyme with high fibrin selectivity and a long-terminal half-life derived from vampire bat saliva. Fibrin-selectivity is important since the agent tends to bind at the site of the thrombus and not cause systemic fibrinogenolysis. In DIAS, patients were selected for fibrinolysis if they had a diffusion/perfusion mismatch on MRI and were treated within a 3-9 hour window. The patients treated with desmoteplase had a higher rate of reperfusion and better clinical outcomes than placebo-treated controls [26].

The Diffusion and Perfusion Imaging Evaluation For Understanding Stroke Evolution (DEFUSE) Trial studied whether MRI criteria helped determine responders to IV tPA in patients treated 3 to 6 hours after stroke

symptom onset [27]. A perfusion/diffusion mismatch was found in 54% of patients with interpretable PWI scans and in this group early reperfusion was associated with a favorable response in 56% of patients compared to only 19% of patients with no mismatch. Those patients who had large DWI lesions fared worse with a very low rate of good clinical response and a high rate of hemorrhage when reperfusion occurred [27]. MRA showed that 65% of patients had a symptomatic arterial occlusion before treatment. Complete early recanalization occurred in 27% and partial recanalization in 16% as determined by follow-up MRA. Patients with early recanalization had a 74% reduction in PWI volume compared with 16% with no recanalization [27].

DIAS and DEFUSE showed that MRI and MRA could be used effectively to select patients for thrombolysis even within the 3-9 hour window. Modern CT profiles that included CTA and perfusion CT should also be able to select patients with arterial occlusions with no or small infarcts and larger perfusion defects that would be amenable to thrombolysis irrespective of time.

C. Action responses and guidelines

Release of the results of the NINDS trial stimulated a movement in the USA to quickly (much too quickly in my opinion) introduce IV thrombolysis widely into the community. During the summer of 1996, about one-half year after publication of the NINDS trial, despite the failure of the ECASS l trial, the United States FDA approved the use of rt-PA to treat stroke patients within the first 3 hours. A meeting was called by NINDS shortly after FDA approval to urge immediate institution of IV thrombolysis into every hospital in the USA. The American Heart Association [29] and American Academy of Neurology [30] published treatment guidelines that followed exactly the inclusion and exclusions and the treatment protocols of the NINDS trial. A CT scan done before thrombolysis should not show major infarction, mass effect, edema, or hemorrhage. The guidelines did not require or suggest MRI or vascular tests before treatment. Guidelines updated in 2007 concerning early management of adults with ischemic stroke did not substantially alter the original guidelines concerning IV rt-PA administration [31].

Canadian and European authorities approved the use of rt-PA much later than the USA. The European Medicines Evaluation Agency (EMEA) conditionally approved alteplase (rt-PA) in September 2002 to treat ischemic stroke by experienced clinicians within 3 hours of symptom onset. A condition mandated by the European Union regulatory authorities for definitive approval of thrombolytic therapy was that treatment safety would be monitored during a three year period by entering all treated patients in a web register, the SITS

Monitoring Study – SITS-MOST Registry. In this registry, during a 4-year period, data from 6483 patients from 285 centers in 14 countries were entered [32]. At 24 h, 1.7% of patients had symptomatic intracerebral hemorrhages compared with 8.6% in the previously reported pooled randomised controlled trials. The mortality rate at 3 months in SITS-MOST was 11.3% compared with 17.3% in the pooled randomised controlled trials. The investigators concluded that intravenous rt-PA use was safe and effective in routine clinical practice when given within 3 h of stroke onset.

D. Critique and moving forward

If an unbiased committee wrote a report card on the status of IV thrombolysis to date, they would find much good and much to be desired. Finally there was a drug that all agreed was an effective stroke treatment. Before rt-PA therapeutic nihilism prevailed. Approval of rt-PA was a wake-up call. *Stroke can and should be treated.* Stroke patients must be taken quickly to medical centers, and doctors and hospitals must become prepared and able to treat them. Doctors and the media, politicians, and authorities called the attention of the public and of doctors to stroke.

Unfortunately, doctors and medical centers have been slow to heed the call. Only about 1-2% of acute stroke patients are now treated with thrombolytics. About 4-5% of patients who arrive at medical centers in the USA and are eligible for thrombolysis under present guidelines actually receive it. Many hospitals, doctors, ambulance services, and emergency room units are still inadequately prepared to treat acute stroke patients. Some physicians, especially emergency room doctors, remain unconvinced about thrombolysis and are unwilling to give thrombolytic drugs for stroke patients. The guidelines for treatment are hopelessly outdated and do not consider advances made since the randomized NINDS and ECASS Trials. There are not enough doctors sufficiently trained and experienced to handle acute stroke patients. There is still much that is not known about thrombolyis (and is not likely to be learned unless the present guidelines are updated).

When the ECASS and NINDS studies were planned, available technology was limited. Since then there has been a dramatic upgrade in MRI, CT, and ultrasound technology that can safely and quickly yield information about the presence, location, and amount of infarcted brain and arterial and venous occlusions. Thrombolysis can be effective if given within 3 hours following present guidelines, but the present guidelines are not optimal. Patients now excluded such as those who awaken with neurological symptoms, those who have minor deficits or have improved substantially, and those treatable only after 4.5 hours could respond to treatment. Are there also patients now treated

under the guidelines who should not be treated because of little likelihood of success and high risk of hemorrhage or edema?

Knowledge gained from modern brain and vascular imaging can select for treatment some patients now included and excluded under present guidelines. The knowledge used to best choose treatment is listed in Table 1. The present guidelines: use firm time windows, do not suggest or even mention vascular imaging, exclude patients who awaken with deficits, have mild or improving signs, or have seizures.

Patients who awaken with neurological symptoms often have brain and vascular imaging that show treatable vascular occlusion patterns and no or small infarcts and are excellent candidates for thrombolysis [33]. Many patients who enter with slight deficits or improving signs later develop severe strokes. Improving or slight deficits are one of the most common reasons for present exclusion from thrombolysis. A substantial number of patients who later deteriorate have occlusive vascular lesions that are amenable to thrombolytic treatment [34]. Some patients already have large infarcts and little recoverable brain when brain imaging is performed within 3 hours. These patients can be harmed by thrombolysis. Seizures at or near onset do occur in some acute ischemic stroke patients, especially those with embolic strokes [36]. Other reperfusion strategies including initial IA treatment, bridging IV then IA thrombolysis if arteries are not opened, mechanical thrombus removal, primary stenting of occluded arteries are now being used clinically in many advanced stroke centers. Knowing whether there is an arterial occlusion and its location and the extent of infarction already present might lead clinicians to choose no thrombolysis, IV treatment, or to consider IA treatment, or combined IV then IA treatment.

The site of arterial occlusion strongly affects the likelihood of reperfusion after IV and IA thrombolysis. The more one knows about the patient, the more logically the clinician can choose acute and more chronic treatment. The present guidelines desperately need revision to account for information

1. The nature, location and severity of the causative vascular-cardiac-hematological conditions
2. The mechanism of ischemia – hypoperfusion or embolism
3. The cellular and serological components of the blood
4. The state of the brain – normal, "stunned", or infarcted.

Table 1. Data needed to logically choose treatment for patients with acute brain ischemia.

gained since the NINDS trial was published. The guidelines should build in flexibility according to the technology available and the experience and training of the treating physicians and the desires of the patient.

II. Carotid artery surgery vs angioplasty/stenting

A. Background

Randomized trials clearly showed that carotid endarterectomy was more effective than best available medical therapy used at that time in patients with neurologically symptomatic, severe (70% luminal narrowing) carotid artery stenosis [36-38]. Endarterectomy removed the obstructing lesion dramatically augmenting flow and also removed the source of intra-arterial emboli. Endarterectomy was also shown to be somewhat effective in selected patients with luminal stenosis in the 50-69% range [39-40].

Until recently, endarterectomy was the most common method of unblocking an artery by direct surgery. Capillaries, small arterioles, and neurons were often damaged during ischemia. When flooded with blood under high pressure, these abnormal vessels might bleed. The carotid sinus was also damaged during endarterectomy, leading to failure of the carotid sinus reflex and accelerated hypertension in the hours and days after carotid endarterectomy. Elevated blood pressure and flooding of damaged vessels was a recognized cause of brain edema and ICH after carotid endarterectomy.

The successful use of angioplasty and stenting to treat coronary artery stenosis led to application of stenting for carotid artery and other neck and intracranial arterial stenosis [41,42]. Between 1996-1999, 11 carotid stent series published results in 1,311 patients [42]. The overall reported rate of technical success was >95%; procedure-related mortality rates (including cardiac deaths) were 0.6%-4.5%; major stroke rates were 0%-4.5%; minor stroke rates were 0%-6.5% ; and the 6-month restenosis rate was <5% [42]. Some series that included very high-risk cohorts reported less favorable results.

Clinicians and surgeons asked how carotid endarterectomy and stenting compared. There now have been 5 major trials: Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS) [43], SAPPHIRE [44], SPACE [45], EVA-3S [46], and CREST [47]. These trials all had different inclusions and exclusions, different rules for including surgeons and interventionalist, and different use of various protection devices. In the CREST trial stenting was followed by more strokes but endarterectomy was followed by more myocardial infarctions. Younger patients seemed to do better after stenting while older individuals fared better after surgery [47].

During the time that the various surgery and stenting trials were performed, medical therapy improved dramatically especially with the more widespread

use of statins, newer antithrombotic agents, and more available agents for the control of blood pressure and abnormal glucose metabolism. Spence published data derived from aggressive medical therapy of patients with carotid artery disease and posited that now medical therapy might be equal or better than either surgery or stenting in controlling carotid artery disease [48,49].

B. Critique and moving forward

It is rather naïve to posit that one treatment is best for all patients and all situations. One treatment – endarterectomy – may be better in some circumstances and stenting be preferred in others. Table 2 tabulates the factors used to choose one treatment or another. None of the trials considered the nature of the vascular lesions, yet studies show that some lesions might pose more risk for stenting and others for surgery [50].

1. We need further studies of treatment of carotid artery and vertebral artery occlusive disease in the neck
2. Studies should include an arm of optimal modern medical treatment (high dose statins, ACE-inhibitors or ARBs, antiplatelets, and life-style modifications, in addition to surgery and angioplasty/stenting)
3. Studies should include more detailed analysis of the vascular lesions using advanced technology
4. Studies should include analysis of the risk/benefits of distal and other protection devices and strategies.

1. Nature of lesions
    - Level of carotid bifurcation
    - Length of lesion especially extent rostrally
    - Severity of the stenosis
    - Distal severe tandem stenosis
    - Smoothness vs irregularity; ulceration
2. Age, sex, and comorbidities
3. Coronary artery disease
4. The benefits vs risks of using needed double antiplatelet use during and after treatment
5. Hypertension and diabetes if poorly controlled
6. The experience and record of the surgeon
7. The experience and record of the interventionalist
8. The benefit vs risk of angioplasty and/or employing protection devices during stenting
9. The patient's and family's preferences.

Table 2. Factors used to choose treatment for patients with carotid artery disease

III. Increasing the brain's tolerance and resistance to ischemia ("Neuroprotection")

A. Background

Theoretically, there might be substances or strategies that make the brain relatively resistant, at least for some time, to the deleterious effect of lack of oxygen and energy delivery, that is keeping brain cells alive despite poor perfusion. Trials of putative neuroprotectants, when used alone without adjunctive measures to enhance reperfusion, have all resulted in failure. Agents that were effective in experimental animal models of acute ischemia had no or little benefit in humans with brain ischemia. Many failures are likely due to suboptimal trial design and testing [17].

Armchair ideas and theories abound and far outweigh the data, but this field of investigation still may prove fruitful in the future. Trials in human stroke patients have not always been well designed to show an effect of the various therapies. They have customarily been given to all patients with acute stroke, and in most studies full brain and vascular imaging have not been mandated at entry or follow-up.

Among all patients with acute brain ischemia:

1) Many would have already developed large infarcts. These could be identified by DWI MRI scans or full CT protocols. Dead brain cannot respond to neuroprotection.
2) In many patients the blood vessels supplying the ischemic brain are occluded. The neuroprotective agents might not reach the ischemic neurons because the entry main road is blocked. Administering the agents to patients who have open arteries or are undergoing thrombolysis or other reperfusion techniques would be most effective.
3) White matter infarcts especially lacunes might not respond to neuroprotective agents that are cytoprotective since the white matter consists of tracts and not neurons.

B. Moving forward

If a neuroprotective agent proves effective among patients investigated thoroughly using modern neuroimaging who have small or no brain infarcts, open arteries (or are undergoing reperfusion), and non-lacunar mechanisms, and the agent is safe, it will become widely used. Because cerebral cortex is mostly the aim of protection, cognitive and behavioral testing is needed to show a benefit. The presently pursued strategy of treating all acute stroke patients provides a very difficult barrier for any neuroprotective agent to hurdle. Small studies of fully evaluated patients, after thorough animal

and pharmacokinetic data, might identify suitable neuroprotective agents for larger trials of well evaluated patients.

IV. Randomized therapeutic trials of secondary prevention of stroke and guidelines

The term "evidence-based" has become a sacrosanct icon almost like motherhood. Who could possibly argue against basing medical treatment decisions upon evidence. It is difficult to think of a polite term for decisions based on no evidence. The only evidence now given credence in determining the evidence-base is that garnered from randomized controlled trials (RCTs) especially those that are double blinded. Lectures and reports on treatment are now customarily ended by the authors calling for a new RCT or demanding that future treatment of the condition be evidence-based.

The emphasis on RCTs as a basis for all treatment has been overstated especially in relation to Neurology [51-53]: 1) many, if not most, treatment conundrums, are not suitable for RCTs; 2) RCTs have significant limitations that reduce their applicability to individual patient therapeutic decisions, 3) the quality of the evidence and the context of how the evidence was acquired and the situation in which it will be applied are given insufficient attention, and 4) the evidence does not consider the personal- the complexities of the individuality of each patient.

Marriage of the therapeutic and computer eras has led to the proposition that all treatment should be based on data from therapeutic trials. This is also the managed care era. Some managers warmly embrace evidence-based treatment. Realizing that little that doctors now do is based firmly on trial results, managed care organizations and insurance companies save money if they only pay for scientifically proven treatments. An alarming scenario has evolved. One or more RCTs are performed that show positive results. The treatment is then assigned an "evidence-based" label and organizations promulgate guide-lines based on the results of the RCTs. Managed care organizations and lawyers embrace these guidelines and physicians who deviate from the guidelines in treating individual patients (whether or not the context of the RCTs is relevant to that patient) become potentially culpable. Treatments that are not "evidence-based" are not approved by payers. Medico-legal suits are sometimes pursued against physicians who have not followed "evidence-based" guidelines.

Randomized therapeutic trials placed in clinical perspective

Trials have important limitations. Trials require enormous resources. To provide statistically valid results, randomized trials must contain large num-

bers of patients with enough end points for analysis. Sufficient end points must be reached in a short period of time. The condition studied must either be acute and cause adverse end points or rapid improvement within a short time. Chronic conditions must be severe enough to cause clear end points within 1-5 years of follow up. Many medical and neurological conditions are unsuitable for trials. Patients who are too ill, too old, too young, female and "of childbearing age", incapable of giving informed consent, too complex, or too full of coexisting illnesses are excluded from trials.

The major limitation of trials is the numbers vs specificity issue. To include large numbers of patients, the condition studied must be common and multiple physicians at multiple centers must be recruited. One center would have too few patients or would take an unacceptably long time to accrue the number of patients needed. Uncommon conditions cannot be studied in RCTs because doctors are unable to acquire enough patients for statistically valid analysis. To achieve numbers, a "lumping" strategy must predominate over "splitting". The more a study lumps diverse subgroups, the more general are the results and the less they are applicable to specific patients. General answers are useful to introduce subjects, however, for practicing physicians, treatment must be very specific. To be useful, trial results must help physicians treat complex individual patients in given situations. In the free world, no physician is likely to be faced with treating thousands of individuals with the same treatment irrespective of their individual characteristics but that is the situation in trials. RCTs mandate that numbers of patients with a general condition will be given treatment X and the results will be compared with patients given a placebo or treatment Y. The results will be useful to the treating physician only if the general data is applicable to the specific problem.

Brain ischemia and drugs that alter platelet functions

RCTs have shown definite but relatively small benefit for aspirin, aspirin combined with dipyridamole, ticlopidine, cilostazole and clopidogrel in patients lumped together as having TIAs or minor strokes [17]. The patient mix studied and treated with antiplatelet aggregants or placebo was not representative of patients in the community. Classification of the nature and severity of the causative vascular and cardiac lesions was not required for entry in any of these trials. Many trials antedated recent advances in modern vascular imaging. Patients with lesions thought favorable for carotid surgery were often operated on and were ineligible for the trials. Patients with "surgical" lesions deemed unfit for surgery – and patients unfit for angiography were included in medical treatment groups. Some patients with detected

cardiac sources of emboli were not entered. No systematic evaluation for carotid artery or cardiac disease was mandated in any of the studies. Subgroup analysis was only by sex and tempo of ischemia (TIA or minor stroke). The tempo of ischemia does not predict the nature, severity, or locale of causative vascular lesions. Since cardiac studies were not required, the groups also must have included patients with cardiac-origin brain embolism. The studies did not analyze the effect of race on treatment. A meta-analysis of randomized control trials of antiplatelet agents in the secondary prevention of stroke found "for aspirin compared with placebo a nonsignificant reduction in stroke of 15% ... a trend in reduction of stroke for any regimen containing aspirin". . . . "It is still conceivable that aspirin alone may decrease the incidence of stroke by as much as 40%, but a sample of >13,000 patients would be needed to confirm the benefit observed in our analysis" [54]. Guidelines use the results of these trials to recommend the use of antiplatelet aggregants for patients with TIAs and minor strokes. However, the results of these studies are difficult for physicians to apply to individual stroke patients with identified stroke mechanisms e.g stenosis of the MCA or cardiogenic embolism. The result is that the trial data, despite enormous expense, is not very useful for physicians treating patients with the conditions studied in the trials. Are platelet antiaggregants useful in patients with microangiopathies (lipohyalinosis and atheromatous branch disease)? Are antiplatelet aggregants more useful than anticoagulants or other drugs in patients with slight or moderate stenosis of the carotid and/or vertebral arteries in the neck or for intracranial artery stenosis?

Critique and moving forward

Future trials of antiplatelet aggregants should contain sufficient subgroup data related to the presence and severity of vascular lesions and various stroke mechanisms to be meaningful to practicing physicians. Guidelines for antithrombotic use need to build in flexibility and context. Medical treatment decisions are often difficult. It takes time to get to know patients and their particular conditions, comorbidities, social-psychological-economic backgrounds, and desires. Table 3 lists the key factors in choosing treatment for an individual patient. Each patient is unique. Comorbidities clearly effective decision-making. So does the social-economic-psychological background of the patient. The opinions, concerns, and desires of spouses, family, children, and other members of the patients' milieu also often need to be factored into decisions. Some patients are risk-takers while others are very conservative and risk-adversive. Some patients relish statistics and choose therapies logically. Others eschew "science" and smoke, eat too

much, drink too much, take harmful drugs, exercise too little, and rely on herbs, vitamins and alternative medicines.

RCTs that answer clinically relevant questions are clearly needed. We also need more careful observations from experienced clinicians and more observational studies. More patients with complex illnesses need management by specialists as well as primary care physicians. RCTs and evidence-based medicine do not hold as much promise for the future as their advocates posit. We need to convince young physicians and medical students to go back to the bedside and to learn as much as possible about their patients and about the fundamental anatomy, pathology, and pathophysiology of the patients' diseases. Decisions take time, patience, experience, and repeated patient encounters. But these key ingredients are not valued highly in our money-driven managed care dominated environment.

1. Understanding what is wrong with the patient in as much detail as possible
2. Understanding the patient's risks for disease and for complications of potential treatments
3. Understanding the patient – their background, genetics, stresses, socio-economic milieu, psychology, responsibilities, goals etc.
4. Understanding the benefits and risks of potential therapeutic strategies to treat the patient's conditions (often multiple) and to prevent conditions that they are at risk for developing
5. Communicating with the patient and often family members and friends, listening and conveying information, and teaching.
6. The patient and their families' preferences.

Table 3. Factors important in choosing treatment for individual patients.

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