Evidence, Education and Practice

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Key Words

Antiplatelet agents • Brain infarction • Carotid surgery • Intracerebral haemorrhage • Neuroprotective agents • Statins • Stroke prevention • Stroke units • Subarachnoid haemorrhage • Thrombolysis

Abstract

Stroke causes greater loss of quality-adjusted life years than any other disease and is also one of the most expensive disorders. The burden of stroke will increase in the future due to change in the age structure of populations. We have a vast body of evidence on how to prevent stroke and how to treat stroke patients. Good examples are treatment of hypertension, antithrombotic agents and carotid surgery in stroke prevention, thrombolysis in ischaemic stroke and stroke unit care for all stroke patients. We only have to translate scientific evidence into daily practice. If some pieces are missing, it is our duty to generate them through research. While taking part in randomized clinical trials (RCTs), the discipline, an essential part of RCTs, will improve the daily care of all stroke patients. Besides RCTs there are many other sources of scientific evidence for stroke management, one of which is the European Stroke Initiative (EUSI). The mission of the EUSI is to improve and optimize stroke management in Europe through education and by offering best practice guidelines. Also national and international societies and organizations play an important role in providing education. The human factor is one obstacle to more successful stroke management because to be more effective we must change our own clinical routine. We can make a difference by applying available evidence to our daily practice.

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Introduction

As a first-year medical student I heard of a young talented neurosurgeon at the Department of Neurosurgery of our teaching hospital. I asked him if I could start to investigate experimental head injuries and cerebral blood flow under his supervision. He was an excellent teacher and a very critical tutor and from him I learned a lot of experimental and clinical research. Since then I have studied epidemiology [1–3], risk factors [4–14], pathophysiology of atherosclerosis [15–17], acute stroke [18–29], and aftermath of stroke [30–42]. In this review I discuss some points of stroke prevention and acute care in which I have been involved, how results of these studies have translated into daily clinical practice, and the role of education in this process.

Stroke causes greater loss of quality-adjusted life years than any other disease [43] and stroke is one of the most expensive disorders. In Finland only mental diseases and dementia are more expensive than stroke. Annually 6.1% of total health care and social welfare costs are incurred by stroke [44]. In our country incidence and mortality of stroke are decreasing in all age groups [2, 45]. In spite of declining incidence, both the loss of quality-adjusted years of life and the amount of money spent to treat stroke patients will increase in the upcoming decades due to changes in the age structure of populations [46]. If we are not able to improve the prevention and acute care of stroke in the future, we will not be able to provide decent care to all stroke patients. If some pieces of effective prevention and acute care are missing, it is our duty to generate the missing information through scientific research.

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In few other fields of medicine there is as much scientific evidence based on randomized clinical trials (RCTs) as in stroke prevention and acute care of stroke. The human factor is one of the most important obstacles because it often means that we need to change our own routines and the way we view stroke and treat stroke patients.

Prevention

Prevention is the most cost-effective way of stroke care but quite often there is not too much time. Many patients suffer stroke during the first few days after a transient ischaemic attack (TIA) [47], and accordingly the threatened stroke patients must be evaluated as an emergency to tailor the best prevention.

Carotid Surgery

Years ago we did not know which TIA and stroke patients to operate on and which to treat medically. The complication rates of carotid endarterectomy (CE) could be over 10% [48, 49], which was not satisfactory. These were good reasons to start randomized trials both in Europe and in the United States of America. We joined the NASCET trial and when the NASCET and ECST trials were executed, we knew who was in need of surgery [50–52]. Only skilled surgeons were allowed to perform CEs with low complication rates as a result. The same idea was transferred to routine daily practice thus leading to low complication rates outside RCTs as well. After the NASCET and ECST trials, we knew the criteria for CE in symptomatic patients with tight carotid stenosis but not for patients with asymptomatic stenosis. This was a good reason to join the ACST trial carried out in Europe. The ACST, and the ACAS trial carried out in the USA, revealed that patients with asymptomatic stenosis benefit from CE [53, 54], but the risk of complications must be lower than in symptomatic patients to justify surgery. If the rate of surgical complications in a hospital performing CEs is over 5–6% in symptomatic and over 2–3% in asymptomatic patients, medical therapy is the best alternative for the patients. Discipline required in these trials was transferred to everyday practice and translated into reduction of complication rates.

Angioplasty and Stenting

Angioplasty and stenting are time-honoured ways to prevent myocardial infarction but not stroke. In the CAVATAS trial the complication rates were over 10% in both CE and angioplasty arms, i.e. much too high to jus-

tify either in threatened stroke [55]. The recommendations of the American Heart Association and the European Stroke Initiative say that carotid angioplasty and stenting should only be performed in well-designed and well-conducted randomized trials. The results of SPACE and EVAS-3S were presented at the ESC 2006 in Brussels [56, 57]. Especially the results of SPACE were encouraging and together with ongoing trials such as e.g. SAPPHERE, ICSS (CAVATAS 2), and CREST they will give an answer to what the role of angioplasty and stenting is in stroke prevention.

Medical

Hypertension is the most important risk factor for stroke and accordingly, antihypertensive treatment has for a long time been the backbone in prevention of stroke. This also became evident in trials such as LIFE aimed at prevention of myocardial infarction [58]. Antiplatelet agents are another backbone in stroke prevention. Numerous antiplatelet trials and the meta-analysis of the Antithrombotic Trialists' Collaboration have verified the efficacy of acetylsalicylic acid (ASA), ticlopidine, clopidogrel, and the combined ASA plus slow-release dipyridamole in stroke prevention [59]. The results of ESPRIT presented at the ESC 2006 in Brussels confirmed those of ESPS 2 [60]. Because the efficacy of ASA is far from optimal, we have taken part in such trials as CAPRIE [61] and MATCH [62], the results of which have left space for more effective therapies in stroke prevention. Therefore we are now taking part in the PROFESS, PERFORM and CASTIA trials.

The MRC/BHF Heart Protection Study [63] revealed that statin prevented the combined end point of stroke, myocardial infarcts and vascular deaths in patients with stroke or TIA significantly, as they had prevented strokes in patients with coronary heart disease in such trials as CARE and LIPID [64–66]. To find out whether statin treatment could prevent stroke in patients with TIA or stroke we took part in SPARCL [67], the results of which were presented in the European Stroke Conference in Brussels [68]. The results were positive and may change the role of statins in stroke prevention. Taking part in all these trials of medical prevention of stroke has taught us the value of systematic evaluation of the aetiology and risk factors of stroke as well as the importance of compliance and follow-up of patients in stroke prevention. The discipline required in these randomized controlled trials was reflected in everyday clinical practice by improving it significantly.

Treatment of Acute Stroke

Subarachnoid Haemorrhage

While there are many options in stroke prevention, the situation is more difficult when trying to find treatments for acute haemorrhagic and ischaemic strokes. Finland has the highest incidence of subarachnoid haemorrhage in the world [2, 3, 69]. In the past, with an insufficient capacity for neurosurgery, patients were operated on late and surgery seemed not to make any major difference for the outcome of patients with aneurysmal subarachnoid haemorrhage. A 10-year follow-up after a randomized trial was needed to show that late surgery was effective [70]. Surgery within the first 3 days turned out to be the optimal time in another randomized trial [71]. How to prevent recurrent subarachnoid haemorrhage before contemplated surgery was a dilemma. Tranexamic acid seemed to be a promising drug but a randomized double-blind placebo-controlled trial revealed that the drug had no place in the prevention of recurrent haemorrhage [72] and early surgery together with nimodipine therapy offered the best outcome [73].

Intracerebral Haemorrhage

Therapy of spontaneous intracerebral haemorrhage is still a challenge. We carried out a randomized trial of emergency surgery which revealed that emergency surgery cannot help such patients [74]. Our results were later on verified by the large STICH trial [75]. While surgery was not effective in improving the outcome of patients with spontaneous intracerebral haemorrhage, treatment with recombinant activated factor VII turned out to be effective in a phase II trial in which we took part [76]. The study gave a strong positive signal, and now we are trying to verify it in a larger FAST trial. If the FAST trial is positive, we have the first effective treatment for spontaneous intracerebral haemorrhage.

Brain Infarction

For acute ischaemic stroke we have tested numerous promising drugs in multiple randomized double-blind placebo-controlled trials [77–84] and failed until SAINT I [85]. In the first of them, a single-centre double-blind placebo-controlled trial of combined dexamethasone and dextran, we found out that the combined therapy was not able to improve the outcome of patients with ischaemic stroke [78]. We understand now that the therapy was started too late and the trial was underpowered. STAIR meetings have improved the methodology of clinical trials of acute ischaemic stroke therapies [86]. If

SAINT-2 will verify the results of SAINT-1, we have the first effective neuroprotein for acute ischaemic stroke.

Thrombolysis

We have succeeded better with thrombolytic agents. Although two European trials studying intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA), ECASS and ECASS II, were not able to show positive results, probably because their sample sizes were too small in relation to their 6-hour time window [87, 88], the American rt-PA trial with a 3-hour time window was positive [89] and led to the first approved treatment for ischaemic stroke. While participating in these trials we learned how this demanding treatment can be provided effectively. The pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA studies suggested that the time window is probably longer than 3 h for some patients [90], and in the currently ongoing ECASS 3 we are trying to extend the time window up to 4.5 h. Modern neuroimaging may be better than a watch in patient selection. We took part in DIAS-1, which suggested a time window up to 9 h [91]. DEDAS, a sister trial of DIAS, revealed similar results [92] and now we are trying to verify these results in DIAS-2.

Mechanical Recanalization

Proximal carotid terminus and M1 middle cerebral artery thrombi show a poorer response to intravenous thrombolysis and for this reason the MERCI retriever is an interesting alternative that seems to recanalize such thrombi [93]. It is not known whether it improves the clinical outcome of patients and therefore there is a need for further studies. We are currently planning such a new trial.

Thrombolysis in Stroke and SITS-MOST

Thrombolysis in stroke is more effective than thrombolysis in acute myocardial infarction (fig. 1). We have provided thrombolysis for selected stroke patients since the end of ECASS II and our results are good [94, 95]. When the European Health Authorities approved thrombolysis with alteplase for treatment of ischaemic brain infarction within a 3-hour time window in 2002, they also recommended that all patients treated with rt-PA according to the licence specification should be included in the SITS-MOST register to make sure that the therapy was safe also outside randomized trials. This made it possible for doctors and hospitals treating stroke patients with rt-PA to compare their own performance with the general data pool of the register. The SITS-MOST register re-

Fig. 1. Comparison of the relative efficacies of thrombolysis in acute myocardial infarction (AMI) and acute ischaemic stroke (stroke) per 1,000 patients treated. End points are death in AMI and death and disability in stroke. Reproduced with kind permission from Lindsberg and Kaste [111].

vealed that since the start of the register the neurological emergency room of our department treated more stroke patients with thrombolysis than any other hospital in Europe and also the number of ultra-early patients was higher than in any other European hospital. A well-organized service has made it possible and we have kept the position all the way up to the end of the SITS-MOST register on April 31st, 2006. The early results of SITS-MOST presented at the ESC 2006 in Brussels verified that thrombolysis delivered in routine stroke care is equally safe and equally effective as in RCTs [96]. In 2004, our neurological emergency room treated 100 patients with rt-PA. In 2005, the number of stroke patients receiving thrombolysis was 183 and during the first 4 months of 2006 when the register was still running, we treated 64 patients with rt-PA, i.e. the number of treated patients was increasing until the end of the SITS-MOST. The functional outcome of our patients continues to be good: 2 out of 3 patients treated within 90 min, 3 out of 4 of those treated within 80 min, 4 out of 5 of those treated within 70 min and almost all of those treated within 60 min from the onset of symptoms reach modified Rankin grades 0–2 at 3-month follow-up.

Colleagues from other Finnish hospitals served at our emergency room and we organized educational courses on stroke thrombolysis on behalf on the Finnish Neuro-

logical Society. These courses included training of CT reading and tests arranged by Rüdiger von Kummer. Education, training and taking part in ECASS, ECASS II and ECASS 3 may have contributed to the fact that according to the SITS-MOST register more stroke patients per 1,000,000 inhabitants receive thrombolysis annually in Finland than in any other European Union member country. This example shows that it is possible to provide thrombolysis for stroke patients nationwide.

Stroke Units

We have been a part of Stroke Unit Trialists' Collaboration because stroke unit care reduces the likelihood of death or disability and the need for institutional care [97, 98]. All patients with stroke regardless of age, sex and severity of stroke benefit from stroke unit care and it is cost-effective as well. Well-organized acute care and early rehabilitation of patients by a multidisciplinary team are the key to success in stroke care. University teaching hospitals are often considered to be too expensive for stroke patients. We carried out a randomized trial which is part of the database of Stroke Unit Trialists' Collaboration. The study showed that non-selected stroke patients treated by our multidisciplinary team were able to leave the hospital earlier, went more often straight home, and at 1-year follow-up were more often independent in the activities of daily life [99]. The results convinced the decision makers of Helsinki of the fact that a well-organized stroke service is cost-effective albeit provided by a university teaching hospital and they decided that we should be responsible for all acute stroke patients of Helsinki.

Education

National Recommendations and Guidelines

Translating scientific evidence reached in clinical trials into everyday clinical practice is not an easy task but education of professionals and laypeople provides an effective way. National and international guidelines are an essential part of this education. In this process Finland has quite a long history. In 1979, I chaired a task force, which wrote the first national guidelines for the management of stroke [100]. I co-chaired the second Task Force nominated by the National Board of Health which updated the guidelines [101]. These guidelines stated that all patients living in their own homes suffering from stroke should be brought to the emergency room of the nearest big hospital, and there neurologists should be responsible for their care. Because it was an official statement, it was

followed nationwide. Now I am chairing the third task force updating the national guidelines.

International Recommendations and Guidelines

The Helsingborg Declaration 1995 stated that in Europe all patients with acute stroke should have access to care in specialized stroke units by the year 2005. The organizers of the consensus conference, WHO and the European Stroke Council in collaboration with the European Federation of Neurological Societies, International Stroke Society, World Confederation for Physical Therapy and World Federation of Occupational Therapists, had nominated a few people to write drafts for the five parts of the consensus declaration. I was responsible for the draft of acute care. Because a few of us were not sure whether the Helsingborg Declaration could make a difference in stroke care in Europe, we founded the European Stroke Initiative (EUSI) in 1996, a joint activity of the European Stroke Council, the European Federation of Neurological Societies and the European Neurological Society.

European Stroke Initiative

The mission of the EUSI is to reduce the incidence and burden of stroke by changing the way stroke is viewed and treated in Europe. EUSI aims to achieve this mission through educating medical professionals and the public. EUSI recommendations for general practitioners and specialists are an essential part of education [102–110]. These recommendations written by experts are first approved by the three scientific societies behind EUSI and then published in *Cerebrovascular Diseases*. The recom-

mendations are updated regularly and have been translated into ten major languages. Educational activities of EUSI include annual Stroke Summer Schools for young physicians interested in stroke and symposia in connection with European Stroke Conferences. EUSI has set up the Virtual Stroke UniversityTM providing CME credits and a well-visited website (www.eusi.org). This year EUSI will launch a 2-year academic programme for Master of Science in Stroke Medicine as a joint effort of many esteemed European universities.

Conclusions

Due to changes in the age structure of populations stroke will be more common in the future, although at present it is the third most common cause of death and the most important cause of long-standing disability. For these reasons stroke causes major economic losses. However, stroke can be prevented and it is possible to recover from it. Both prevention of stroke and acute care of stroke patients are evidence-based medicine. We can make a difference in stroke care by applying scientific evidence to our daily practice. It is our responsibility to achieve the still missing information through research, and we must take the challenge now so that we do not need to explain to our children and grandchildren, why we did not do it when there still was time. The examples listed above show that it is possible to improve stroke care nationwide and also on a larger scale. It only takes years of hard work in research, education, and organizing stroke services but it is time well spent.

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