Implication of the Recent Positive Endovascular Intervention Trials for Organizing Acute Stroke Care
European Perspective
Turgut Tatlisumak, MD, PhD

Abstract—Timely recanalization leads to improved patient outcomes in acute ischemic stroke. Recent trial results demonstrated a strong benefit for endovascular therapies over standard medical care in patients with acute ischemic stroke and a major intracranial artery occlusion ≤6 hours or even beyond from symptom onset and independent of patients’ age. Previous studies have shown the benefit of intravenous thrombolysis that had gradually, albeit slowly, reshaped acute stroke care worldwide. Now, given the superior benefits of endovascular intervention, the whole structure of acute stroke care needs to be reorganized to meet patient needs and to deliver evidence-based treatments effectively. However, a blueprint for success with novel stroke treatments should be composed of numerous elements and requires efforts from various parties. Regarding the endovascular therapies, the strengths of Europe include highly organized democratic society structures, high rate of urbanization, well-developed revenue-based healthcare systems, and high income levels, whereas the obstacles include the east-west disparity in wealth, the ongoing economic crisis hindering spread of fairly costly new treatments, and the quickly aging population putting more demands on health care in general. Regional and national plans for covering whole population with 24/7 adequate acute stroke care are necessary in close cooperation of professionals and decision-makers. Europe-wide new training programs for expert physicians in stroke care should be initiated shortly. European Stroke Organisation has a unique role in providing expertise, consultation, guidelines, and versatile training in meeting new demands in stroke care. This article discusses the current situation, prospects, and challenges in Europe offering personal views on potential solutions. (Stroke. 2015;46:1468-1473. DOI: 10.1161/STROKEAHA.115.008386.)

Key Words: organization ■ thrombectomy ■ thrombolysis

Timely recanalization is the most powerful predictor of improved outcome in patients with acute ischemic stroke (AIS). However, delay in presentation at a fully equipped stroke center is the major reason why patients with AIS are not eligible for recanalization therapy with intravenous thrombolysis (IVT) or endovascular interventions (EVI). Early presentation not only increases the proportion of patients treated, but the earlier the treatment is given, the greater the treatment benefit will be: saving 1 minute in initiating IVT leads to one additional healthy day of life in average (hence the term: “save a minute, save a day”). Conversely, delayed treatments are associated with mitigated or no benefits along with an increasing risk for intracranial hemorrhages. Timely arriving patients are evaluated for eligibility for IVT, which improves significantly patient outcomes and is now widely offered across Europe. After the recent publication of the 3 randomized controlled trials and the presentation of a 4th trial reporting positive results for EVI over standard medical care (majority of the patients in the control groups received IVT) in AIS patients, stroke physicians now have another effective treatment option to offer to their patients. However, EVI makes substantial requirements for healthcare systems and needs a substantially new operational plan in each stroke center and nation-wide.

The ESO quickly published a consensus statement on EVI in ischemic stroke patients, setting the indications for EVI and the target group of patients. This statement will likely become the standard of care with some modifications in most centers in Europe and probably will largely help local physicians in their negotiations with decision-makers in the healthcare field.

Implementing the results of these recently published positive trials require that their conclusions must be successfully communicated and disseminated both within the profession and to other parties, including political decision-makers. Health authorities must recommend or set standards through legislation to enforce widespread organizational changes.
that guarantee eligible AIS patients receiving this treatment 24/7 in a timely manner. Second, support, cooperation, and know-how from related professional organizations, such as the ESO and patient associations, will be extremely helpful. A new obligatory criterion for becoming a comprehensive stroke center may well be offering intra-arterial treatments in a 24/7 fashion. Basically, it is reasonable to expect that most European university hospitals start offering 24/7 thrombectomy for AIS patients.

In practice, the establishment of a functioning EVI-delivery pathway may proceed either at a local/regional level (eg, within a university hospital’s catchment area) or at a national level (likely slower, but preferable). If at national level, the process will likely involve legislative changes with a clear order to local/regional health systems to start offering this service. The paradigm may be (1) local stroke physicians take the evidence to hospital administration, local decision-makers, and national decision-makers, such as ministry of health or national parliament, (2) official decision to start offering EVI, (3) resourcing for space, equipment, and other hardware within the hospital and prehospital care elements, (4) skin ware resourcing, such as hiring and training stroke experts, interventionists, nursing staff, and ambulance staff, (5) regional plan for recognition, triage, and rapid transfer of potentially eligible patients to the regionally agreed stroke center that is capable of giving the treatment, and finally (6) regular examination of achievements, bottlenecks, and needs for improvements.

### Basic Facts on Europe

Among the ≈7.1 billion inhabitants of the world, ≈740 million live in Europe with a population density of 73 persons per square kilometer (world average 54). Slightly over half of the world population (54%) lives in urban areas, whereas this number approaches to 73% in Europe. Urbanization brings people closer to fully equipped hospitals given that hospital care is affordable for them: eligible patients living in rural communities are 10x less likely to receive IVT than those living in metropolitan communities.8 Among the ≈50 megacities in the world, only 4 (Istanbul, Moscow, Paris, and Rhine-Ruhr) are in Europe, but Europe is home to numerous large, medium, and small-sized cities (with usually small distances in-between), practically most of them having university hospitals or large-sized nonuniversity hospitals equipped with reasonable stroke-care facilities. Practically, these hospitals could easily develop regional plans with good geographical and temporal coverage of all acute stroke patients for adequate care given that expert manpower and financial resources are available. Europe has a significantly higher life expectancy compared with the world average (76 versus 67 years, respectively). Europe is wealthier than most of the rest of the world with an average income of ≈$260000 per person (the rest of the world average ≈$13000).9 Europeans are highly educated, have stable democratic structures, and have faced few military conflicts after the World War II. Most European countries have publicly funded fairly well-functioning healthcare services. Generally speaking, people living in wealthier countries and especially those living in urban areas have excellent access to adequate stroke care.

But the continent suffers from vast heterogeneity among its population and wealth. Fifty-two countries and territories accommodate populations differing from only 842 (Vatican) to ≈110 million (European part of Russia), density differing between 3 (Iceland) to ≈15000 (Monaco) persons per square kilometer. Population distributions along with income levels are a major factor in organizing accessible and affordable health care. Wealth distributes unevenly throughout Europe: although Lichtenstein and Luxembourg have a $100000 per capita income, Georgia reaches only $55000 annually. In general, European Union member countries are much wealthier than their Eastern European neighbors. The east-west gap in Europe is not reflected in number of physicians, hospital beds, or stroke units, but the disparity is in gross domestic product and total health expenditures. Certain areas in Europe are scarcely populated, with the nearest stroke center being too far away for any acute treatment time windows, some islands and mountainous regions are hardly accessible, and northern parts have severe winters complicating rapid patient transfers. Further disadvantages in Europe are the rapidly aging population (16% of population aged ≥65 years compared with world average of 8.5%) with low population growth and that Europe was struck hard by the economic crisis, currently having annual growth rate of 0.4% (world average 3.8%). Therefore, despite the many advantages, widespread implementation of the necessary changes for covering all inhabitants with EVI is a challenge here as it is elsewhere.

### What Portion of Ischemic Stroke Patients Needs EVI?

When planning reorganization of stroke services to cover all eligible patients with EVI, the first step is to determine patient volumes. Unfortunately, little data are available for estimating what percentage of the AIS patients would indeed require EVIs. Current practices underestimate the need for several reasons, for example, late arrivals, failed referrals, limited access, various criteria applied, and the highly dynamic nature of the patient flows. Epidemiologically, there are ≈1.3 million stroke cases annually in European Union, Iceland, Norway, and Switzerland combined.10 However, large-scale data lack on the percentage of patients presenting with a treatable intracranial artery occlusion, the percentage of patients arriving timely enough for interventions, and a clear definition of the target populations. A reasonable estimate of EVI-eligible patients may be close to 10% of all ischemic stroke patients.11-14 This may total to 130000 interventions Europe-wide and necessitates a large number of highly trained expert physicians, other health staff, suitable facilities and equipment, and well-organized prehospital and emergency room care.

### Recognizing and Triaging EVI-Eligible Patients to Stroke Centers Offering EVI

Early treatment requires increased patient awareness, faster ambulance transfers, clear and quick in-hospital patient pathways, and readiness in hospitals for acute interventions. Sometimes patient transfer is complicated because of reasons, such as the distance, unconventional location, or weather conditions, and no system will ever cover 100% of the patients. However, when the benefits of thrombolysis and thrombectomy are put together, it is time to take all possible organizational changes in the system to ascertain that as many patients...
as possible who are reasonable candidates for acute treatments can have access to adequate care.

Patient and lay-person awareness of stroke, functional emergency telephone support (ie, 112 in the European Union), quickly assigning an ambulance to reach a stroke suspect, triaging immediately in the field, and clear regional patient transfer plan are essential for success. Ambulance staff should be supported by consulting emergency medicine and stroke experts reachable by telephone. Use of easy prehospital screening tools is helpful in improving detection rates of stroke cases in the field.

Ideally, almost all stroke patients should be treated in dedicated stroke centers, but it is extremely unlikely that this will be achieved shortly in Europe. Even a full consensus among stroke experts is lacking on where stroke patients should be treated and by whom.\textsuperscript{15} Considering the safety and efficacy profiles of IVT and EVI in AIS patients and presuming that EVI will also receive approval from authorities in near future, now, there is robust scientific evidence to rapidly transfer any patient with a suspicion of stroke that started approximately within 5 hours to a stroke center where the patient can receive IVT and EVI if deemed eligible. This approach is in line with the recently published ESO consensus statement on the topic.\textsuperscript{7} For other patients, local resources will dictate the patient pathways. However, a crucial point is to always transfer an AIS patient to a comprehensive stroke center if feasible. If a comprehensive stroke center is not within reach, then the patient should be taken to a local hospital with imaging facility and infrastructure for delivering IVT. Hospitals that cannot guarantee 24/7 brain imaging, delivery of IVT, and reasonable acute monitoring of the patient (equal or similar to that in a stroke unit) should not be admitting stroke patients at all.

National acute stroke patient transfer plans with a detailed map ascertaining that the whole country population is covered with 24/7 adequate acute stroke care wherever and whenever the disease hits should be set as the goal when EVI is implemented to health care in near future.

Small hospitals without 24/7 coverage of stroke physicians should join to telestroke networks. Telestroke networks are playing a major role in bringing adequate care to patients living in underserved areas and in reducing inequities in access to care. Numerious publications have already addressed that telestroke is safe and reliable, as well as cost-effective.\textsuperscript{16,17} Establishing regional or national telestroke networks can be facilitated through legislation. Telestroke systems may help identification and quick transfer of potentially EVI-eligible patients as follows: nowadays, all new computer tomography devices in the market are equipped with capability of contrast-enhanced angiography and perfusion imaging. Noncontrast computer tomography can demonstrate in a percentage of large artery occlusion patients the so-called hyperdense artery sign rather reliably, indicating a major intracranial artery occlusion that is usually fairly resistant to IVT.\textsuperscript{1} Further imaging with angiography and perfusion gives more precise information on several aspects and can easily be done by radiology technologists in small hospitals. In the lack of local radiological expertise, the images can be read at a larger hospital by stroke physicians and radiologists through the telestroke audiovisual device or simple digital image transfer systems, preferably by the physicians who are expected to perform EVI if deemed necessary. This approach helps quick recognition of patients eligible for EVI and allows for initiation of IVT locally with a quick transfer to the reference hospital for EVI.

When imaging is not available on-site or the decision where to take the patient must be made in the field, time of symptom onset is certainly the first criterion. Stroke severity may also help in triage: a National Institutes of Health Stroke Scale (NIHSS) score $\geq 9$ within 3 hours and NIHSS $\geq 7$ within 3 to 6 hours suggest a major intracranial artery occlusion with $\approx 85\%$ positive predictive value.\textsuperscript{18} However, predictability was lower in patients with posterior circulation artery occlusions.\textsuperscript{18} Patients with good collaterals may sometimes present with mild symptoms and signs, despite harboring a proximal intracranial artery occlusion and later deteriorate often dramatically over several hours. These patients are usually good candidates for both IVT and EVI, but will remain undetected with a NIHSS-based patient triaging. Therefore, NIHSS-based patient triaging should be avoided, and in the long run, the preferred approach should be transferring all hyperacute stroke patients to a comprehensive stroke center where and when possible. This may lead to a crowded emergency room in comprehensive stroke centers, but is manageable with correct allocation of resources.

In addition to the Netherlands with their Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial logistics and experience, other countries, such as Austria and Switzerland, as well as regions, such as Greater London and many regions in Germany, have developed well-functioning triage plans for 24/7 coverage of patients eligible for EVI. These systems developed for different conditions may help as live examples to those who are initiating their own national or regional systems.

**Manpower and Need for a Whole New Stroke Physician Training Program**

The change in medical practice EVI is bringing will require additional well-trained physicians, especially interventionists. The net manpower need for the health sector might, indeed, be the opposite (ie, savings in labor) because early successful recanalization treatment may well shorten acute hospital stays, diminish the need for long-term rehabilitation, as well as reduce permanent institutional care. The first important question is how to find sufficient number of neurointerventionists for 24/7 coverage at comprehensive stroke centers all over Europe?

The European Union (EU) directive 2005/36/EC regulates free mobility of professionals within the EU.\textsuperscript{19} This directive reorganized medical specialties in Europe. For the sake of harmony, this EU directive listed a limited number of medical specialties that are recognized as official degrees in the whole EU community. This list includes neurology and diagnostic radiology, but not neuroradiology, interventional radiology, vascular neurology, or stroke medicine. Member states may establish other degrees and programs and may grant national diplomas as they wish; however, these degrees are not valid in other member
states. Considering how rapidly medical knowledge is expanding and how new treatments requiring new skills are emerging, the correct direction is increasing number of specialties and educating professionals into continuously narrowing well-focused high-expertise fields. Maintaining and further developing of these skills again require high patient volumes and quality measures, especially when considering interventional treatments. Regarding the constant developments in the field and with an eye on the future scenarios, the second important question is what kind of a stroke specialist training we need in the future and who should be doing neurointerventions in the next decades?

Although in some centers in the United States and Australia neurologists can train in neuroradiology and interventional radiology as subspecialties and that neurosurgeons perform neurovascular interventions in Japan, in Europe, neurovascular interventions are exclusively executed by radiologists, neuroradiologists, or interventional radiologists. Having a 24/7 on-call system for neurointerventionists require a large number of them concentrated in a center. This may be accomplished by organizing regional reference centers where experts from several hospitals within the catchment area are having one single on-call list. Additionally, this activity should be adequately supported by the emergency room, stroke team, imaging facilities, angiography suits, and intensive care services in that reference center.

The majority of stroke physicians have neurology training background. However, the concept is heterogeneous in Europe and elsewhere. After adequate subspeciality training, many internists and geriatricians become great stroke physicians. Therefore, the future subspeciality in stroke field better is named as stroke medicine fellowship rather than vascular neurology fellowship. Stroke medicine training may require a minimum of 2 years after completion of neurology, internal medicine, geriatrics, or alike specialization program. Regarding radiology, official subspecialties, such as interventional radiology and neuroradiology, can include necessary training for EVI procedures. As the stroke physician will primarily be in charge of the patient and is already on-site 24/7, a completely novel approach suitable in highly specialized large centers is additional training of stroke physicians in interventional radiology limited to procedures of the head and neck region vasculature. This will bring flexibility and additional speed to patient care. Different countries or even regions have largely differing conditions; therefore, allowing for novel approaches and solutions without preconceived notions is most welcome. Each training program, new or old, requires a full quality-control aspect, including the numbers of procedures to be performed during training and afterward for maintaining skills, as well as regular participation in continuing education. Interest groups, such as professional organizations, hospital administrations, and patient organizations, could bring these aspects to national and EU-level decision-makers for legislative changes help reorganizing training modules quickly.

ESO has anticipated the growing need for training in stroke field and established several successful training programs, such as the European Master in Stroke Medicine Program, the annual European Stroke Summer School, the biannual European Stroke Science Workshop, the annual ESO Stroke Winter School, the biannual ESO-Karolinska Stroke Update Conference, Department-to-Department Exchange Program, and finally the initiation of the annual ESO Conference. Each of these programs has a unique concept and target group.

Reshaping the Emergency Room
Progress in medicine challenges our present way of thinking and necessitate reevaluation of our health systems, including the structure of the emergency room. Emergency rooms should be easily accessible, well-organized, and have clear pathways for all critical patient groups. The concept of critically ill neurological patient who requires immediate attention includes all acute stroke patients. Effective reorganization of the emergency room includes a prenotification call that alerts a stroke physician and anesthesiologist along with nursing staff ready to take care of the acute stroke patient immediately on arrival, not through a beeper after initial evaluation of the patient by an emergency room physician. In most hospitals, critically important time is lost with patients being transferred between places and with negotiations between parties preceding each transfer. These time losses must be minimized by reshaping emergency procedures both geographically and administratively. The pathway should include all necessary diagnostic and therapeutic procedures merged together, and each step should be accomplished without interruptions. A diagnostic-therapeutic complex in the center of future’s emergency room includes so-called shock rooms where the patient can be quickly evaluated and stabilized and directly transferred to the next room of imaging facility that includes both CT and MR scanners. Finally, an angiography suit should be part of this complex. The patient can be evaluated, stabilized, intubated, imaged, blood sampled, and undergo therapeutic procedures within a distance span of 30 m safely and without wasting time. After all urgent issues are completed, then the patient can be transferred to the stroke unit, which is preferably residing close to the emergency room, imaging facilities, and the intensive care unit. These changes can be incorporated to emergency room structures always when the next renovation becomes timely.

Future Challenges
As for most novel discoveries, several challenges remain to be solved. The first issue is how to quickly and successfully implement the results of the trials in real life across Europe. Conditions differ and interpretations of the trial results will differ, too. Therefore, we will likely see slightly differing criteria between centers. Nevertheless, the success of the EVI trials will likely improve stroke care in Europe more than the magnitude of the therapeutic benefit it is offering. The positive results in randomized controlled trials were gained in dedicated comprehensive stroke centers, but need to be confirmed in real life clinical practice, or, can better be put as that all hospitals treating stroke patients should over time achieve the quality of the stroke centers participated in the EVI trials.

One of the first questions we will be facing is whether EVI is cost-effective. The impressive results reported make it rather self-evident, but proof is required. Appropriate cost-effectiveness analyses will follow in near future and will help in convincing decision-makers. Different reimbursement
models (or lack of them) makes it difficult to compare costs across Europe, but one EVI procedure seems to cost 5 to 7000 € in various countries. One must note that each time the interventionist changes the catheter, it adds a similar amount to the price tag. The high cost of this treatment will be one reason for slow dissemination of its availability across Europe, especially in the Eastern parts.

An ethical question is how to proceed with the ongoing or planned trials in the field. Some trials are prematurely ended, whereas some may continue with amended protocols concentrating on patient groups where clinical equipoise still exists. Whatever the decision is, it is of utmost importance that all randomized controlled trial results will be reported. Because there are several unsolved issues, it is a universal hope that all patients treated with EVI are entered to registries for several reasons, such as how it works in real-life scenario, serve as a quality measure, and help in answering several yet unanswered questions.

Regarding scientific and technical questions, exclusively general anesthesia versus selectively general anesthesia with use of conscious sedation in majority of patients, dealing with futile recanalization (frequency, causes, mechanisms, and possible treatments), device selection and developments, role of sophisticated imaging approaches (patients were selected with plain computer tomography in MR CLEAN trial and the therapeutic benefit remained smaller compared with the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Minimizing CT to Recanalization Times (ESCAPE) trial where Alberta Stroke Program Early CT Score (ASPECTs) was utilized or the Extending the Time for Thomboysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) trial where penumbral imaging was used), role of collaterals, how to better select patients who will benefit from EVI and how to avoid patients who will be harmed (eg, developing future scores incorporating clinical, laboratory, and imaging data, as well as biomarker and genetics data strongly supporting precise individually tailored patient treatment decisions), when is IVT and when EVI is the primary treatment approach, shortening onset-to-groin times, and ensuring high quality (eg, annual minimum number of EVIs at a center and by a single operator, recanalization, and serious complication rates, pre- and postintervention care quality, door-to-puncture times, eligible patients not receiving treatment, just to name a few) are emerging as the next issues to tackle with. Although EVI research is done all around the world, European research input is extremely valuable taking into account the size and age distribution of its population along with high stroke frequency in the Eastern Europe, well-organized research infrastructure, high patient consent rates stemming from confidence in physicians and healthcare systems, motivation of stroke physicians to improve patient outcomes, and the financial resources for high-quality research. The most imminent challenges specific to Europe will be the slow progress in EVIs systems because of ongoing economic crisis and the west-east divergence in wealth that becomes more pronounced when a costly treatment is in question.

Intravenous thrombolysis is approved for patients <80 years of age in Europe by the European Medicines Agency. This remained unchanged, although accumulating data have shown that it is worth treating older patients with IVT. Because EVI trials demonstrated benefit in patients >80 years of age, there is a risk of (mis)interpretation that AIS patients >80 years undergo directly to IVT without IVT in some centers. If otherwise eligible, these patients should not be left without IVT before undergoing EVI.

Ambulances with computerized tomography scanners are currently few in number and have high running costs. In the future, they may well offer a great opportunity to yet a limited number of acute stroke patients by speeding up their acute treatment. Diagnosis of ischemic stroke and presence of a major intracranial artery occlusion leads to initiation of IVT already on the ride, decision to transport to a comprehensive stroke center, and prenotification call for preparation to EVI already before admission.

In conclusion, the investigators of the recently published EVI trials should be congratulated for their excellent work. The first positive trial, MR CLEAN, being a solely European trial, and the quick response of ESO to scientific evidence hopefully will improve the dissemination of knowledge and the realization of better acute stroke care systems in Europe.

Acknowledgments

I thank the Helsinki and Gothenburg stroke teams for inspiring discussions on this topic.

Disclosures

None.

References


Implication of the Recent Positive Endovascular Intervention Trials for Organizing Acute Stroke Care: European Perspective
Turgut Tatlisumak

Stroke. 2015;46:1468-1473; originally published online May 5, 2015; doi: 10.1161/STROKEAHA.115.008386

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/6/1468

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/