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Abstracts

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Abstracts

1

The Results of the Best Trials Influencing More Recent Guidelines on Therapeutic Behaviour

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The results of the "good quality" trials represent the basis of guidelines on therapeutic behaviour. Observational studies, Randomized Controlled Trials (RCTs) and Systematic overviews all contribute to formulate guidelines. The development of guidelines represents a complex path leading a clinical observation, through its challenge and thorough evaluation in large populations, to ultimately result in an appropriate therapeutic approach for the individual patient.

The classification of the results from a randomised, controlled study only as statistically "strong" or "weak" appeared unsatisfactory for the actual practice. It was necessary to consider the strength of the evidence, the methodological quality of the studies, the external validity, by applying a "considered judgment" on the whole amount of the data. The direct applicability of the results of a study to the target population addressed by the guidelines was considered as well. The classification of the strength of evidence and the grades of recommendations was derived from a methodology developed by integrating the principles of the SIGN (Scottish Intercollegiate Guideline Network)[1] with the statistical considerations on alpha and beta error size suggested by the CEBM (Centre for Evidence-Based Medicine)[2] methodology. This methodology was used in the Italian Guidelines on Stroke[4] (in the 3rd, 4th, and 5th editions). The development of these guidelines has been a collaborative process, involving a multidisciplinary working group, named the "SPREAD Collaboration" (Stroke PREvention and Awareness Diffusion), in which at present 36 different professional organisations and two patients' associations are represented. A dedicated task force and an editorial board are responsible for coordinating and reviewing the texts progressively produced and processed. Since 1998, when works officially started, five versions were released at two-year intervals thanks to multidisciplinary cooperation in the processing phase and in the consensus achievement performed by the Rand method. Finally the ultimate versions were submitted for approval to the medical associations involved. The aim of these guidelines is to provide recommendations about the best management of acute stroke and the primary and secondary prevention of stroke in clinical practice. The sources of evidence to formulate these recommendations have been the Cochrane Database of Systematic Reviews and electronic medical literature databases (e.g. MEDLINE), as well as data from both Italian and international researches directly available to the experts involved in the guidelines formulation. Documented consensus on developing topics was also taken into account. The recommendations are judged valid when they: 1) explicitly consider all the important steps of the clinical decision making process and the relevant outcomes; 2) identify the best evidence concerning stroke treatment and prevention, and critically evaluate its reliability; 3) identify and take into account the preferences of the involved subjects concerning the outcomes of the decisions taken[3].

There is a similar approach about treatment of acute ischemic stroke (IS) in 5th edition of Italian guidelines and the more recent Antithrombotic and thrombolitic therapy 8th ed. ACCP Guidelines 2008 (tab. 1)[4].

Table 1 Recommendations on acute IS treatment

SPREAD 5th edition	ACCP guidelines 8th edition
R 10.2 The treatment with intravenous r-tPA (0.9 mg/kg, maximum 90 mg, with 10% of the dose given as a bolus followed by an infusion lasting 60 min) **is recommended** within 3 h of onset of IS. **Grade A**	1.1.1. For eligible patients we recommend administration of IV tPA in a dose of 0.9 mg/kg (maximum of 90 mg), with 10% of the total dose given as an initial bolus and the remainder infused > 60 min, provided that treatment is initiated within 3 h of clearly defined symptom onset (Grade 1A). 1.1.2. We recommend that patients who are eligible for tPA be treated as quickly as possible within the 3-h time limit (Grade 1A). 1.2. For patients with acute IS of > 3 h but < 4.5 h we suggest clinicians do not use IV tPA (Grade 2A). For patients with acute stroke onset of > 4.5 h, we recommend against the use of IV tPA (Grade 1A).

A more appropriate grade for Recommendation 10.2 of Italian guidelines should be considered a "B". In fact there is still some dissent concerning the grade to be attributed to the above recommendations, which cannot be influenced by the otherwise important results of the SITS-MOST, which was not a RCT. Clinical Evidence in its June 2007 release, accounting for the results of the systematic reviews on thrombolysis where a definite statistical heterogeneity was seen that make not fully reliable the results favourable to the treatment, continues classifying the treatment as "trade-off between benefit and harm", and specifies that the treatment decreases dependence among survivors but increases total mortality and fatal haemorrhages (Synthesis 10–1). Furthermore **"**The benefit from the use of i.v. r-tPA for acute IS beyond 3 h after onset of the symptoms is smaller, but present up to 4.5 h. When r-tPA is administered between 4.5 and 6 h of stroke onset, only a statistically non-significant trend towards effectiveness is obtained"(Synthesis 10–2)[3]. The double-blind, randomised, placebo-controlled trial ECASS III (European Cooperative Acute Stroke Study III) recently published on the New England Journal of Medicine[5] provided good evidence that even within 4.5 hours of the onset of symptoms intravenous alteplase is associated with favourable clinical outcome. "The ongoing double-bind, randomised, placebo-controlled trial, denominated IST 3, is estimating in a large population of patients with acute IS the risk-to-benefit ratio of the administration of r-tPA within 6 h of onset. This trial also evaluates efficacy and safety in patients over 80 years of age" (Synthesis 10–2)[3].

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2

Clinical Evidences Supporting Acute Stroke Treatments

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Stroke is the third cause of death worldwide and the first for long term disability. Current clinical evidence supports that stroke unit admission and intravenous thrombolysis with tPA are the main emergency treatments able to reduce the risk of post-stroke death and disability in about 50% of patients. Stroke unit, described as an hospital area with dedicated beds and trained multidisciplinary staff with expertise in caring for patients with cerebrovascular disease, is proved to be the best model for in-hospital care of any kind of stroke regardless of aetiology, age, sex, severity. However, in Italy only 12% of wards that admit stroke patients has such organization. Indeed in Europe less than 5% of ischemic stroke are treated with tPA because of the strict selection criteria and narrow temporal window within 3 hours. An acute stroke care pathway should start from an accurate and fast evaluation from emergency medical service, going through the emergency department to the stroke unit in order to give the best treatment to the majority of stroke patients.

Recently the ECASS3 trial confirmed the hypothesis derived from meta-analysis from previous randomised control trials that intravenous thrombolysis with TPA is safe and efficacious up to 4.5 hours from onset. The treatment efficacy is confirmed to be time dependent but still present after 3 hours. Indeed this implies that more patients are treatable but not that stroke physicians should take more time to treat every patient.

Intra-arterial thrombolysis in patients with severe stroke and ineligible to intravenous treatment is an option that seems to improve functional outcome despite an higher risk of intracranial bleeding. Clinical evidence supporting invasive thrombolytic therapy are scanty and no trials proving clinical efficacy of mechanical approach are available at the moment.

Multimodal imaging techniques, as perfusion or diffusion MRI, seem to be able to detect cerebral tissue salvageable from irreversible ischemic damage until 9 hours from symptom onset. If ongoing trials will confirm this hypothesis, patients could be selected for thrombolysis according to a tissue window after 3 hours from onset.

Some clinical experiences, recently described, support that carotid endo-arterectomy performed within few days from minor stroke or TIA onset seems to be quite safe and to improve functional outcome.

At the moment we have clinical evidences drawing the best care pathway for stroke and ongoing research seems to indicate further improvement; nowadays we need to translate trial results into clinical practice in order to improve the whole stroke care system.

3

Intravenous Thrombolysis: Results of the Italian Sits-Most Study, ECASS III Study and SITS-ISTR

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Intravenous (i.v.) thrombolysis with rt-PA within 3 h from symptom onset is the only available effective, specific reperfusion therapy in acute ischemic stroke. In the European Union, this treatment was approved in 2002 by the European Medicine Evaluation Agency (EMEA) on two conditions: the setting in place of an observational safety study, the Safe Implementation of Thrombolysis in Stroke - Monitoring Study (SITS-MOST), to investigate whether the safety of i.v. alteplase given within 3 h of ischemic stroke reported in randomised controlled trials (RCTs) could be replicated in routine clinical practice, and the initiation of a new RCT, the European Cooperative Acute Stroke Study (ECASS) III, with a therapeutic window extended beyond 3 h. In Italy, only few centers were expert in thrombolysis before the SITS-MOST; globally, 586 patients were included. The results of the SITS-MOST study showed that in Italy, i.v. alteplase is safe and effective in routine clinical use compared with the other european centers and the RCTs, in terms of SICH (symptomatic intracerebral hemorrhage) as per the NINDS/Cochrane definition (p 0.56), mortality (p 0.75) and independence (mRS 0–2) (p 0.09) at 3 months, even in centers with little previous experience of thrombolytic therapy.

A meta-analysis of the pooled data of the main RCTs showed that earlier is the treatment better is the patient outcome but also that a significant benefit of i.v. thrombolysis persists up to 3–4.5 h from the symptom onset. Recently, waiting for the results of the ECASS III study, within the SITS-ISTR (Safe Implementation of Treatment in Stroke - International Stroke Thrombolysis Register) (a prospective internet-based register of thrombolysis in ischemic stroke, used also for the SITS-MOST study), it was assessed the outcome in patients treated intravenously within 3–4.5 h (n = 664) and compared the results with patients treated within 3h (n = 11865) until November 15, 2007.

Half of patients in the 3–4.5 h cohort were treated within 15 min of the 3 h time limit and the difference between the median onset to treatment times between both cohorts was 55 min. That can be seen as an indication of physicians striving to stay as close to 3 h as possible. There were no significant differences between the 3–4.5 h cohort and the within 3 h cohort for any outcome measure - rate of SICH: 2.2% vs 1.6% (OR 1.18, 95% CI 0.89–1.55, p 0.24; adjusted

OR 1.32, 1.00–1.75, p 0.052); mortality: 12.7% vs 12.2% (OR 1.02, 0.90–1.17; p 0.72; adjusted OR 1.15, 1.00–1.33 ; p 0.053); and independence: 58.0% vs 56.3% (OR 1.04, 0.95–1.13, p 0.42; adjusted OR 0.93, 0.84–1.03, p 0.18).

These positive results were confirmed by the ECASS III RCT that tested the efficacy and safety of alteplase administered between 3 and 4.5 hours after the stroke onset. A total of 821 patients were enrolled in the study and randomly assigned 418 to the alteplase group and 403 to the placebo group. The median time for the administration of alteplase was 3 hours 59 minutes. More patients had a favorable outcome with alteplase than with placebo (52.4% vs 45.2%; OR 1.34; 95% CI 1.02–1.76; p 0.04). In the global analysis, the outcome was also improved with alteplase as compared with placebo (OR 1.28; 1.00–1.65; p<0.05). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0% vs 17.6%; p = 0.001; for SICH 2.4% vs 0.2%; p 0.008). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; p 0.68).

These findings give to patients the chance to be treated more later but for medical doctors having more time does not mean we should be allowed to take more time.

4

Stroke Services in Italy: The Research Project Prosit

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The effectiveness of organized care for hospitalised stroke patients was assessed in several randomised controlled trials. The results, combined in a Cochrane systematic review, definitively showed the benefit of stroke-unit care. However the implementation of stroke-unit (SU) wards in European countries is spreading very slowly. The Italian National Ministry of Health has promoted a stroke-unit research project (Research Project on Stroke services in Italy, PROSIT) since 2000. A last survey, in 2004, identified 785 hospital wards in Italy admitting at least 50 stroke/year. Only 68 were SU, defined as dedicated beds/geographical area with at least 1 dedicated full-time physician and 1 nurse. 75% of SU were in Neurological setting. The most striking differences between SU and General Ward were related to the staffing and care organisation with higher number/patients ratio in SU as far as physicians and nurses, speech therapists and social workers were concerned. A geographical gradient was evident as the SU were more frequent in northern regions than in southern ones.

Starting from a survey conducted in seven Italian region, an observational follow-up study was conducted on a sample of 11572 acute stroke patients hospitalised within 48 h of the onset of symptoms either in a stroke unit (n = 4936) or in a conventional ward (6636). The primary outcome was mortality or disability (Rankin score greater than two), assessed prospectively by independent, masked assessors 2 years after admission. Compared with conventional-ward care, SU care was associated with a reduced probability of death or being disabled at the end of follow-up (odds ratio 0·81, 95% CI 0·72–0·91; p = 0·0001). The potential benefit was significant across all age ranges and clinical characteristics, except for unconsciousness. No specific elements of setting, organisation, or process of care were associated with outcome.

Some points must be considered. Recently the need to implement thrombolysis in clinical practice (SITS-MOST: Safe Implementation of Thrombolysis in Stroke: Monitoring Study) was the trigger for a further diffusion of the SU in Italy. However, the focus on the thrombolytic treatment may favour an hyperacute model of SU, in which monitored patients stay only 3–4 days, a model not yet validated by clinical trials. Indeed, the studies evaluated in the systematic review were conducted in comprehensive stroke units, combining acute and subacute care, namely early mobilization and prevention of complications of stroke.

The new hospital model, based on care intensity and now proposed in Italy by Regional and National Health Authorities, may stand out against SU care. By this model the patient is admitted in ward differing for the intensity level of the care needed but not for the specificity of the disease. So the specifity of the stroke team and the dedicated beds are lost. A possible strategy to cope with this model is the creation of Emergency Neurologies, where to set true stroke units.

Another critical point is the relationship between the emergency system and the post-discharge organisation, warranting the continuity of care. Care pathways or integrated care strategies may offer a means for achieving better integration among practitioners, community-based services, and SU care

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5

Stroke: The Emergency Starts Out-of-Hospital

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Stroke represents the second cause of disability and death after ischemic heart disease in Western Countries. The etiology of stroke can be mainly identify in a focal cerebral ischemia due to an acute arterial flow interruption (80%), whereas haemorrhage represents 20% of events.

It is widely accepted the importance of a very early treatment of stroke: this concept is based on the knowledge of the dynamic physiopathology following the acute injury. The arterial occlusion produces a very low perfusion central area (“ischemic core”) surrounded by a cerebral tissue (“ischemic penumbra”) with metabolic alteration without, in the early phase, damages. This peri-ischemic

area represents the goal of the early treatment, because its evolution in necrosis or recovery (even partial) depends on the time and the rate of reperfusion.

This feature of the acute cerebrovascular accident can be considered very similar, in organizational aspects, with that observed in the ischemic heart attack in which a very early treatment, beginning "at the home of the patients", is able to increase the recovery. A correct diagnosis and initial treatment of stroke in pre-hospital phase, should therefore be considered a priority.

After a territorial first-line treatment, the correct intra-hospital diagnosis and assessment of ischemic or hemorrhagic injury with neuroimaging (CT-scan, NMR, angiography, trans-cranial ultrasonograpy) can lead the decision to treat with intraarterial thrombolysis (and other procedures) or with medical care and intravascular embolization. Beside these conventional treatment, the evaluation of patient from an "intensivist point of view" (based on a cerebral perfusion pressure optimization) , might also open "less-conventional" therapeutic options such as decompressive craniotomy and mild-therapeutic hypothermia. This approach needs a strict collaboration between various specialists, and it must be considered an emergency intensive care regimen of treatment.

Growing evidences support that the creation of dedicated "in-hospital pathway" for an early diagnosis/treatment of stroke produces a decrease in mortality and an improvement of recovery after acute cerebrovascular event. According with these consideration, a correct territorial management of stroke and the hospitalization in specialized center should be considered the corner stone of stroke treatment. An intensive-care approach might be guarantee to optimize the possibility of an early reperfusion of peri-ischemic area.

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6
Triage of Patients with Suspected Stroke

S. Grifoni, S. Vanni

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Suspected stroke patients require rapid clinical evaluation to identify those who may benefit from timely thrombolytic administration. The diagnosis of stroke requires focused history and physical examination as well as clinical judgment. At the moment, only standardized stroke scales have sufficient evidence to be used in the pre-hospital and very early (triage) hospital setting in patients with suspected stroke. In our emergency departments the CPSS is used at triage due to its extreme simplicity (requiring only 1–2 minutes to be administered), and its high reliability. Interestingly, in previous studies conducted in emergency scenarios CPSS showed a lower sensitivity than expected, missing the diagnosis in about one third of patients with stroke. Our data supports these findings as we observed high percentage of false negatives (29%) for the CPSS in our study population. In our experience a multi-marker had an accuracy similar to pre-hospital standardized stroke scale (CPSS), misdiagnosing about one third of patients, thus discouraging their use as stand alone tests in triage of patients with suspected stroke. The combination of the two tests seems to increment diagnostic yield, encouraging further studies to investigate the potential clinical utility of biomarkers in triage of patients with suspected stroke.

7
Integration Between Triage Physician and Neurologist

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Intravenous thrombolysis with tPA within 3 hours from onset is the principal approved drug treatment for acute ischemic stroke. Acute stroke must be managed as an emergency for the narrow treatment time windows. Indeed the efficacy of tPA in term of recovery from disability is time dependent.

The recent ECASS 3 trial confirmed the hypothesis, derived from a previous meta-analysis of randomised control trials, that tPA could be efficacious up to 4.5 hours from symptoms onset, but, now the administration of tPA beyond 3 hours is "off label".

An organized acute stroke care pathway with the integration of several personnel is essential. The implementation of a red code for stroke from the emergency service to the triage physician and first clinical evaluation of patients is necessary for a rapid assessment of acute stroke patients. A trained emergency department staff in caring for acute cerebrovascular disease patients is necessary to improve screening and selection for acute phase treatment.

This model of integration between several professionals in the emergency department should be used even for patients with TIA in order to identify those patients with higher risk of stroke recurrence within 72 hours according to the ABCD2 score.

8
A Rapid Access to Secondary Prevention: "Day T.I.A. Project"

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The transient ischemic attack (TIA) is a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction. In the literature preceding the advanced neuroimaging with CTscan-angiography and diffusion weighted MRI , the duration of the neurological deficits lasted at least 24 hours but in 2002 a new definition was proposed because only a deficit less than one hour is probably to occur without permanent brain injury (Albers GW et al. N. Engl J. Med. 2002;347:1713–1716). According to the new definition, the diagnosis of TIA needs to be confirmed by CT or MRI in order to exclude acute stroke. The TIA can recur showing in this way the possible severity of transient episode. Often the

TIAs are due to embolism from large vessels pathology extra and/or intra cranial; also cardioembolic sources are identified as causes that, if they aren't removed, can recur as TIAs or stroke. The risk of stroke in people affected by TIA or minor stroke is ten-fold more frequent than in general population in the first year from the initial episode; moreover during the 5 years following the transient ischaemic attack in non-treated patients, the risk of cerebral infarction is estimated to be 25%. Therefore time window for prevention is very short : the better setting for effective procedures to prevent the stroke after TIA is hospitalization if :

1. the onset of TIAs is within the previous 48 hours
2. TIAs last for more than 10 minutes
3. frequent recurrence of TIAs.

However many transient neurological symptoms are not properly transient ischemic attacks: the mimic TIAs are frequently due to seizures, subdural haematoma, migraine. For these reasons the investigations about the major categories of symptom presentations associated to cerebrovascular risk factors have to be taken into consideration to formulate the ABCD and ABCD2 (Rothwell P.M. et al., Lancet 2005, Jonsthon C. et al, Lancet 2007). The ABCD2 is meaningful for a stroke risk during the next two and seven days following TIA ,because the delayed arrivals into hospital of patients with elevated score (6–7 ABCD2) is barely effective to prevent the onset of a major risk. The great value of SOS TIA study (Lavallee, Lancet Neurol 2007) was the demonstration that early admission to locally structured ad hoc organization (TIA clinic) permit the reduction of 79% of relative risk of stroke to 90 days.

On the basis of these studies we propose an organization model modulated according to the score and the time of TIA by creating the hospital pathways. This project can rely on neurologists and dedicated nurses, computerized reports, CT/ MRI imaging, carotid neurosonology and TCCD. The "Day TIA" is a 48 hours admission in Stroke Unit for patients with a score ABCD2>6; with a score of 4–5, patients are admitted into OBI at the ED; with a score <4 they can be evaluated at cerebrovascular service within seven days. At the same time we informed the Reggio Emilia province population about "why, when, where," they could take benefit from going to "Day TIA" hospital, prevention offices, ALICE group (Italian association for stroke) and GPs. The aim is the primary prevention by simultaneous scheduling neurosonologic and cardiologic examinations for people aged more than 60 years , with elevated blood pressure and/ or diabetes in order to realize the novel paradigm of prevention.

9

Diagnostic and Therapeutic Pathways in Acute Stroke: The Point of View of Neuroradiologist

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Diagnostic imaging modalities in evaluation of acute ictus play a fundamental role for a correct clinical approach. The early detection and knowledge by widely available and unintrusive techniques, such as CT and MR, of brain ischemic damage still in reversible phase have important therapeutic and prognostic implications, also particularly in planning revascularization of intracranial arterial segments, by intravenous or intra-arterial thrombolytic therapy, and thromboendoarterectomy or stenting of epiaortic vessels.

Diagnostic-therapeutics pathway in patients with suspected stroke provides, first of all, to discriminate between ischemic brain injuries and other pathologies leading acute neurological deficit (intracerebral hemorrhage, tumors, abscess, post-traumatic lesions, seizures ..), successively to determinate the etiologic mechanism of ischemic event on the basis of clinical data and further aimed investigations. With regards to specific investigations it is possible to outline guidelines that, starting from clinical findings, articulate in terms of priority and correlation with other methodics (ultrasonography), also considering the accessibility to more advanced technologies.

The study of extracranial arterials and cerebral circulation, including the research of the kind and site of endovascular lesion, represents a preliminary procedure to therapeutic decisions in the majority of ischemic events.

Noncontrast-CT is still now the imaging modality of choice for identifying the underlying pathology in the initial hours of acute stroke, because immediately exclude intracranial hemorrhage or tumor, and can also be used to detect early signs of an infarct (iperdensity of middle cerebral artery, early parenchimal low-density, mass effect due to cytotoxic edema).

At present noncontrast-MR is a complementary technique to confirm the diagnosis of acute ischemic event because of high sensitivity especially in infratentorial or lacunar lesions.

CT and MR remain the standard acute stroke imaging modality in the first 12–24 hours after clinical onset; in the light of recent treatments by intravenous or intra-arterial trombolysis and neuroprotective agents to improve the clinical outcome, other diagnostic tools are needed that quickly (within 3–6 hours) shows not only lesion size but also vessel occlusion and that provides information about the collateral circulation, tissue at risk and salvageable brain (ischemic penumbra).

In the evaluation of epiaortic and intracranial vessels ultrasonography is actually employed, in association with Angio-CT and Angio-RM, also if this methodic present some limits to assess the degree of stenosis and characterize the pathologic arterial walls.

Dynamic contrast-enhanced CT and MR imaging techniques such as the Perfusion-Weighted CT and Perfusion-Weighted MR imaging, associated with Diffusion-Weighted MR, arouse great interest helping predict clinical outcome at very early time points and allowing the identification of optimal candidates for therapeutic interventions, including thrombolysis (ie, those patients with a sizeable volume of potentially salvageable tissue at risk).

Cerebral angiography, non risks exempt and performing only in qualified centers, is not recommended in the iperacute phase of stroke with the exception of selected cases for revascularizing treatments (i.a. thrombolysis, stenting).

Digital angiography, besides confirming site and nature of the vascular occlusion, gives information about existence and goodness of collateral circulation, involvement of deep territories, wideness of avascular area by parenchimography, and about the endovascular accessibility for thromboembolic therapy. With regard to this interventional procedure is of primary importance the site of embolic occlusion and it is essential to observe "therapeutic window" of 4–6 hours for carotid districts, but wider for vertebro-basilar occlusions.

10

Is Vascular Diagnosis only a Luxury Option in Acute Ischemic Stroke?

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Different trials have investigated the benefit of intravenous thrombolysis in acute stroke but only few prospective studies have evaluated the recanalization rate after therapy and the rate of hemorrhagic complications according to the initial vascular status. Despite the lack of prospective data the knowledge of the baseline vascular status is fundamental for prognostic purposes and its assessment may provide very valuable information to plan the appropriate therapeutic strategy. Indeed retrospective analyses have clearly demonstrated that the proximal extension of arterial occlusion is correlated with a technical success of lysis, neurologic recovery and risk of intracerebral hemorrhage. In addition it has been reported that despite comparable age and NIHSS scores before IV tPA, the rate of recanalization and clinical outcome are sharply different and definitely better in patients with MCA obstruction compared with those affected by ICA occlusions. Patients with proximal carotid occlusion may achieve early recanalization only after combined IV/intra-arterial or mechanical thrombolysis. To assess the effects of the vascular assessment in the clinical management of the acute stroke patients admitted to our hospital, we have retrospectively analyzed the results of cerebrovascular ultrasound (US) examinations performed between November 2005 and the end of March 2008 and we have matched the results with neuroradiological and clinical data. 551 patients were evaluated by the stroke team physicians for a suspect cerebral ischemic attack. 330/551 underwent a cerebrovascular US examination either soon after admission or within 48 hour after symptoms onset (59.8%). Only 247 patients were transferred to the stroke unit; 178/247 did have an acute cerebral ischemia (TIA or stroke). The results of brain CT and vascular ultrasound examination and exhaustive informations on the clinical course (up to one week of hospitalization) could be retrieved exclusively from the 178 stroke unit patients. 83 of the 330 (25%) patients with suspect cerebral ischemia were studied during the acute phase, soon after admission in the emergency room (ER). US examination was limited to neck arteries in 43; both extra- and intracranial vessels tests were performed in the remaining 40 patients. 3/40 had a significant MCA stenosis; 4 showed an M1 MCA occlusion. 112 patients were treated with fibrinolysis: tPA was administered intravenously to 63 patients, and intra-arterially to the remaining 49 patients. A bridging strategy was adopted in 4. US examination was performed in 33 patients receiving I.V. tPA (19 extracranial; 14 extra- and intracranial evaluation). US examination was performed in 9 of the 49 patients intra-arterially treated (6 extracranial; 3 extra- and intracranial evaluation); in all patients the ultrasound evaluation was readily feasible within 3 hours after symptoms onset. 51% of the patients receiving systemic rTPA were studied by carotid ultrasound; 37.8% were studied also with TCCD and TCD. Continuous TCD monitoring was performed during tPA infusion in 4 patients and provided direct evidence of progressive recanalization in two; lack of effects in the remaining two. The recanalization anticipated by more than one hour the functional neurological recovery in one of the patients successfully treated. Significant (70–95%) carotid stenosis was diagnosed by ultrasound in 10.8% of the patients investigated during the acute phase and were subsequently treated; a total carotid occlusion was found in 16.9%. Carotid dissections were present in 6.1% of cases. During the acute phase 12 patients underwent an angioCT, 7 angioMR, 19 an angiography. The results of the neuroradiological and ultrasound examinations were similar in all patients examined by both techniques. The detection of a pathological finding at vascular Doppler examination was significantly correlated with clinical worsening, both at ER admittance and within the stroke unit ($p<0.05$ and $p<0.01$ respectively). Statistically speaking present data do not allow to jump to absolute conclusions since the sample analyzed is not fully representative of the whole population with acute stroke admitted to our hospital. Nonetheless the results clearly indicate that the eligibility to fibrinolysis is not the only issue to face in the presence of an acute stroke patient. In fact in our study the assessment of the vascular status prior to fibrinolysis has allowed to characterize some subgroups in which a different therapeutical strategy was indicated like for example a surgical or procedural correction in the case of carotid stenosis or heparin infusion in carotid dissections. The early neurosonological findings proved to be very effective to define patient prognosis. This holds true not only for main stem M1 MCA occlusions but especially in the presence of T occlusions of the internal carotid arteries where any thrombolytic treatment can hardly succeed and is too often associated with hemorrhagic complications and clinical deterioration. Unfortunately none of the methods that are commonly used to establish the eligibility to fibrinolysis of an acute stroke patient can reliably assess the site and extension of an occlusion. The systematic adoption of US vascular evaluation can achieve the vascular diagnosis at ER admittance and since it can be repeated according to the very common clinical fluctuations, it is the only method that can instantly provide an anatomic correlate to clinical symptoms and an accurate bedside monitoring of cerebral hemodynamics. From an organizational point of view US evaluation may be prospectively considered a mandatory choice rather than a luxury option.

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Diabetes and Ischemic Stroke

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In many (1–12) but not all (13–14) epidemiological studies, type 2 diabetes mellitus (DM) has been reported as an important risk factor for ischemic stroke with relative risks (RRs) that have varied widely, from 1.3 to 4.9 (1–11). The disparate RRs may be explained in part by differences in populations, definitions of diabetes, types of stroke studied, and analytical methods. Further, only a few small studies have examined the risk of stroke in patients with type 1 diabetes (8,9). This relationship remained a long time partially unsettled until Janghorbani et al reported cerebrovascular complication distribution pattern in subjects with type 1 diabetes showing that the RR of ischemic stroke was increased sixfold in type 1 diabetes and twofold (2.3 [2.0–2.6]) in type 2 diabetes. (15)

The increased risk of stroke has been linked to the pathophysiological changes seen in the cerebral microvessels (*small vessel disease or SVD*) of individuals with type 2 diabetes mellitus owing to the fact that DM is responsible of a tipical microangiopathy of cerebral vessels that differs in comparison with non-diabetic ones. Indeed, while pathological studies indicate that the diabetic angiopathy is different from the atherosclerotic angiopathy on the basis of pathological and autopsy reports (16,17), epidemiological data do not find a unique clinical and prognostic profile for ischemic stroke in diabetics. For example, whereas Lithner et al (19) and Toni et al. (20) reported that ischemic stroke severity, in both diabetics and non-diabetics, was similar, Kiers et al. (21) found that diabetic patients had more severe strokes. Moreover in a retrospective study, Pulsinelli et al. (22) reported that the neurological outcome of stroke was poorer in diabetics, whereas Toni et al (20). found a comparable functional outcome for both diabetics and non-diabetics patients.

Small vessel disease of deep perforating arterioles plays a crucial role in ischemic stroke pathogenesis in diabetic subjects, although the higher cerebrovascular risk is also related to the additional risk factors and the characteristic atherogenic diabetic profile and significant appears the pathogenetic role of acute hyperglycemia as a direct neuronal damage mediator and negative prognostic marker.

More recently two studies analyzed the differences regarding clinical features of stroke in diabetic and non-diabetic subjects. Megherbi et al. (22) reported that diabetic patients compared with those without diabetes were more likely to have limb weakness, dysarthria with a handicap (Rankin Scale) and significantly higher disability (Barthel Index) grade, while Karapanayotides et al. (23) reported that diabetic stroke patients are not associated with a poor functional outcome. Furthermore our group (24) reported that diabetes, hypertension, and a history of transient ischemic attack were more frequent among patients with lacunar stroke and that mean SSS score on admission was significantly lower in patients with lacunar stroke in comparison with patients with LAAS and CEI subtypes. In a subsequent study (25) we compared 102 diabetics and 204 non-diabetic subjects with acute ischemic stroke, matched by sex and age confirming that diabetes was associated with lacunar ischemic stroke subtype, with a record of hypertension, and with a better SSS score at admission and that association of diabetes with lacunar stroke remained significant even after adjustment for hypertension or other stroke subtypes . Our group (26) also recently reported that lacunar stroke (more prevalent in diabetes) has a lower immuno-inflammatory activation of the acute phase compared to other subtypes of stroke, so partially explaining clinical and prognostic difference of this subtype and furtherly contributing to characterize the peculiar profile of ischemic stroke in diabetic subjects .

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Relationship Between Preclinical Carotid Atherosclerosis and Cardiovascular Events

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Cardiovascular diseases remain today the first cause of death in the world. Understandably, the knowledge and the prevention of cardiovascular risk factor have attracted particular attention. Beyond "traditional" risk factors such as age, gender, family history of CV disease, hypertension, hyperlipidemia, smoke and diabetes, very important as well are the "emerging" marker of risk such as carotid Intima-Media Thickness (IMT).

IMT is a not invasive, low cost, no radiation, cost-effective and highly reproducible procedure to screen for atherosclerosis. Carotid Artery IMT is measured with laser Doppler velocimetry.

The Doppler mode permits the visualization of vessels and an evaluation of flow disturbances. It measures the IMT and the size and number of atheromatous plaques. IMT is defined as the distance between the media-adventitia interface and the intima-media interface. IMT is measured at five locations on each side and, in particular, it is measured at internal carotid artery (ICA) about 1 cm distal from the flow divider, at bifurcation enlargement (BIF) and at proximal, middle and distal segment of the common carotid artery (CCA) is measured.

Carotid IMT has been shown to be an independent marker of multifocal atherosclerosis. Now it is established that IMT is an independent predictor for cardiovascular events: increase in IMT of the carotid artery, as measured non-invasively by ultrasonography, is directly associated with an increased risk of myocardial infarction in adults without a history of cardiovascular disease.

Cardiovascular RF are associated with an impaired endothelial function and an increased IMT, and the presence of carotid IMT is significantly related with endothelial dysfunction ($p < 0.01$). In a study of our group impaired flow mediated vasodilatation (FMD) and values of carotid IMT have been found to be higher among patients with cardiovascular risk factors than among patients without RF (1). Clinical studies have shown an important relation between smoking and IMT (2). In fact, IMT increases with age and hypertension, hyperlipidemia and non-insulin-dependent diabetes mellitus are related to a greater IMT (3).

Interestingly, there is a good correlation between Framingham risk score and IMT (4).

Another study examined the relation between IMT and a number of arterial beds with significant (> 50%) stenoses, including coronary, supra-aortic, renal and iliac/femoral arteries. It showed that IMT was significantly correlated to the number of coronary vessels with stenoses ($p < 0.001$). So, IMT has been shown to be an independent predictor of significant multifocal atherosclerosis, showing high sensitivity and specificity for indicating more advanced atherosclerotic involvement (5, 6).

Observational studies have shown a relationship between carotid intima-media thickness (IMT) and coronary artery disease (CAD); for example, studies such as the "Prospective Finnish Study", "Atherosclerotic Risk in Communities (ARIC)", "Rotterdam Study" and "Cardiovascular Health Study" showed a significant relationship between IMT and cardiovascular risk and provided evidence that carotid IMT is related to future cardiovascular events (7–11).

In a study of our group, performed in asymptomatic high risk subjects followed for 5 years, a significant increase of fatal and non fatal cardiovascular events in those subjects that at baseline present IMT or asymptomatic carotid plaques in comparison to subjects with normal carotid arteries at baseline was shown (12).

In conclusion Carotid ultrasound can add information beyond assessment of traditional risk factors which may help to make decisions about the necessity to institute medical treatment for primary intervention.

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Genetics and Stroke

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Hereditary factors play an important role in stroke and cerebrovascular diseases in general and this effect may be commonly appreciated in the daily practice. Studies performed on animal models and epidemiological investigations on twins have well demonstrated the role of hereditary factors in the etiopathogenesis of stroke. In this regard, the search of a candidate gene as cause of stroke has been long-lasting and intensive but until now disappointing except for a few specific but relatively rare diseases. Among monogenic cerebrovascular diseases the following are listed: CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) and Anderson-Fabry disease both small vessel diseases, HCHWA-D and HCHWA-I (hereditary cerebral hemorrhage with amyloidosis respectively of Dutch and Icelandic type) causing hemorrhagic stroke and dementia, and Marfan syndrome associated with arterial dissection, in which the involved genes have been definitively identified. CADASIL is caused by mutations on Notch3 gene, Anderson-Fabry disease by a defect in α-galactosidase A gene, HCHWA-D and HCHWA-I respectively by mutations on AβPP and cystatin C gene, while Marfan syndrome is due to mutations in the fibrillin-1 gene or in the transforming growth factor-β receptor2 gene. In particular, CADASIL has an autosomal dominant pattern of inheritance and is characterized by recurrent strokes, migraine, often with aura, psychiatric disturbances and cognitive decline. CADASIL is also a useful model for understanding the relationship between small vessel disease and cognitive impairment.

A recent meta-analysis by Casas and co-workers found that there is a genetic component also to sporadic stroke. No single gene with major effect was identified; rather, common variants in several genes, each exerting a modest effect, likely contribute to the risk of stroke. The failure of the candidate gene approach has a number of possible explanations and the first is that stroke consists of many different subtypes, each of whom may have a different genetic profile. Finally, it should be considered that stroke is a multifactorial disease and the effect of genetic factors is strictly related with that of the environmental and common cardiovascular risk factors.

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Bone Marrow-Derived Progenitor Cells in Cadasil Patients: Association with the Disease and Phenotipic Expressivity

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Introduction: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare hereditary small vessel disease with many cerebral manifestations such as recurrent stroke, migraineous headache, mood disturbances, cognitive decline, and epilepsy. To date, the pathogenetic mechanism of CADASIL is not fully understood and recently an involvement of the endothelium dysfunction has been hypothesised. A number of studies have shown a participation of endothelial progenitor cells (EPCs) and haematopoietic progenitor cells (HPCs) in the maintenance of endothelium health and in the neovascularization of brain artery ischemic syndrome, suggesting a role for both in cerebrovascular disease. However no data are available about EPCs and HPCs in CADASIL patients.

Aim: To analyze the number of EPCs and HPCs in a populations of CADASIL patients and in a population of healthy subjects in order to clarify the possible relationship with the pathology.

Methods: In 27 CADASIL patients [11M/16F; median age 51.3 (29–81) years] and in 27 non-CADASIL healthy subjects [12M/15F; median age 50.5 (29–88) years] EPCs and HPCs were evaluated with the use of flow cytometry. Were defined as EPCs cells positive for CD34+KDR+, CD133+KDR+ and CD34+CD133+KDR+ and HPCs cells $CD45^{dim}$ and positive for CD34+, CD133+ and CD34+/CD133+.

Results: Circulating EPCs levels were significantly reduced ($p = 0.003$) in CADASIL patients with respect to healthy subjects, while circulating HPCs levels were similar between patients and controls. In a logistic regression analysis, after adjustment for age, gender and traditional cardiovascular risk factors, an increased risk of CADASIL for patients with low EPCs levels was demonstrated [OR (95%IC): CD34/KDR 6.79 (1.19–38.6) $p = 0.031$; CD133/KDR 6.84(1.08–43.8) $p = 0.040$; CD34/CD133/KDR 9.4(1.35–65.8) $p = 0.023$]. By dividing CADASIL patients into two groups, (group A comprised patients with a "severe clinical picture" with a previous documented stroke and/or dementia and group B identified patients with a "mild clinical picture" without stroke and dementia) group A showed a significant lower number of HPCs than group B. In a multivariate model, adjusted for age and hypertension, higher number of HPCs remained significantly associated with the mild clinical picture [OR(95%IC): CD34+: 0.25 (0.07–0.90), $p<0.05$; CD133+ 0.21 (0.05–0.83) $p<0.05$; CD34+/CD133+ 0.25(0.07–0.90) $p<0.05$]. In addition, significant associations ($p<0.05$) were observed between the numbers of all the three types of HPCs and cognitive, functional and motor tests, such as Mini Mental State Examination, Stroop III test, Delayed word recall, Verbal fluency and Short Physical Performance Battery.

Conclusions: In the present study we investigated, for the first time, peripheral blood EPCs and HPCs levels in CADASIL patients and in a comparable group of healthy subjects, documenting an involvement of EPCs and HPCs in the pathogenesis of CADASIL and in relation with a phenotypic expressivity.

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Atrial Fibrillation and Stroke: Prevalence, Prevention and Secondary Prophylaxis

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Atrial Fibrillation (AF) is the most common arrhythmia in clinical practice, with incidence and prevalence increasing with age, up to more than 10% over the age of 80. The absolute risk to develop AF during the whole life is about 25% at any age and is higher for men than for women. AF is associated with cardiac and not-cardiac comorbidities, and has a tremendous impact on clinical status, as it doubles the overall risk of death and increases 4–5 fold the rate of stroke, being responsible for more than 20% of all of them. To prevent the occurrence of embolic stroke, anticoagulation has proved to be effective both in primary and in secondary prevention. CHADS2 score identifies the best therapeutic strategy for each patient.

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Nurses Care and Clinical Monitoring of Acute Stroke Patients

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The efficacy of stroke units has been extensively examined showing that stroke patients who receive organised inpatient care in a stroke unit are more likely to be alive, independent, and living at home one year after the stroke(1).

Experienced and multidisciplinary team,continuing stroke education,early rehabilitation therapy and the active involvement of the family are at the basis of stroke unit organization.

Nursing plays a crucial role in stroke treatment, prevention, and education(2).

The primary tasks for nurses staff are

– monitoring and evaluation of vital parameters
– neurological evaluation with acute stroke assessment scale
– intensive monitoring of thrombolysed patients
– evaluation of the nutritional status and "nutritional risk"
– diagnosis and management of disphagia
– diuresis monitoring and management of urinary retention
– evaluation ef stipsis and fecal incontinence
– early mobilization and good bed positioning
– prevention and treatment of pressure ulcers
– falling prevention
– communication with patients affected by speech disturbance
– deep venous thrombosis prevention
– information

The Scandinavian Stroke Scale is an acute stroke assessment scale used for the evaluation and for the clinical monitoring in stroke acute phase and based on scored assessment of: level of consciousness, eye movement, arm motor power, hand motor power, leg motor power, orientation, speech, facial palsy and gait. It has the advantage to be simple and fast (about 5 minutes to be completed) (2).

All the stroke patients should be screened for the nutritional status. Dysphagia is a common complication following stroke and affects up to 80% of stroke victims.Because the complications of dysphagia are great (aspiration leading to chest infection, malnutrition, increased length of hospital stay, remission to the hospital and mortality), it is important to perform an early evaluation of dysphagia with a standardized scale and determine if alternate means of feeding are required. Diet modification and fluid consistency should be evaluated considering the severity and the presenting signs and symptoms of dysphagia(2).

Urinary infection is the most frequent infective complication of acute stroke patient. The incontinent patients should be carefully examined and the urethral catheter placed only if behavioural changes, nursing care, special clothes and special device to collect urine have not been successful.

Pressure ulcers are a frequent complication in stroke patients and they are associated with an higher risk of mortality and bad functional outcome.Risk factors are diabetes, obesity and malnutrition. Stroke patient should be regulary moved (every 1 to 4 hours). This reduces the chance of getting pressure ulcers (bed sores) . There are also devices that can help to relieve pressure like the air mattresses, It is also very important to keep the skin clean and dry, especially if the patient may be incontinent.

It is important to identify patients at risk of falling and to make the hospital setting adequate to disabling people.

The shoulder is really vulnerable to capsular stretching due to gravity effect or to incaute mobilization. This is the reason why it is necessary to prevent thraumas by a correct bed and wheelchair positioning.(3).

Deep venous thrombosys is a frequent complication of stroke patients with impairment in motor function. Compression stockings should be routinely used after a careful examination of peripheral circulation, sensory function and of the presence of skin lesions(2,3).

The nurses should encourage the communication with patients even if affected by speech disturbance. It is also important to establish a good relationship with the family and to inform them even by written informative brochure. It is important to identify the caregiver that should be informed about his important role to make easier the transition of the patient from hospital to home, to encourage as much independence as possible even supporting the participation in leisure activities.(2,3).

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Early Rehabilitation for Acute Stroke Patients

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Strong evidence show that organised care provided by dedicated staff (stroke unit care) is not only cost effective, but highly effective in preventing death and long term disability in stroke patients compared to care provided on general medical wards alone. Stroke unit care is typically provided by a coordinated multidisciplinary team operating within a discrete ward, which can provide a substantial period of rehabilitation when required. Favourable outcomes appear to be independent of patient age, sex, or stroke severity.

Fundamental aspects of effective stroke unit care include:

- accurate and rapid diagnostic workout
- evidence based treatment
- close monitoring of neurological status and physiological parameters
- prevention of the complications of stroke and recurrent stroke
- early institution of multidisciplinary rehabilitation focused on achieving functional goals and early development of an individualised discharge plan.

Scientific evidence and specific expertise in stroke care recommend experienced, dedicated, multidisciplinary team as a key principle in the optimal management of stroke patients. The team should comprise non-medical (nurses, physiotherapists, speech therapists, occupational therapists, neuropsychologists, social workers) as well as medical professionals.

The main features of effective stroke rehabilitation include a functional approach targeted at specific activities e.g. walking, activities of daily living, frequent and intense practice, and commencement in the first days or weeks after stroke.

In particular a retrospective analysis of patients who received stroke unit rather than general medical ward care, showed that very early rehabilitation, with an emphasis on mobilization, is one of the greatest contributors to better outcome. It is well accepted that stroke rehabilitation should start as early as possible for the best achievable recovery. Exactly how early rehabilitation should begin is controversial. Early mobilization (getting up out of bed within 24 h of stroke onset) is a well-established feature of acute stroke care in many advanced hospital settings, nevertheless widely diffused clinical practice still enforce bed rest for the first few days or foster long periods of bed rest after stroke. Preliminary data from a phase II, multicentre, randomised controlled trial, A Very Early Rehabilitation Trial for Stroke (AVERT), provided evidence that getting stroke patients out of bed and engaging in early intensive exercise therapy within 24 hours of symptom onset is a safe method of rehabilitation — even among individuals who have been treated with tissue plasminogen activator (tPA). Furthermore it showed also that very early mobilization is likely to be cost-effective. It is potentially deliverable to 85% of the acute stroke population and may help reduce acute stroke complications such as deep vein thrombosis, skin breakdown, contracture formation, constipation, and pneumonia.

In the early phase of acute stroke, rehabilitation is not exclusively focused on secondary and tertiary prevention but also on enhancement of neurological recovery, by early therapy initiation, starting with range-of-motion exercises and changes of bed position and continuing with a progressive increase in the level of activity as soon as medically tolerated. The rehabilitation project and the related programmes are generally designed in few days after a stroke and they undergo a regular audit and reassessment. Functional assessment of stroke patients should therefore be based on validated standardized assessment tools to tailor a comprehensive treatment plan.

Information and education of the patient and family is fundamental for increases the probability of informed decision making social adjustment, and maintenance of rehabilitation gains.

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Assessment of the Psychological and Emotional Burden on Patients and Caregivers

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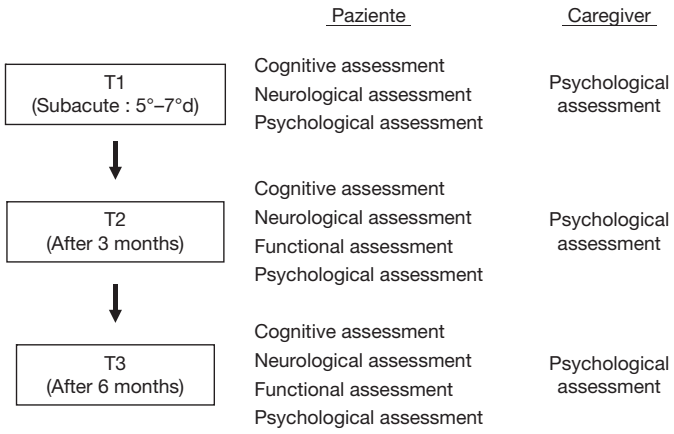
It has become increasingly clear from clinical practice with stroke patients and recent publications that attention must be given to the role of the caregiver. A sudden pathological event such as a stroke implies not only direct consequences for the patient but also indirect consequences for the family members and, in particular, the person who assumes responsibility for looking after the patient (the caregiver). The long-term fulfilment of this role may lead to disruption of the individual's personal psychological equilibrium, increasing the probability of the insurgence of depression.

Until now, the literature has only dealt with " post-stroke depression" in relation to the patient, without taking into consideration the likelihood of depression arising in the caregiver who has to give moral and physical support to the patient on a daily basis.

Various studies have brought to light certain characteristics in the patient and the caregiver whose interaction could influence the onset of symptoms of depression. For instance, if the caregiver is a partner and, therefore, more deeply emotionally involved with the patient, if he/she is over 65, or uses coping strategies of a passive kind, they would seem to have a greater tendency to become depressed than others. Among the characteristics affecting the patient, the most relevant, apart from being over 65, appear to be the seriousness of the stroke (assessed through NIH), the entity of the disability (indicated by MRS), the neuro-psychological symptomatology associated with the event (evaluated through STMS and MMSE) and previous strokes or periods of depression. (Berg et al., 2005; Cameron et al., 2006; Paolucci et al., by DESTRO Study Group 2006).

Our study was inspired by the need to define the precise role of the variables and assess their level of contribution to the manifestation of depression in the caregiver.



Patients from the Stroke Unit of the Careggi University Hospital in Florence were asked to participate and a protocol was created designed to assess the presence of the variables and their interplay with the patient's and the caregiver's backgrounds.

Even if this study is still underway and the results are, therefore, not yet definitive, it has clearly shown the importance of applying the protocol in the sub-acute phase. Evidence has also emerged that the employment of active coping strategies on the part of the caregiver and his/her full involvement in the care-giving, favour adaptability and help prevent the insurgence of depression in the caregiver him/herself.

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Barcelona Stroke Unit

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Continuous and comprehensive clinical, hemodynamic and imaging monitoring of stroke patients has demonstrated to improve not only patients selection for specific treatments but also clinical outcome. Early detection of clinical deterioration by means of serial NIHSS score assessment, blood pressure drop or marked BP variability by continuous BP monitoring and vascular status by carotid US and TCD monitoring is crucial for isquemic tissue and clinical a outcome. Specific monitoring protocol according to stroke subtype may optimize the efficiency of care in an acute Stroke Unit.

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Stroke Unit Organization in Lombardia, Northern Italy

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Despite a different approach to the problem of stroke unit (SU) organization in the different italian regions, a quite similar concept may be considered as a guideline in the different realities. It derives from the study planned and realized in Italy by the PROSIT study group, coordinated by researchers from Lombardia after preliminary results obtained in 7 italian regions. Data obtained by that survey demonstrated that also in our Country, SU showed a clear beneficial effect on death and disability in acute stroke patients and this effect was mainly due to structural and functional organization of this units as well as from the hospital setting.

In the Lombardia region the concept of SU as Cerebrovascular Unit (UCV) was developed since 2002 in the regional heath program which defined as SU (or UCV) semi-intensive, neurological unit similar to the coronary unit. In the following health plans the idea of SU was further developed and some of the main concept concerning their organization have been described in a programmatic document very recently (September, 18) issued. Together with a distinction of SU (UCV) into three different levels of organization (first level: dedicated personnel and beds but no authorization to thrombolytic treatment; second level: the same plus thrombolytic treatment authorized; third level: the same of the second one plus neurosurgery, neuroradiology, endovascular treatment and intraarterial thrombolisis, vascular surgery) this plan describe the exact pathway from home to hospital (and also after hospitalization) of a patients with stroke, in particular when the critical event occurs within 120'. In this case a quick activation of 118 (emergency number for our Country) is followed by the administration of Cincinnati pre-hospital stroke scale by the 118 personnel which is authorized to treat stroke as a high level emergency (red code) and to bring patients to the closer hospital provided by a SU (UCV). At the arrival to hospital, a very defined path, well characterized in terms of exams and time to spent in their realization, has been described by the regional document in order to guarantee a quick definition of diagnostic and therapeutic approach to this pathology in every case. Of course, this path describe the definitely access to SU(UCV) as soon as possible, also allowing to threat patients in emergency room if it could be the case (for example in the case of temporary occupied SU beds or when time is vey limited for thrombolytic treatment). A very interesting hypothesis of work is represented by the extension of the emergency service protocol of Milano city to the remaining services of the entire region. In this case each emergency service could have every time the occupancy of beds in each SU in the region territory, so that patients is transported directly to the hospital with non-occupied beds in SU.

Another interesting and organized approach to the treatment of acute stroke in our region is represented by the realization of the regional stroke unit network, called Stroke Unit Network (SUN) Lombardia. Thirty-seven units of the region agreed to participate into the project which is characterized by the use of a common data base for the monitoring of the process of care realized in each SU, as well as to verify the application of Italian stroke guidelines (SPREAD) and their effects of the outcome of single patients.

The realization of this network represents the basic element for the creation of a pathology network dedicated to cerebrovascular diseases, similarly to that realized for tumors or haemathological diseases. The aim of this projects is, at the moment, to facilitate the coordination of centers with different experiences and background as well as to promote the adoption of common protocols of diagnosis and treatment of acute stroke and its follow up. An hospital registry has been realized started last year and now collecting more than 6 thousand records of patients treated in 29 SU (UCV) of our Region. The participation to this project and registry of different actors (emergency service, rehabilitation, neurosurgery, vascular surgery, general practitioners) which are interested in the treatment of stroke patients, together with the implementation of telemedicine models able to simplify the correct distribution of patients on the basis of their severity and needs represents the target of this organization which we have to develop in the future in order to better assist patients with stroke.

21
Multidisciplinary Italian Guidelines. A Statement of Diagnosis and Treatment of Carotid Pathology

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Relying on the most important trials in literature and on the multidisciplinary Italian Guidelines for Stroke – SPREAD (www.spread.it), in order to examine the latest indications for diagnosis and therapy in case of carotid atherosclerotic lesion, we are distinguishing patients as for symptomatic (maximum interval of three months from symptom) and asymptomatic for cerebral ischemia, and applying to the NASCET and ECST evaluation criteria for carotid stenosis.

Echo-Doppler examination of supra-aortic vessels is recommended in patients with TIA or recent stroke for the pathophysiologic work-up, and in asymptomatic subjects with a high carotid stenosis prevalence.

Carotid endarterectomy (CE) is recommended in case of symptomatic carotid stenosis (SCS) more than 70% (NASCET method), but CE is not recommended for SCS less than 50%. In patients with SCS between 50% and 70% CE is indicated mainly in case of recent ischemia, non ocular symptoms, ulcerated plaque, old age, male sex and presence of diabetes.

Surgical indications are relative in case of asymptomatic patients with carotid stenosis more than 60% (NASCET method), under the assumption that the perioperative major complications are much less than 3% and with respect to life perspectives of patient.

As pre-operative examination for the diagnosis echo-doppler examination can be assumed to be satisfactory enough, if validated by comparison with angiographies or surgical findings. Complementary RMI angiography is indicated when multiple lesions, proximal or distal stenosis at carotid bifurcation and vascular malformations are suspected.

The use of traditional angiography is indicated either in presence of conflict between echo-doppler and RMI angiography, or when RMI is contraindicated or not at disposal.

Deciding the timing of CE in symptomatic patients, in case of TIA or minor stroke and a negative or small lesions on cerebral CT scan the surgical approach is recommended as soon as possible, but in case of large CT lesions the early surgical procedure is not recommended, independently of the neurological impairment.

Regarding to cerebral protection in case of surgical procedures un-randomized studies suggest a potential benefit from locoregional anaesthesia in comparison to general anaesthesia, which anyway requires a well controlled monitoring with EEG or Somatosensory Evoked Potentials. Endoluminal temporary shunt is indicated not for routine, but in case of cerebral intolerance to the clamping.

At present percutaneous transluminal angioplasty and primary stenting of carotid stenosis are not considered safe as CE and long term results are necessary, together with randomised controlled trials of comparisons, in order to assess an evaluation about these innovative endovascular procedures. At the very moment, they are suggested in selective cases where advantages over CE are very evident: restenosis, stenosis with regular surface and homogeneous to echographic findings, stenosis not of the carotid bifurcation or post-radiotherapy.

Antiplatelet therapy is recommended before and after surgical intervention and the surgical correction of restenosis is recommended if severe and clinically symptomatic.

In presence of emergency, e.g. in case of acute stroke or stroke in evolution, studies in literature or experiences in centers of excellence seem to show benefits from the surgical therapy in comparison to the medical one. The indications to surgical procedures in emergency (within the first hours) are severe carotid stenosis or thrombosis, the lack of haemorragic cerebral lesions through TC scanning and the absence of severe cerebral compromissions such as coma.

Intra-arterial thrombolysis can be associated to CE in case of thrombosis in the intracranial internal carotid artery. Cases with perviety of the cerebral medial artery can surely offer a better prognosis.

Echo-Doppler examination of supra-aortic vessels is recommended in patients who have undergone CE to monitor for recurrence, timing the follow-up examinations at 3 and 9 months after and every year thereafter.

22
Medicine Anticipatory

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To compare the numbers reflecting the high incidence and prevalence of stroke brain with those of modest results obtained with drug therapy in secondary prevention, clearly highlights the importance of well-established primary prevention in reducing the risk of stroke. The percentage of outcomes of debilitating strokes in Italy is 40% of stroke accidents per year and corresponds to a number of about 70,000 people. From owerview therapy and with an effective waiting on a population of 2,400 strokes per million inhabitants, being in Italy calculated the incidence of stroke around 2.4 per thousand, the number of events avoided defining the end point as death or dependance, is 23 per million for the ASA (12 events avoided per 1,000 treated with a target population treatable 80%) of 34 for rt-PA <3 h (143 being the number of events per 1000 patients treated and 10% the number of potential patients who may require treatment) and 120 per million

benefit from the shelter in Stroke Unit (50 events avoided per 1000 hospitalized where 100% is the target population). It follows that, the best organization, we can have a benefit of 20% that, compared to the real world, can mean a decrease of 15% less, in absolute terms, the number of patients with serious outcomes. Hence the need for a ceiling is to decrease the number of stroke incidents. Prevention is the first reference to this goal.

Detect, monitor and treat risk factors is the most successful strategy in combating the stroke brain. In the Italian Health Service the general practitioner is the figure that more than any other can perform this function for identifying and monitoring treatment. In recent years a general was prompted by the passage from the "medicine waiting" in which design should try to respond to the needs of the patient, to the "anticipatory medicine" for which an early aggressive stance on risk factors, is expressed through "strategies mass" with the increase of healthy lifestyles, or through "individual" targeted at people with high risk (by convention> 20%). The anticipatory medicine recognizes two methods of intervention: "The medical initiative" that sees its implementation in screening programs aimed at the population of early diagnosis and the consequent pre-emption (not required and not expected of course) and "medicine opportunities where screening and subsequent intervention takes the form prior to subjects that are addressed to the doctor for quite different reasons and not related to a stroke or any risk factors themselves. The latter represents the most effective and simple as it provides that in five years will see any doctor at least once all its patients. This methodology to be truly effective it will complement a motivational speech of the person with whom there will be an education that will represent the therapy itself.

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23
Management & Leadership

M. Cecchi

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The regional law N. 40 says that "hospitals have to be structured in differentiated areas in according to care modalities, intensity of care, length of stay, and type of hospitalisation, changing the single discipline ward structure". This model has been applied in our Azienda Sanitaria di Firenze since October 2007.

In our surgical department this view has lead to the use of a single ward with all surgical specialities but with similar intensity of care (at last in the most of cases).

One of the most controversial aspect of this re-engineering of the hospital circuit of the surgical patient has been the directors' new way of considering "own ward, own nurses, own beds and so on".

In our experience this critical aspect has been managed by stimulating the new role of "leader & tutor of the patient" instead of "simply manager".

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How to Prepare a Protocol for a Randomised Controlled Trial

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Why a busy physician should bother about randomised controlled trials (RCT)? Ideally, when we are faced with a patient, for whose condition or disease there is no proven treatment, we should offer participation in a clinical trial to solve both his or her problem and our uncertainty. Although frequently this is not the case, and we treat patients with procedures which have a very low level of evidence, we may well ask ourselves "why not to find out what is the best treatment for this disease?". Then we will probably ask ourselves again "how can I do that?". The answer is easy: we have to design and conduct a RCT.

It is impossible to describe here all the details related to the writing of a protocol for a RCT: we will just focus on a few strategic points.

The first step is to state what the objective is; it must be clear, it must be relevant, it must be one! Usually, we clinicians prefer qualitative endpoints (dead or alive, new event or no event, etc.); however, sometimes it might be more appropriate to use quantitative endpoints, even with ordinal scales; for sake of simplicity, we will just focus here on qualitative endpoints. We need to know (from epidemiology, our experience or previous trials) what is the percentage of patients who "do badly" (that is, have the index endpoint) with our usual treatment; than, we need to establish what advantage we expect from the new treatment: it must be both clinically sound and credible. The decision on what degree of advantage is worth looking for should be taken in agreement with the health authorities and the patients' organisations, whenever possible; the results should be able to modify the clinical practice, if we end up with a positive effect.

The second step is to calculate the sample size; we need to know whether we are actually able to recruit enough patients to answer the question we are asking; if we are not, either we change the question (or the degree of advantage, if clinically acceptable), or we add more centres to the study. To calculate the sample size, we need to know 4 numbers: the percentage of patients with the endpoint in the control group (that is, those who do badly with the usual treatment), the possible absolute risk reduction (that is, the degree of advantage we want to see), the alpha error (that is, the probability we are ready to accept to say that something works when in fact it does not), and the beta error (that is, the probability we wish to accept to say that something does not work when in fact it works); usually, these two last figures are set at 5% and 20%, but may vary according to the clinical situation. Then the sample size can be calculated with a computer

statistical package (although we recommend to consult a statistician for more complex designs, for instance when the time to event is considered).

Just suppose that you end up with a number of patients you think you can recruit in a reasonable time (say, a couple of years); then you can start to prepare a detailed protocol, with a rationale, a list of inclusion and exclusion criteria, and an explanation of the clinical evaluation, both for inclusion and for follow up, as well as for the endpoint evaluation; all these steps should be as similar to the daily clinical practice as possible.

Do you need always a "double blind" design? We think you don't. If the outcome measure is done by someone who is actually blind to the treatment, then there is no need to bother you and the patient with all the procedures related to blindness; if however the outcome evaluation may be influenced by the knowledge of the treatment, then blindness is necessary. In any case, you must ensure a very secure randomisation procedure (the so called randomisation concealment), which is the key factor to obtain comparable groups and trustable results.

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Review of Different Thrombolytic Treatment Procedures: Intravenous, Intra-Arterial, Combined Intravenous and Intra-Arterial, Mechanical Including Thrombectomy or Stenting

R. Sztajzel

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The benefit of intravenous thrombolysis with tPA has been demonstrated within 3 hours of onset of cerebrovascular symptoms. When compared with placebo, patients treated within this time frame are 30% more likely to exhibit complete or nearly complete recovery at 3 months. Moreover, a recent study showed that there were more patients with a favourable outcome when treated with intravenous alteplase between 3 and 4.5 hours after onset of symptoms as compared with placebo. As it has been shown in the PROACT II study, patients treated with intra-arterial thrombolysis (pro-urokinase, urokinase or tPA) within a 6-hours window are also more likely to regain independency at 90 days than those assigned to placebo.

Furthermore, bridging therapies have been advocated with administration of systemic thrombolytics followed by infusion of intra-arterial tPA to help dissolve clots. These combined intravenous and intra-arterial thrombolysis offer some advantages over either technique alone: intravenous treatment may be administered very early while the resources to deliver intra-arterial are organized; furthermore intravenous thrombolysis is easy of use and of widespread availability. On the other hand, intra-arterial thombolysis, as it has been suggested in several studies, may offer possible superior and earlier recanalization. Combined IV-IA thrombolysis has been studied in several trials.

Recent works emphasized on the potential role of mechanical thrombolysis, including thromboaspiration, percutaneous transluminal angioplasty and implantation of stents, yielding recanalisation rates of more than 75% when intra-arterial thrombolysis is added. Other studies also demonstrated a potential benefit of a multimodal approach combining mechanical disruption and platelet GPIIb/IIIa receptor antagonists mainly as a rescue therapy after failure of intravenous or intra-arterial therapy.

The efficacy and safety of intravenous tirofiban combined with intra-arterial pharmacologic and mechanical thrombolysis has been evaluated in a cohort of 21 patients. Immediate recanalization was successful in 17 of them; however, intracranial bleeding occurred in 5 of the 21 patients. Another study evaluated self-expanding stents for recanalization of acute cerebrovascular occlusions and showed that stent-assisted revascularization increased prevailing recanalization rates for vessel occlusions recalcitrant to thrombolytics.

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Microbbubble-Enhanced Sonothrombolysis for Acute is Chemic Stroke

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Experimental and clinical studies have consistently demonstrated the capability of ultrasound (US) to enhance enzymatic thrombolysis. US application increases the transport of tPA into the thrombus, promotes the opening and cleaving of the fibrin polymers, and improves the binding affinity of tPA to fibrin. In an observational pilot trial of combined therapy with 2-MHz continuous US monitoring and intravenous tPA in 55 patients with a documented MCA occlusion treated <3 hours of stroke onset, complete recanalization at 2 hours of tPA bolus was achieved in 36% of patients. In a small study using transcranial color-coded sonography (TCCS), 32 patients were randomly allocated to be treated with combined TCCS and intravenous tPA or tPA alone <6 hours of symptom onset. Combined treatment was associated with higher rates of recanalization but also with a higher rate of ICH. CLOTBUST, a phase 2 multicenter randomized trial, recently demonstrated that 2-hour continuous monitoring with 2-MHz TCD, a commercially available device widely used for diagnosis, in combination with standard tPA is safe and may improve outcome. Among 126 patients randomized to tPA plus 2-hour TCD monitoring (target group) or tPA alone (control group), symptomatic ICH occurred in 4.8% of target and 4.8% of control patients. Complete recanalization or dramatic clinical recovery at 2 hours after tPA bolus were observed in 49% of target and 29% of control patients ($P = 0.02$). Moreover, trends toward better clinical outcomes at 24 hours and long term were noted in sonothrombolysis patients. A phase 3 of the CLOTBUST trial is planned to begin in 2006. Enhancement of enzymatic thrombolysis by US may allow testing regimens with low-dose tPA to reduce the risk of ICH.

Microbubbles (MBs) are small air- or gas-filled microspheres with specific acoustic properties that make them useful as US contrast agents for sonographic examinations. In diagnostic US, MBs create an acoustic impedance mismatch between fluids and body tissues, increasing the reflection of sound. Experimental studies have shown that US-accelerated thrombolysis may be further enhanced by administration of MBs. Low-frequency US with high power has been demonstrated to produce cavitation and fluid motion into the

thrombus.MBs, by acting as cavitation nuclei, lower the amount of energy needed for cavitation. Application of high-acoustic-pressure US has been shown to induce nonlinear oscillations of MBs, leading to a continuous absorption of energy until the bubbles explode, releasing the absorbed energy.Thus, US-mediated MB destruction may further accelerate the clot-dissolving effect of US.

The synergic effect of US and MBs on sonothrombolysis has been demonstrated in clinical studies in patients with arteriovenous dialysis graft thrombosis.However, whether MBs further accelerate US-enhanced systemic thrombolysis in stroke patients remains unknown. Therefore, we sought to investigate the effects of galactose-based MBs on the beginning, degree, and time to maximum completeness of middle cerebral artery (MCA) recanalization during systemic thrombolysis and continuous 2-Hz pulsed-wave TCD monitoring.

We evaluated 111 patients with acute stroke attributable to MCA occlusion treated with intravenous tissue plasminogen activator (tPA). Thirty-eight patients were treated with tPA plus continuous 2-hour TCD monitoring plus 3 doses of 2.5 g (400 mg/mL) of galactose-based MBs given at 2, 20, and 40 minutes after tPA bolus (MB group). These patients were compared with 73 patients who were allocated to receive tPA plus continuous 2-hour TCD ultrasound (US) monitoring (tPA/US group) or tPA plus placebo monitoring (tPA group), most of whom were enrolled in a previous study of US-enhanced thrombolysis. The beginning, degree, and time to maximum completeness of recanalization during the first 2 hours of tPA bolus were recorded. Median prebolus National Institutes of Health Stroke Scale (NIHSS) score was 18. Eighty patients (72%) had a proximal and 31 (28%) a distal MCA occlusion on TCD. Thirty-seven patients (33%) received tPA/US, 38 (34%) received tPA/US/MB, and 36 (32%) were treated with tPA alone. Stroke severity, time to treatment, location of MCA occlusion, and presence of carotid artery disease were similar among groups. Two-hour recanalization was seen in 14 (39%), 25 (68%), and 27 patients (71%) in the tPA, tPA/US, and tPA/US/MB groups, respectively ($P = 0.004$). Two-hour complete recanalization rate was significantly ($P = 0.038$) higher in the tPA/US/MB group (54.5%) compared with tPA/US (40.8%) and tPA (23.9%) groups. The time to beginning of recanalization after tPA bolus was 26±18 minutes in the tPA/US group and 19±12 minutes in the tPA/US/MB group ($P = 0.12$). Four patients (3.6%) experienced symptomatic intracranial hemorrhage: 2 (5.5%), 1 (2.7%), and 1 patient (2.6%) who received tPA only, tPA/US, and tPA/US/MB, respectively, experienced symptomatic intracranial hemorrhage. At 24 hours, 31%, 41%, and 55% of tPA, tPA/US, and tPA/US/MB improved >4 points in the NIHSS score. Administration of MBs induces further acceleration of US-enhanced thrombolysis in acute stroke, leading to a more complete recanalization and to a trend toward better short- and long-term outcome.

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CT Perfusion: Rationale in Acute Stroke Patients

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At present we have different therapeutic options in acute ischemic stroke, ranging from e.v. thrombolysis, sonothrombolysis, local intra-arterial infusion of thrombolytic drugs, mechanical removal of the thrombus, mixed mechanical/farmacological strategies.

In any case the therapeutic window during which we can operate is a limiting factor as the result of reperfusion of an arterial district is strictly dependent on its timing: as time passes by the less is the probability of recovery and greatest the risk of an haemorragic transformation.

Beside timing other elements to take into account during planning of a treatment are the site of occlusion, the nature of the occluding agent, the pathophysiological state of the involved brain parenchyma.

CT Perfusion (CTP) associated to a CT Angiography (CTA) study can give an answer to most of these questions.

Adding a few minutes (approximatively 10–15) to the acquisition of the basic standard brain CT we can obtain precious data regarding -the site and extent of arterial occlusion, -about the state of the collateral pathways, -about the presence and extension of ischemia and –about viability of the affected tissues. CTP technique, in fact, can identify not only the extension of the ischemic territory in a very precocious time but also its pathophysiolocial state predicting the extent of tissue already irreversibly damaged and the extent of tissue at risk if not re-perfused, but still salvable. The results of numerous studies in the international literature and our own data confirm the high predictive value of this kind of information.

The great challenge to the neuroradiologist and to the stroke specialist is to clarify the proportion of dead/salvageable tissue (so called "mismatch" or core/penumbra) to consider for rationale treatment. Perhaps not only the respective volumes of core/penumbra are to be considered but we should also weight the "nobility" of the salvageable brain tissue.

Another outstanding advantage of CTP in acute stroke is the possibility to overcome the timing limitations in that it could help in choosing to treat a given patient even if the usual time window is passed-by or if we have no information about the time of onset (for example the so called awakening stroke); on the other hand we could decide not to treat a patient, even if a short time has elapsed since the onset of symptoms, should the CTP tell us that all the involved tissue is already irreversibly damaged.

The new generation of CT scanner permits today to obtain CTP and CTA acquisitions in a very short time, really adequate to patients that in the majority of cases are not or only partially cooperative.

This new generation of scanners, moreover, overcome the problem of the limited spatial coverage which characterized the old versions and permits to explore wide thickness of brain parenchima in a very short time.

The risks for the patients and adverse effects are really low: the total amount of contrast media infused for both CTP and CTA is similar to that used for a standard contrast brain CT; the X-ray exposure is well contained within the limits recommended for clinical use.

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Perfusional Studies in Acute Stroke

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The perfusional evaluation of the cerebral parenchyma in acute stroke patients has its main rationale in the distinguishing the portion of brain tissue irremediably damaged and therefore non salvageable from the one ischemic but not irreversibly infracted and then salvageable by a rapid treatment. Such an approach is feasible and useful both in situations where no clear time of onset is disposable and in situation when the classical time window for thrombolysis is passed. Besides its usefulness is also well documented in acute stroke patients within the classical time window. There are several tools that can measure the perfusional status, both radiological and neurosonological, namely MRI with diffusion/perfusion software, CT perfusion and TCCS (Transcranial Colour Coded Sonography) with the administration of second generation contrast media and the use of non linear properties of interaction contrast-tissue of harmonic imaging generation.

No direct comparison between these methods are disposable at our knowledge and the best method is not yet well defined. For practical reasons, MRI, although well studied and documented in the literature with the diffusion-perfusion mismatch definition, is not usable in many hospitals in an acute setting and the execution time or the not applicability in a significant portion of patients (pacemakers or metal prosthesis, heart disease with the poor tolerance of the supine position for a long time, significant decrease of blood oxygen saturation in 20% of patients) limit the application of this technique. CT perfusion is a reliable and most practicable tool, with some technical limitations, as the limited brain volume examinable with a single contrast bolus, the use of iodinated contrast media (adverse reactions, impaired renal function) and the different performance of deconvolution algorithm by operator expertise. Neurosonological techniques use the same mathematical rules than radiological methods and can measure perfusional parameters in a limited portion of brain tissue, namely a single oblique scaning plane in the axial access from temporal bone window. This latter technique is markedly influenced by the suitability of temporal bone window, that is insufficient in 15% of patients, mainly in older patients and females and this feature is not overcame by contrast media use for the microvasculature examination. Therefore is not yet clear which are the threshold for hypoperfusion in gray matter versus white matter and in the single restricted time window more and more away from symptom onset.

This approach can give a more attractive and physiological tool of evaluation in acute stroke but its practical use is actually in progress.

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Neurological Functional Scales: National Institute of Health Stroke Scale (NIHSS), Modified Rankin Scale, Glasgow Scale

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Functional neurological scales, including NIHSS, Rankin scale and Glasgow scale, are routinely used in clinical practice and in randomised controlled trials in patients with cerebrovascular diseases.

Functional scales are often utilized to standardize stroke severity in the acute phase, to describe functional variations, and to quantify improvementt.

NIHSS specifically assesses stroke severity while modified Rankin scale and Glasgow scale described handicap and disability, respectively. Furthermore the Barthel Index evaluates the ability to perform activity of daily living in order to draw and supervision the rehabilitative programs in stroke patients. The modified Rankin scale is worldwide used to assessed functional outcome in patients with stroke.

However a single scale describes only some features of the patient and stroke physician should take together all the information derived from different scales in order to describe the present and the future neurological status of every patient.

Only the routinely use of these scales in stroke care on clinical and research programs can ameliorate the whole clinical evaluation of stroke patient in order to select them to the most appropriate treatment in the hyperacute phase and after.

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Aspects Score

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In 1995 the National Institute of Neurological Disorders and Stroke rtPA (NINDS) study demonstrated the efficacy of systemic thrombolysis for the treatment of acute ischemic stroke when administered within 3 hours of symptoms onset. In the NINDS trial CT scan was used to exclude the presence of intracranial hemorrhage before randomization. There is now accumulating evidence that the presence of early ischemic changes (EIC) on CT can predict both functional outcome and the risk of intracerebral hemorrhage.

EIC identified on CT during the first few hours after stroke onset represent early cytotoxic edema and possibly the development of irreversible changes (the ischemic core). CT signs of early ischemia consist of sulcal effacement with loss of gray-white matter differentiation in superficial cortical infarctions and subtle hypodensity of the basal ganglia in deep cerebral infarction. The role of extensive EIC on clinical prognosis has been observed in the ECASS trial, where the presence of parenchymal hypoattenuation exceeding one third of the middle cerebral artery territory was associated with increased mortality and higher rate of hemorrhagic transformation. Given the low

reliability of the "one third" rule as an estimate of the extent of EIC, a standardised semiquantitaive CT grading system was validated in 2001, the Alberta Stroke Program Early CT Score (ASPECTS).

For ASPECTS, which is calculated from two standard axial CT cuts (one at the level of the basal ganglia and one just rostral to the ganglionic structures), the territory of the middle cerebral artery is divided in 10 regions, with 1 point subtracted for an area of EIC within each of the defined regions. A normal CT scan has an ASPECTS of 10. In clinical series of patients treated with systemic rtPA, the probability of dependence, death and symptomatic hemorrhage increases as the ASPECTS value decreases. An ASPECTS > 7 predicts a good functional outcome and a lower hemorrhagic risk.

In the NINDS study, patients with ASPECTS > 7 showed no treatment-modifying effect on good outcome, with a trend towards lower mortality at 90 days with rtPA and a number needed to treat of 5. Hence, there is currently no evidence for excluding patients for thrombolytic treatment within 3 hours based on the presence of EIC.

The use of a systematic approach becomes more relevant for patients treated beyond 3 hours, with the presence of extensive EIC (ASPECTS≤7) as a predictor of unfavourable outcome and high hemorrhagic risk. In the PROACT-II trial, which explored the efficacy of intra-arterial thrombolysis within 6 hours from onset, patients with ASPECTS > 7 were 3 times more likely to have an independent functional outcome with thrombolysis compared with controls. In candidates to intra-arterial thrombolysis between 3 and 6 hours, the ASPECTS score, together with a rapid acquisition of evidence of vessel occlusion (with carotid ultrasound, CT angiography), can be a useful tool for selecting patients who are most likely to benefit from treatment.

A novel CT score, called posterior circulation-Acute Stroke Prognosis Early CT Score (pc-ASPECTS) has recently been tested in patients with vertebrobasilar ischemia. In the posterior fossa, the sensitivity for ischemic changes is improved with CT angiography source images rather than with non contrast brain CT scan. The presence of extensive EIC, quantified by a pc-ASPECTS≤7, may identify patients with basilar occlusion who are unlikely to have a favourable outcome.

Conclusion: ASPECTS is a topographic CT scoring system, that divides the middle cerebral artery territory into 10 regions. The baseline ASPECTS value predicts functional outcome and symptomatic intracerebral hemorrhage. The scoring is simple and reliable and, beyond 3 hours, identifies stroke patients unlikely to make an independent recovery, despite thrombolytic treatment.

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MRI: Brain Lesions in Ischemic Stroke

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MRI offers a better (compared with CT) soft tissue contrast and multiplanar visualization of the ischemic area, but conventional imaging (T1, T2 and FLAIR) usually do not identify the ischemic changes within the therapeutic window.

In recent years, diffusion weighted imaging (DWI) has been developed, allowing the recognition of cytotoxic oedema, which represents the first step towards the ischemic necrosis and appears in the very early few minutes from arterial occlusion as an area of markedly increased signal intensity.

This sequence, based on echoplanar fast imaging, has the advantage to be very sensitive and rapid (acquisition time about 30 seconds) and can be coupled with perfusion MR studies, thus identifying the irreversibly damaged ischemic area and the hypoperfused one. The mismatch between these two regions can recognize the so called "ischemic penumbra", i.e. the area that can be saved with a precocious revascularization of the occluded artery.

MRI can also well recognize cerebral infarctions in the watershed areas due to extracranial severe steno-occlusive disease, differetiating between hemodynamic-hypotensive and trombotic strokes.

Moreover, specific MRI patterns may identify non occlusive infarcts due to hypoxiemia, hypoglicemia and metabolic enzymatic deficiencies, such as mitochondrial encephalopathies.

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Ultrasound Vascular Evaluation in the Acute Stroke: How to Perform an Intra and Extracranial Examination in Few Minutes

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In patients with acute cerebral ischemia the clinician must select the optimal therapeutic strategy after careful consideration of different treatment options according to the clinical presentation, the time of symptoms onset and all the different possible underlying obstructive mechanisms. Although according to SITS MOST the assessment of the vascular status is not mandatory to state the patient eligibility to systemic or intraarterial fibrinolysis, in clinical practice a timely vascular diagnosis has proven to be a very valuable tool to make the best choice. The ultrasound vascular examination can effectively depict both the anatomical aspects and the functional characteristics of the cerebral and extracranial vascular compartments and can significantly affect both the therapeutic decisions and the prognostic characterization. Some typical examples are represented by the finding of an hemodynamic stenosis of the internal carotid stenosis in the presence of a TIA, the demonstration of a carotid dissection at the onset of sudden focal neurological symptoms, or an ultrasound demonstration of a extensive T occlusion of the internal carotid artery in a subject with stroke. All these different causes of obstruction imply different clincal outcomes and require peculiar therapeutic options that must be well considered in addition to evaluating patient eligibility to fibrinolytic treatment. In experienced hands the neurosonologic evaluation (carotid Duplex, TCCD and TCD) has proved very useful to achieve a bedside diagnosis in this delicate clinical context, andis more suited than other precise and very sophisticated neuroradiologic techniques (angio MR, angio CT) for bedside examination in the emergency room. In fact US tests can be repeatad whenever needed according to the clinical fluctuations thus providing a real time continuous monitoring of the hemodynamic changes.

The questions to be answered in evaluating an acute stroke patient are almost the same as during an examinaton routinely planned to rule out an atherosclerotic disease of intra/extracranial vessels, with only two main differences: should always be kept in mind: the first is that the test must be clinically oriented. For example in the presence of a left hemiparesis the first site to scan will be the right side internal carotid and middle cerebral arteries. The second main peculiar characteristic is that the examination should be performed in not more than 15–20 minutes to avoid unacceptable delays in patient access to a fibrinolytic treatment (i.e. within the 3 hours therapeutic window).

The ability of TCCD and TCD to detect a vessel viability allows the monitoring of cerebral hemodynamics during the infusion of rTPA and can instantly demonstrate the persistence of an occlusion or the reopening of the artery even long time before a clinical improvement. Therefore TCD monitoring helps to decide whether all fibrinolytic attempts should be interrupted or whether it may be necessary to shift to a more aggressive intra-arterial procedural revascularization by adjunct intra-arterial thrombolysis with low-dose rTPA infusion (the so called bridging protocol).

The carotid Duplex combined with TCD allows to establish whether the extracranial obstruction extends to the origin of the middle cerebral artery and/or anterior artery or if the intracranial perfusion is preserved by intracranial activation of collateral compensatory pathways. The diagnosis of extracranial stenosis relies on both direct morphological visualization of the lumen reduction (2D echo in association with colordoppler and power-imaging) while the grading of the stenosis can be accurately determined by doppler velocity criteria. The focal acceleration (peak systolic velocity) should be measured after 60° angle correction at the level of maximum vessel lumen reduction where the velocity jet can be observed. The velocity in the internal carotid artery should than be compared to that found in a non-stenotic segment of the common carotid artery. The cut-off point for a significant stenosis of the internal carotid artery is the finding of a gretear than 230 cm/sec peak systolic velocity and a greater than 3.5 ICA/CCA peak velocity ratio. These criteria have been validated by parallel angiographic examinations and they have been published on Radiology in 2004. The proximal total occlusion of one of the major neck vessels can be directly diagnosed when the flow velocity signal is totally absent at color/power angio and conventional Doppler examination. The same criteria apply to total main stem MCA1 or ACA1 occlusions. When the blockage of the arterial lumen involves the more distal intracranial branches, the occlusion may not be directly visualized, but its presence can be indirectly inferred in the presence of an ipsilateral velocity reduction in one proxymal segment (>21% Zanette asymmetry index). Focal accelerations can also be found in intracranial arteries; they are consistent with lumen reductions whose severity can be accurately graded according to velocity indices as well. In conclusion an accurate neurosonologic characterization is fiseable in the patient with acute stroke and it is a tool of great utility both for the therapeutic decisions and for the near and long term follow up of the patients.

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TCD and Cerebral Hemodynamics

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Transcranial Doppler Sonography (TCD) is able to explore and monitor the cerebral hemodynamics regarding the study of movements of blood and of the forces concerned in brain circulation. The evaluation of flow velocities (FV) as an index for cerebral blood flow (CBF) is based on the assumption that arterial diameter and several other hemodynamic parameters are stable during the period of measurement. The normal condition for blood flow throughout most of the circulatory system occurs in long, straight blood vessels, under steady flow conditions. It is characterized by concentric layers of blood moving in parallel down the length of the vessel.

The highest velocity (V max) is found in the centre of the vessel while the lowest velocity (V = 0) is found along the vessel wall. This gives rise to a parabolic flow profile**.** The disruption of laminar flow in the vessels leads to turbulence and increased energy loss. It occurs when flow velocities exceed a certain threshold value called Reynolds number (Re) which is defined by the following equation:

$$Re = 2rv\rho/\eta$$

where r = vessel radius
v = flow velocity
ρ = blood density
η = blood viscosity

Therefore turbulent flow depends on flow velocity, on blood viscosity and is consequent to a sudden change of the vessel lumen that can occur in the zones distal to stenotic arterial vessels, in arteries with tortuous course and at vessel branch points. The physical laws that determine steady laminar flow are also helpful in understanding in vivo cerebral hemodynamics, even though blood vessels are not rigid tubes and blood is not a perfect fluid but a 2-phase system of liquid and cells.

The application of Ohm's law to cerebrovascular hemodynamics is reflected by the formula:

$$CBF = CPP/CVR$$

where CBF = cerebral blood flow
CPP = cerebral perfusion pressure
CVR = cerebrovascular resistance

This means that any change in CPP must be matched by a proportional change in CVR, and vice versa, in order for CBF to remain constant: this mechanism is called "Cerebral Autoregulation".

In cerebrovascular circulation most of the resistance is provided by the arterioles and their precapillary sphincters, while the basal cerebral arteries that form the circle of Willis play only a minor role. This implies that the vessels evaluated by TCD have a relatively constant diameter and that the role of the arterioles in regulating CVR and therefore CBF is fundamental.

Consequently the velocities measured by TCD directly reflect the hemodynamic changes occurring in the vessel segment being studied. The diameter of the basal cerebral vessels are only insignificantly responsive to pCO2 while the resistance vessels are very sensitive to changes in arterial pCO2. Therefore the flow velocity can be assumed

to be proportional to CBF during CO2 testing. Variations in PaCO2 are significant vascular modulator of CBF and the flow velocity relationship with PaCO2 is linear, with an approximately 4% change for every unit change in PaCO2. In conclusion TCD is a useful tool in exploring the cerebral autoregulatory mechanisms consequent to activation of collaterals (intracranial macrocirculation) and is also able to show the functional vascular reactivity of cerebral resistance arteries (intracranial microcirculation). Therefore TCD can be considered a qualified and reliable non invasive approach able to detect the variations of cerebral hemodynamics in a large variety of clinical and research settings.

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TCD for Guiding Therapeutic Decision

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In the last few years, a tremendous progress and widespread implementation of noninvasive neurovascular techniques including transcranial Doppler (TCD), computed tomography angiography (CTA), and magnetic resonance angiography (MRA) have been achieved. These imaging modalities are being increasingly performed in the acute stroke setting without substantial delay in a large number of centers worldwide. Far beyond the simple demonstration of an intractranial artery occlusion responsible of patient´s neurological deficit, detection of arterial occlusion provides valuable prognostic information and may predict response to different reperfusion strategies. Several studies have demonstrated that the absence of an intracranial artery occlusion represents an independent predictor of early clinical recover and good long-term outcome. Conversely, persistent arterial occlusion predicts clinical fluctuations and early neurological worsening. The location of arterial occlusion may represent a marker of clot burden and response to thrombolysis. So, the more proximal the occlusion the larger the clot. In a multicenter study including 253 acute strokes due to MCA occlusion, the probability of complete recanalization at 2 hours of tPA bolus varied depending on the location of MCA clot. Complete recanalization was achieved in 45% of patients with M2-M3, 29% of those with M1 and only 11% of patients with terminal ICA occlusion achieved a complete recanalization. Therefore, a rapid detection of clot location may be useful for selecting patients for more aggressive reperfusion strategies. On the other hand, in patients with basilar artery occlusion, the site of arterial obstruction may indicate the patho-physiologic underlying mechanism. While distal basilar artery occlusion suggests an embolic source, proximal occlusion basilar is in most cases the result of a complicated atherothrombotic plaque.

Transcranial Doppler ultrasound is a non invasive technique that uses ultrasound to obtain information of the flow velocity in the intracranial arteries of the circle of Willis and vertebrobasilar system as a surrogate of the regional cerebral blood flow. In acute ischemic stroke, and particularly in the setting of stroke thrombolysis TCD provides rapid, reliable and real-time information on the presence and location of arterial occlusion and on recanalization at different times after stroke. Even continuous monitoring of the recanalization process can be done with TCD. The patterns of intracranial artery occlusion on TCD have been validated against conventional angiography showing sensitivity and specificity values higher than 90%. The Thrombolysis in Brain Ischemia (TIBI) grading system has been developed to be applied rapidly in the acute stroke setting. These TCD grading system clearly reflects the dynamic nature of recanalization process during stroke thrombolysis and are based on the relative relationship between the insonation depth where the sample volume is placed and the clot location, so the closer the ultrasound bean to the thrombus the lower the TIBI score. Under good insonation conditions, an experienced operator can accurately identify the location of the offending clot in few minutes (typically 2–4 minutes), and in patients with suboptimal windows it takes <15 minutes. Ultrasound testing can be performed at bedside simultaneously with neurological examination, vital signs monitoring, and drawing blood, causing no delay in tPA administration.

In the last five years, several TCD studies have improved our knowledge and understanding of the dynamic nature of the recanalization process during stroke thrombolysis. TCD provides a unique opportunity to assess several aspects of clot dissolution by means of continuous monitoring of recanalization during and after tPA administration. This approach allows us to evaluate at the patients bedside and in real time the beginning, timing, speed and degree of artery reopening as well as to document re-occlusion after successful recanalization. Moreover, the simultaneous clinical assessment during TCD monitoring permits to correlate the hemodynamic changes with the clinical course and outcome.

Several angiographic and TCD studies have shown that spontaneous recanalization is a frequent, but unfortunately, delayed phenomenon after acute ischemic stroke. While spontaneous recanalization occurs in only 13% of patients <6 hours of cardioembolic stroke, up 66% of patients who receive tPA recanalized in the same time frame. tPA administration increases in 3- and 8-fold the rate of partial and complete recanalization, respectively. The time-to-artery reopening has been shown to be inversely correlated with clinical recovery and a time window of complete recanalization of <300 minutes from symptoms onset has been identify in human stroke to achieve full clinical recovery.

Recanalization is a continuous process that usually begins early after tPA administration. In most cases, recanalization occurs during the hour following tPA bolus, clot lysis starts at a mean time of 17 minutes and ends at 42 minutes after tPA bolus. However, the time until complete clot dissolution and restoration of blood flow may vary widely, depending on location of occlusion, clot composition, area of clot surface exposed to blood flow, and pressure-driven permeation of tPA into the clot structures. Alexandrov et al described the patterns of the speed of clot dissolution during continuous TCD monitoring. Based on the time required to achieve the maximum completeness of recanalization, the speed of clot lysis is categorized in: Sudden (recanalization is defined as an abrupt normalization of flow velocities lasting seconds shortly after tPA administration), stepwise recanalization (progressive improvement in flow velocities lasting less than 30 minutes) and slow (progressive improvement in flow velocities lasting more than 30 minutes). Sudden recanalization reflects rapid and complete restoration of flow; stepwise and slow recanalization indicate proximal clot fragmentation, downstream embolization, and continued clot migration. Unlike in acute myocardial infarction, the underlying pathophysiological mechanism of vascular arterial occlusion in acute stroke is heterogeneous. Composition of cerebral embolic material may vary, depending on specific endothelial and flow conditions of the embolic source. Old, platelet-rich,

and well-organized thrombi formed under flow conditions have been shown to be more resistant to thrombolysis than fresh, fibrin- and red cell–rich clots formed under conditions of stasis. Moreover, clot structure may differ depending on whether the embolic source is a thrombus engrafted in a proximal atherosclerotic lesion or a clot formed in cardiac cavities. In this context, stroke subtypes may represent a surrogate of the composition of offending clot. Our group demonstrated that in patients with proximal MCA occlusion treated with intravenous tPA, early recanalization is more frequent, faster, and more complete in patients with CE stroke. A cardiac source of emboli was identified in most patients who experienced sudden clot breakup during tPA administration. Sudden recanalization was associated with a higher degree of neurological improvement and better long-term outcome than stepwise and slow recanalization. On the other hand, the presence of a concomitant ipsilateral severe carotid artery disease was associated with low MCA recanalization rate and poor clinical outcome. Cardioembolic stroke probably represents the stroke subtype with more uniform fibrin-rich clots. Given the high binding affinity of tPA for fibrin, in fibrin-rich clots, tPA penetrates and distributes homogeneously, leading to an entire and rapid clot dissolution (sudden recanalization). In contrast, in well-organized and platelet-rich clots, penetration and distribution of tPA are limited, which may result in non-uniform clot softening and degradation from the outside of the clot. As a result, the clot shrinks and moves distally, lodging in smaller arteries (stepwise or slow recanalization), which would prolong ischemia. This may explain the fact that the stepwise and slow patterns of recanalization were associated with a lower degree of neurological improvement and worse long-term outcome than sudden recanalization shortly after tPA administration. The heterogeneity of clot composition is well illustrated in some patients with a documented MCA occlusion at arrival to the emergency room who experience a partial spontaneous recanalization before tPA bolus, but after treatment they remain with a persistent distal occlusion. This phenomenon may indicate that external fibrin-rich layer of the thrombus would be smooth enough to respond to endogenous fibrinolysis while the hard well-organized clot core would remain intact even in the presence of exogenous tPA (peach-like clot).

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Usefulness of the Ultrasound Contrast Media in Great Vessels and Microvasculature Examination of Brain

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Ultrasound contrast media are microbubble –base moisture of different composition. First generation contrast agents are air filled bubble with a stabilized shell, but their size, durability and pressure resistance are not so favorable for the prolonged examination of cerebral vessels as echoamplificators for large vessels of the base of skull. Second generation contrast agents are gas filled microbubbles covered by lipidic and saccaridic shell, that guarantees a longer persistence in the bloodstream and a stronger resistance to pressure. Therefore second generation contrast agents for ultrasound examination can offer some facilities in respect to first generation ones, both in large vessel examination and in microvasculature examination. Then they can provide some advantages like as the harmonic generation and the non linear behavior of this feature can improve the visualization of small vessels and perfusional status in several situations, e.g. acute stroke, intracranial stenosis, vasculitides, moya-moya disease, brain tumors, brain hemorrhages, etc.

This approach has enlarged the spectrum of application of contrast media for ultrasound from its origin, i.e. the overcoming of insufficient temporal bone window.

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Differences and/or Analogies Between Coronary and Cerebrovascular Risk Factors

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Atherosclerosis is a systemic, chronic inflammatory process that mainly involves medium-sized arteries and affects the arteries of different vascular beds simultaneously, but with differing degrees of progression. Atherosclerosis tends to develop in the coronary arteries that supply blood to the heart, to the brain (the carotid, vertebral, and cerebral arteries) and the lower extremities (the iliac, femoral, popliteal and infra-popliteal arteries). Clinically, it can become apparent as ischemic heart disease, cerebrovascular disease, or peripheral arterial disease. The presence of atherosclerosis in a particular vascular bed is frequently associated with disease in other vascular territories. The risk factors are the same for all affected vascular beds, regardless of location, and there is compelling evidence that established causal risk factors such as smoking, hypertension, diabetes mellitus, hyper-lipidemia play an important role in the development of vascular disease. Although the exact mechanisms have yet to be clearly explained, causal risk factors promote the development of arteriosclerosis, predispose to coronary artery disease, act independently of one another and their effects are additive. There is also accumulating evidence supporting the role of emerging risk factors such as hyper-homocysteinemia, protrombotic factors (fibrinogen, PAI-1) and inflammatory markers (C-reactive protein). Emerging risk factors are associated with an increased risk of ischemic heart disease, but for which a causal relationship has not been documented, because their atherogenic potential is lower and/or because their prevalence among the population is not high enough. Although all the risk factors favor the development of atherothrombotic disease in the different vascular beds, the predictive power of the risk factors differs from one territory to another. For example, the cholesterol level has a greater predictive power for the coronary territory, smoking for the peripheral vascular territory and hypertension for the cerebrovascular territory.

About the prognostic role of established risk factors, *smoking* is a powerful risk factor for all vascular diseases. A large number of epidemiological studies have clearly demonstrated that there is a linear relationship between cigarette smoking and the increased risk of

ischemic heart disease, stroke, peripheral arterial disease and sudden death. Cigarette smoking impairs flow-mediated endothelium-dependent arterial vasodilatation, and, additionally, nicotine itself alters the structural and functional characteristics of vascular smooth muscle and endothelial cells. In addition, smoking favors atherothrombosis through multiple mechanisms, including endothelial damage produced by circulating carbon monoxide, increased fibrinogen and factor VII, increased platelet adhesion and aggregability, increased LDL oxidation, and decreased HDL-C concentration. Low-nicotine cigarettes increase cardiovascular risk to the same extent as the regular type. Even passive smoke exposure has a considerable effect on the flow-mediated vasodilatation and the risk of coronary heart disease in passive smokers is between 10% and 30% higher. Vice versa, the smoking cessation decreases by 50% the risk of coronary heart disease during the first year and approaches that of nonsmokers in two years. Smoking is associated with a variable magnitude of cardiovascular risk, because the risk is highest for peripheral arterial disease and abdominal aortic aneurysm and lowest for cerebrovascular disease.

Hypertension is one of the major risk factors, independently of age, sex, or race. Arterial blood pressures, both systolic and diastolic, are correlated with the incidence of coronary heart disease and stroke. In a recent study of Tacoy et al, after evaluation of coronary segments, it was demonstrated that hypertension is associated with distal rather than proximal atherosclerosis of coronary arteries. A high blood pressure is more than just a predictor of hemorrhagic stroke and a systematic review of 54 studies, by Cordonnier et al in 2007, showed that hypertension is a robust predictor (OR 3.9) of brain microbleeds, associated with both first-ever and recurrent ischemic and hemorrhagic stroke. Little is known about the role of hypertension in the atherothrombotic process: it has been postulated that the excessively high pressure would damage the endothelium and increase its permeability. In addition, hypertension could stimulate the proliferation of smooth muscle cells or induce the rupture of the plaque. A number of clinical trials have demonstrated that a decrease in arterial blood pressure is associated with significant reductions in the rate of stroke and, to a lesser extent, in that of coronary events, circumstances that produce an overall decrease in cardiovascular mortality. Thus, reductions in diastolic arterial pressure of 5 mmHg reduce the five-year incidence of stroke by 34%, that of ischemic heart disease by 19% and that of cardiovascular mortality by 23%.

The association between *hypercholesterolemia* and the incidence of ischemic heart disease and/or peripheral arterial disease has been demonstrated in epidemiological studies. The relationship between cholesterol and ischemic heart disease is continuous, gradual and highly intense. The risk attributed to hypercholesterolemia is due to low-density lipoprotein cholesterol (LDL-C). A number of intervention studies have demonstrated that the lowering of LDL-C by means of hypolipidemic agents (eg, with statins) is accompanied by significant reductions in cardiovascular morbidity and mortality, both in primary and secondary care. Statin use in patients with peripheral arterial disease is also associated with an improvement in renal function and carotid intima-media thickness. An independent, inverse correlation between high-density lipoprotein cholesterol (HDL-C) and the risk of ischemic heart disease has been observed in several epidemiological studies. The protection provided by HDL-C is independent of the LDL-C concentration. The National Cholesterol Education Program (NCEP) considers a HDL-C level below 40 mg/dL to be a risk factor, whereas concentrations over 60 mg/dL are reported to be a negative risk factor. An increased risk of ischemic heart disease of 3% to 4%, in the six-year, is associated with a decrease in HDL-C of 1%. The HDL-C concentration correlates negatively with smoking, body weight and triglyceride concentration, and positively with fat and alcohol intake and physical exercise. There is no clear correlation between the concentrations of cholesterol and the incidence of stroke, although treatment with statins reduces the risk of stroke in patients with ischemic heart disease or with a history of previous stroke. Opposing results have also been published: in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, aggressive LDL-C lowering treatment with atorvastatin 80 mg/d in patients with a recent (1–6 months) stroke or transient ischemic attack was associated with an increase in the risk of hemorrhagic stroke (compared with placebo), but also with an overall significant decrease in risk of stroke and cardiac-related events.

Diabetes mellitus is associated with an elevated risk for ischemic heart disease and/or peripheral arterial disease and/or cerebrovascular disease, regardless of whether or not the individual is insulin-dependent. Cardiovascular disease is the leading cause of death among diabetics. There is a direct relationship between the duration of diabetes in years and risk of ischemic heart disease. Type 2 diabetics present elevated cardiovascular risk which, on occasion, is similar to that of nondiabetic subjects who have experienced a coronary event. For this reason, the major guidelines consider diabetics to be subjects at high cardiovascular risk who should receive the same treatment as patients who have a history of a previous cardiovascular event. Diabetes mellitus favors atherothrombosis through a number of mechanisms: an unfavorable lipid profile (high triglyceride levels, low HDL-C levels, small dense LDL particles), presence of modified LDL, hyperinsulinism, hypercoagulability and increased inflammatory markers. However, surprisingly there is evidence of a negative association between diabetes mellitus and the development of abdominal aortic aneurysm. In a recent pilot animal study of Alnaeb et al, in 2007, were demonstrated differences in the regional distribution of eNOS activity, as well as ET-1 and 5HT receptors between the aorta, renal and femoral arteries obtained from control and diabetic rabbits: these regional receptors differences may explain why diabetes mellitus is linked with a predilection for atherosclerosis in distal arteries and not in the aorta of patients.

In conclusion, current data suggest that established risk factors are associated with specific vascular diseases with a variable magnitude. These risk factors may also influence each other. Smoking is associated with high LDL-C, triglyceride and serum cholesterol levels, as well as low HDL-C concentrations. Smoking acts synergically with other risk factors such as hypertension, hyper-lipidemia and diabetes mellitus, to increase vascular morbidity and mortality. In addition, smoking adversely influences several emerging risk factors (eg, fibrinogen and C-reactive protein). Family history may have an effect on the development of a specific vascular disease: the negative association between diabetes mellitus and abdominal aneurysm may support that a certain genetic background may be prone to the development of a specific vascular disease. Future studies may clarify the association between vascular risk factors and development of certain arteriopathies and may influence both prevention and treatment strategies.

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Effects of Aging and Hypertension on Cerebrovascular Reactivity, Endothelial Function and Cognitive Performance (Fair Culture Test)

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Elevated arterial blood pressure is strongly related with stroke, dementia, and silent cerebrovascular disease. Arterial hypertension, especially in the elderly, can lead to a shift to the left of the lower threshold of cerebral pressure autoregulation curve and it can reduce the CO2 dependent cerebral vasodilatation. On the other hand blood pressure normalization leads to a significant reduction in both ischemic and hemorrhagic strokes and in the prevalence of cognitive deterioration often found in hypertensives. Despite these well known associations, the intimate pathophysiological mechanism underlying the neuronal damage in elderly hypertensives is not fully understood. To investigate the hypothesis that hypertension can alter the autoregulation threshold not only at the lower end but also at its upper limit, and to evaluate the relation between cerebral vasomotion, endothelial function and acute cognitive performance we have evaluated the cerebrovascular reaction to different adrenergic stimulations (i.e. pressor - handgrip, cognitive-fair culture test; ventilatory – 1 minute breath holding) in 5 groups (10 subjects/group): 2 groups of young and elderly healthy subjects; 2 groups of age matched (respectively young and elderly) systo-diastolic hypertensives, one group of elderly patients with isolated systolic hypertension. In all subjects, blood pressure increased significantly during handgrip and in the elderly hypertensive subjects, the pressure increase persisted during the recovery period. The pressure elevation caused a significant increase in mean flow velocity in the middle cerebral arteries (MCA) in the elderly and in young hypertensives ($p<0.05$), a slight though not significant MCA velocity reduction in young normotensives (consistent with an autoregulatory vasconstriction), a slight though not significant increase in MCA velocity in elderly normotensives. Cognitive stimulation significantly increased mean MCA blood flow velocity ($p<0.001$) and blood pressure ($p<0.001$) in all subjects. The velocity increase and the cognitive performance (FCT scoring) was significantly higher in the young than in the elderly ($p<0.001$); the absolute velocity increase and FCT scoring were greater in young normotensives than in hypertensives. Cerebral vasodilatation and cognitive performance was similar in both elderly groups. Mean MCA flow velocity rose less during FCT in young hypertensives than in age matched normotensives, and the FCT scoring was lower thus suggesting a possible link between the sluggish cerebral hemodynamic response and the relative reduction in acute neuronal cognitive function. In elderly hypertensives, on the contrary, there was no evidence of a close neuronal-flow velocity coupling since the vasomotor reaction to the cognitive stimulation was maintained but the cognitive performance (FCT scoring) was low. In all elderly hypertensives, the blood pressure elevation and the mean flow velocity increase persisted well into the recovery period, consistent with a defect of systemic blood pressure and cerebral pressure autoregulation. This defect of feed-back mechanisms can contribute to magnify the pressure burden on cerebral hemodynamics and explain the greater predisposition of the elderly hypertensives to cerebral damage, such as vascular cognitive impairment or stroke. Breath holding increased mean MCA flow velocity by the same extent in all subjects thus indicating that oxygen dependent cerebral vasomotion is not affected by age or hypertension. Endothelial function was studied in all subjects by ultrasound evaluation of the changes in brachial artery internal dimensions after forearm transient ischemia (Flow Mediated Dilatation-FMD). FMD was significantly higher in young normotensives than in the other groups. In addition elderly ISH patients showed a reduced FMD consistent with an impaired endothelial function compared with elderly normotensives (p 0.04). Nonetheless all elderly subjects showed similar FCT scoring. In conclusion the ability of cerebral and systemic arteries to vasodilate in response to a cognitive or hypoxic stimulation are not related with acute cognitive performance. This results confirm the lack of correlation between maximum vasodilatation and cognition in elderly. Compared to the other groups significant differences were found in the elderly after adrenergic HG stimulation suggesting a reduced adaptability of cerebral perfusion to blood pressure oscillations. These findings suggest that an altered cerebrovascular blood pressure autoregulation may be the mechanism underlying the greater prevalence of neural damage such as stroke and/or of vascular dementia in aging subjects, especially in those affected by hypertension.

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Stroke in Patients with Coronary Artery Disease: Natural History and In-Hospital Events (Iatrogenic Morbidity in the Interventional and Cardio-Surgical Era)

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Stroke in the course of percutaneous coronary interventions (PCI) is fortunately a rare complication (0.27–0.5%), but nevertheless a devastating event for patients and caregivers. The incidence of stroke is greater in patients undergoing surgical coronary artery bypass graft (CABG). Stroke is considered to represent a periprocedural complication when occurring <24 hours following PCI, and is most commonly ischemic in etiology (cerebral hemorrage being considerably less common). Its low incidence hinders the identification of predictive factors. Nevertheless, based on the available evidence, periprocedural stroke is more common is the elderly, in women, in patients with diabetes, chronic renal failure, diffuse atherosclerotic disease, and in those with other periprocedural complilcations (coronary perforation, no reflow), intra-aortic balloon pump, or requiring high doses of contrast medium. In patients with periprocedural stroke, in-hospital mortality is high as 27% at six months, as shown by the OASIS study. In this, as in prior studies, most cerebrovascular episodes occur in patients undergoing CABG, compared to PCI.

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State of the Art in Carotid Surgery

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The aim of current surgical approach (CEA and PTA and stenting) to cerebrovascular disease is essentially prophylactic against vascular ischemic stroke.

The high number of studies in literature and the analysis of international trials about the guidelines on carotid endoarterectomy make it right of the huge spread of such intervention: currently in vascular surgery it is the more widely performed intervention in the world. Recently the conceptual settings and methods of these trials were challenged, especially about the treatment of asymptomatic patients. It is argued that in these patients, the majority of stroke occurs on a cardioembolic basis or lacunar stroke. Therefore it is essential to identify patients with carotid plaque "at risk", or those patients who have a high risk of stroke when treated in a conservative way.

If anatomic-pathological features of carotid lesions are known, still lacks the ability to identify in vivo and in a non-invasive way these lesions.

Some contributions in literature and two recent European multicenter studies have identified the echocolordoppler as the tool that could identify the carotid plaque "at risk" on the basis of the assessment not only quantitative but primarily of the quality of the morphology of the lesion.

In literature have been proposed many types of classification of plaque that have generated some confusion. A recent consensus, however, suggested that the evaluation of echogenicity should be indicated by the brightness of the plaque, dividing the lesions in hypoechogenic, isoechogenic and hyperechogenic, identifying the structures of reference: echogenicity of blood for hypoechogenic plaques, echogenicity of sternocleidomastoid muscle for isoechogenic plaques and echogenicity of bones of the cervical vertebrae for hyperechogenic plaques.

A further developement was obtained through the "normalization" of the B-mode imaging that allows an objective and quantitative study by reference to minimum gray scale blood and advential sheet. In this way the characterization is not expressed by an adjective but a number (GSM - Median Gray Scale), eliminating the variability caused by subjective interpretations and numerous classifications.

The relation between ultrasound morphological study of carotid plaque and immediate and late results of the procedure, surgical or endovascular, could allow to detect lesions that are expected of either treatment.

About this, the recent study ICAROS has shown that the periprocedural risk undergoing carotid stenting increases significantly with the decrease of the echogenicity of the lesion. So the ideal lesions to be treated with endovascular procedure are those iso-hyperechogenic, that is full of fibrous tissue and calcifications and those with low lipidic and heamatic structure.

Therefore it is clear that the possibility to characterize with non-invasive approach these components can potentially allow not only to identify the lesion at risk but also to choose which type of procedure is most appropriate in order to minimize the risk of intra and post-procedural thrombo-embolic events.

Previous studies published by our group have enabled us to demonstrate statistically significant correlation between hypogenic plaque and appearance of omolateral neurological symptoms; similarly hypoecogenicity of the lesion appeared related to the presence of silent brain lesions evaluated at CT scan. Moreover, in the plaque, the presence of large cholesterinic and haemorragic areas, assessed in an histological examination, were correlated with the appearance of ultrasonographic hypoecogenicity of the lesion.

In the last years we have also evaluated the preliminary results obtained with a new technique of ultrasonology called RULES (Local Radiofrequency Ultrasonic Estimator), based on elaboration of ultrasonographic signals at different radiofrequencies, which allows to have spectral parameters related to space and mechanical properties of the tissue examined and developed in a Laboratory of the Faculty of Engineering of University of Florence, lead by Prof.Leonardo Masotti, obtaining a good correlation between the histological data and those reported with ultrasonographic technique of radiofrequency in vitro.

In particular, was shown a correlation in 100% of the cases in identification of lipidic and calcific areas in the carotid plaque.

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Statins and Plaque Passivation

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The concept of plaque stabilization was proposed in the 1990s in an attempt to explain the discrepancy between a small amount of angiographically demonstrated plaque regression, and the large reduction in clinical events in trials of lipid-lowering drugs. "Plaque passivation" is a therapeutic concept by which either the structure or the content of the vulnerable and active atherosclerotic plaque is modified to reduce the risk of subsequent rupture and thrombosis.

The process of plaque destabilization begins with endothelial dysfunction against a background of inflammation. Postmortem pathologic studies have revealed that the vulnerable plaque has three hallmark histologic features: (i) a large lipid core occupying more than 40% of the plaque volume; (ii) an abundance of inflammatory cells; and (iii) a thin fibrous cap that lacks proper collagen and smooth muscle cell support. In an unstable plaque, almost every cell type is activated. These cells are mostly monocytes–macrophages, but can also be activated T cells and mast cells. These inflammatory cells secrete certain enzymes (proteases) that degrade collagen. In addition, apoptosis of smooth muscle cells, which are the chief source of collagen, further weakens the plaque. The lipid core is composed of free cholesterol, cholesterol esters, and crystals. In addition, it contains oxidized lipids, and is impregnated with tissue factor derived from macrophages, making it highly thrombogenic. The family of enzymes—matrix metalloproteinases (MMPs)—expressed by macrophages erodes the thin fibrous cap resulting in exposure of thrombogenic subendothelial material to the circulating blood. The acute clinical event is precipitated by the formation of an intimal, platelet-rich thrombus followed in some cases by a fibrin–red cell intraluminal thrombus.

The biology of plaque instability and rupture suggests that therapeutic strategies must revolve around three potential target sites: (i) platelets and the coagulation cascade leading to dissolution of the thrombus and restoration of luminal patency; (ii) passivation of dysfunctional endothelial cells for the reduction of pro-inflammatory and procoagulant activity; and (iii) modification of plaque contents by an aggressive reduction of serum low-density lipoprotein cholesterol (LDL-c) levels and inhibition of LDL oxidation. These target sites are not mutually exclusive. Therefore, an integrated approach to plaque passivation in ACS is required to reduce future adverse clinical events.

Based on evidence from human and animal studies, it can be assumed that lipid-lowering drugs stabilize plaque by several mechanisms. Statin-mediated lowering of lipids may stabilize vulnerable plaque by changes in the lipid core itself. There is a reduction in the levels of oxidized LDL in the plaque's core accompanied by reduction in plaque macrophage content, and increase in the volume of collagen and smooth muscle cells with statins. In a small, nonrandomized study of patients undergoing carotid endarterectomy, statin therapy given for 3 months resulted in a decrease in the lipid pool and increase in fibrosis in carotid plaque. There was 75% less lipid core, 40% less oxidized LDL and MMP, and twice the amount of collagen. In experimental studies, these changes require at least a few months to occur and, therefore, may not fully explain the early benefits observed with statin therapy in patients with ACS.

Statins have "pleiotropic actions" that go beyond the lowering of LDL-c levels, and are relevant to the pathophysiology of ACS. In comparison to lipid-lowering actions, these pleiotropic effects on vascular and cardiac cells may be effective after early initiation of therapy.

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Carotid Artery Disease: Identification of Novel Pathophysiological Mechanisms by Gene Expression Profiling of Peripheral Blood Perturbation

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Carotid artery disease (CAS) is the most frequently identified cause of ischemic stroke and is mostly due to atherosclerotic disease. Inflammation plays an important role in the pathogenesis of atherosclerosis.

Aims of this study were to investigate the systemic gene expression profile of patients affected by CAS versus control subjects, and validate and extend microarray data in two further independent populations of patients and controls.

Total RNAs were extracted from whole peripheral blood of 46 patients affected by CAS and 46 controls comparable for age and sex. We determined the expression of 14,000 genes by two colors microarray technology in n = 10 pooled RNA from patients and n = 10 pooled RNA from controls and validated data by real time PCR in n = 36 CAS patients and n = 36 controls. 82 genes showed altered expression levels between CAS patients and controls: 61 genes resulted up-regulated and 21 down-regulated. Gene ontology analysis indicated an alteration of the following biological processes: immune response, oxygen transport, cytoskeleton organization and lipidic metabolism. Some of the biological process found in CAS and the relative associated genes resulted similarly altered in patients affected by atherosclerotic lesions in an other district (abdominal aortic aneurysm patients). In particular we focused our attention in validating genes associated with the biological process peculiarly observed in CAS patients. These genes encod for the major histocompatibility complexes, expressed by the human leukocyte antigens (HLA) or are involved in the immune response (HLA-DPA1, HLA-DPB1, HLA-DQB1, HLA-DRB3, IFIT1, IGKV1D, TRBJ2-1, DBNL, HLA-B).

This study provides new insights into the regulatory mechanisms controlling the development and the progression of plaque emphasizing the central role of inflammatory and immune cells.

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Detrimental and Beneficial Effects of Ethanol by Stimulation of TRPV1 in Sensory Neurons

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The risk of coronary artery disease (CAD) is reduced by red wine and more in general by consumption of alcoholic beverages (Mukamal et al., *N Engl J Med*. 2003; 348: 109–18). However, the mechanism by which ethanol (EtOH) exerts protection is not fully understood. Ethanol stimulates neuropeptide-containing primary sensory neurons via the activation of transient receptor potential vanilloid 1 (TRPV1), also known as the capsaicin receptor, thus causing a burning sensation and the release of the neuropeptides, substance P (SP) and calcitonin gene related peptide (CGRP). TRPV1 belongs to a large family of ion channels and is gated by noxious heat (42–53ºC). Ethanol potentiated the response of TRPV1 to capsaicin, protons and heat and lowered the threshold for heat activation of TRPV1 from approximately 42ºC to approximately 34ºC. Thus, it is possible that ethanol-induced sensory responses that occur at normal body temperature (Trevisani et al., *Nat Neurosc*i 2002; 5: 546–51). Recently we addressed the question as to whether ethanol may cause coronary vasodilatation by activation of TRPV1 on perivascular sensory fibers and the release of the vasodilating peptide CGRP. Indeed we observed that ethanol relaxes porcine isolated coronary and human isolated gastro-epiploic arteries by TRPV1 stimulation and CGRP release. Ethanol by the same mechanism caused vasodilatation in the guinea pig coronary circulation. Ethanol-induced release of vasodilatatory CGRP may contribute

to the reduced risk of CAD (Gazzieri et al., *Cardiovasc Res*. 2006; 70: 589–99).

In addition to protective actions ethanol also contribute to various diseases. In susceptible individuals ethanol is known to trigger attacks of asthma. We reported that ethanol contracts isolated guinea pig bronchi, via activation of TRPV1 on terminals of airway sensory neurons and releasing the bronchomotor peptide SP. This excitatory effect of EtOH, distinct from that of Acethilcoline, results also in neurogenic inflammatory responses that may contribute to the mechanism of EtOH-induced asthma (Trevisani et al., *J Pharmacol Exp Ther*. 2004; 309: 1167–73).

Alcoholic beverages, are not only cardioprotective, but they also trigger migraine attacks and activation of trigeminal neurons plays a role in migraine. We found that ethanol evokes release of neuropeptides from nerve terminals of the rodent meninges by TRPV1 stimulation, thus provoking a vasodilatation that is abolished by the CGRP receptor antagonist, olgecepant, and is considered to be mediated by CGRP released from perivascular sensory nerve endings. Olcegepant has been reported effective in the treatment of the migraine attack. Thus, arterial vasodilatation of meningeal vessels by TRPV1 activation and CGRP release may be relevant to the mechanism by which alcohol ingestion triggers migraine attacks (Nicoletti et al., *Cephalalgia* 2008; 28: 9–17).

Finally, it is known that ethanol induces hemorrhagic gastric lesions in rodents, but the mechanism is only partly understood. A series of *in vivo* experiments in rats and mice (including neurokinin-1 receptor deleted mice) showed that via stimulation of TRPV1 in gastric nerve terminals, ethanol releases SP that activates epithelial neurokinin-1 receptors to generate damaging reactive oxygen species (ROS) and the highly reactive aldehyde 4-hydroxynonenal. We conclude that gastric lesions are caused by an initial detrimental effect of ethanol, which is damaging only if associated with TRPV1 activation, SP release from sensory nerves, stimulation of neurokinin-1 receptors on epithelial cells, and ROS generation (Gazzieri et al., *Free Radic Biol Med*. 2007; 43: 581–9). The present data indicate that the ability of ethanol to target TRPV1 may be associated to a series of detrimental effects, that range from production of a burning painful sensation to contributing to airway inflammation and migraine. However, it is possible that the neurogenic vasodilatation caused by ethanol in the coronary circulation contributes to the cardioprotective effect of moderate alcohol consumption.

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Intrarterial Thrombolysis for Acute Ischemic Stroke

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Thrombolysis, in its broad sense of recanalization of a vessel occluded by thrombus, is probably the most challenging and promising therapy of acute stroke so far; it has the merit of having played a key role in changing the general perception of acute stroke, which switched from the mere contemplation of a bedridden patient to the consideration of stroke as a medical emergency.

The favourable results of the *National Institute of Neurological Disorders and Stroke* (NINDS) study on recombinant tissue plasminogen activator (rt-PA), a thrombolytic agent already used for myocardial infarction and pulmonary embolism, were followed by the approval of intravenous (IV) rt-PA for ischaemic stroke within 3 hours from symptoms onset in 1996 in United States and three years later in Canada..

Albeit IV r-TPA is today the standard treatment for acute ischemic stroke, just 10–12% of the patients can be treated within 3 hours, as IV rt-PA has many contraindications, and about 50% of those treated die or remain severely disabled. Hence, there is a need for other recanalizing treatments that are more effective and have less contraindications. IA thrombolysis might provide many advantages compared to the intra-venous one, such as to titre the dosage of the thrombolytic agent, having high drug concentration locally and low in systemic circulation, facilitate clot disruption with mechanical thrombolysis, extend the therapeutic time window and increase angiographic recanalization rates. For these characteristics IA in place of IV thrombolysis for acute ischemic stroke has been proposed for patients with severe neurological deficits, vertebrobasilar stroke, occlusion of major supra-aortic and cerebral arteries, presentation beyond 3 hours from symptoms onset, acute stroke caused by cervical artery dissection, recent surgical and invasive diagnostic procedures, pregnancy and anticoagulant therapy. However no data are available on the effectiveness of IA thrombolysis compared to the IV one that is known to be quicker to initiate, cheaper and easier to use.

Intra-arterial (IA) thrombolysis in acute ischemic stroke has a different story from the intravenous (IV) one. The first report was in 1958 about a case of acute carotid thrombosis treated with IA plasmine but this approach was developed later with the diffusion of cerebral angiography and endovascular treatment. IA thrombolysis, indeed, was at first used to dissolve thrombi forming during cerebral angiography or endovascular procedures. The current procedure was introduced by Zeumer in 1982. It starts with an angiogram to identify the site of occlusion and collateral supply to the affected region. The guiding catheter is introduced percutaneously into the femoral, radial or brachial artery and advanced in the supra-aortic vessel of interest. A microcatheter is then positioned close to, or within the thrombus, allowing local thrombolytic agent delivery.

Thrombolytic agent may be aided by mechanical thrombus disruption through the manipulations of the microcatheter tip and multiple advancements of the microguide. In some cases an alternative strategy for thrombus removal is the use of mechanical recanalization techniques such as percutaneous transluminal angioplasty with balloon catheters or clot extraction using retrieval devices. Also, specialised intravascular catheters that emit ultrasound, pressurised saline solution with resorption, or photoacoustic energy are being studied. Some of these devices have been created for other purposes and readapted to perform IA thrombolysis. Their risk to benefit ratio is still uncertain. The description of patients with complete or partial early arterial recanalization during IA thrombolysis and early improvement of their neurological symptoms suggests the likely efficacy of these techniques, but no substantive data exist.

For these purposes the Synthesis Expansion Trial has been designed, to compare IV thrombolysis with rtPA with IA thrombolysis (farmacological and/or mechanical).

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Intrarterial Thrombolysis. New Devices

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Most of ischemic strokes are due to thrombo-embolic events; angiographic studies on patients with acute ischemic stroke within 8 hours from symptoms onset showed complete occlusion of a main cerebral artery in 80% of cases, mostly in the carotid territory. When angiography is performed within 12 hours from the event, in 80–90% of patients a stenosis or an occlusion matching with the neurologic deficit territory can be found . Therefore, the aim of the acute treatment of a patient with severe brain ischemia is to early recanalize the occluded vessel and to restore brain perfusion in order to limit the extension of the ischemic core.

The studies about intravenous systemic thombolysis with rtPA in acute ischemic stroke showed that this therapy can improve the outcome if the infusion is performed within 3 hours from symptoms onset. However, systemic thrombolysis has strict inclusion criteria and its results are promising but not very satisfying. Locoregional intrarterial thrombolysis (LIT) has many advantages over systemic therapy:

1) intrarterial injection allows higher drug concentration inside the clot, therefore the farmacological efficacy is enhanced and the systemic activation of the drug is decreased.

2) thrombolytic injection can be joined with mechanical manoeuvres to fragment and aspire the clot.

3) dose of the thrombolitic drug can be set on the basis of the anatomical response (recanalization). The local infusion can be stopped at any time when the clot has resolved, limiting the delivered dose and the systemic concentration; otherwise, the administered dose with the systemic infusion is predetermined on the basis of the patient's weight.

4) LIT allows a wider therapeutic window compared with systemic therapy, because the treatment can be performed within 6 hours from symptoms onset in anterior territory stroke and 24 hours in case of vertebrobasilar stroke.

5) anatomical efficacy of the treatment can be evaluated during the procedure and the recanalization rate can calculated to assess and compare different techniques.

The main limit to the diffusion of LIT is the low number of published studies on this topic, often with few patients enrolled, while most of observations have been reported outside randomized and controlled trials.

In only two randomized and controlled trials (PROACT I and II), LIT performed with rt-PA within 6 hours from symptoms onset has been compared with controls. A metanalysis of these trials showed that treated patients compared with control cases, had a reduction of the combined endpoint of death and 90 days dependence of 15% (OR: 0.55, 95% CI 0.31–1.00); the hemorrhagic transformation rate was 10% in the PROACT II (OR: 2.39; 95% CI 0.88–6.47). However, both studies only included patients with middle cerebral artery occlusion and did not allowed adjunctive mechanical manoeuvres. Another metanalysis that included different series and patients without selected site of vascular occlusion, reported a good outcome in 41.5% of treated patients vs. 23% of control patients ($p = 0.002$) and a mortality rate of 40% vs. 23% ($p = 0.004$); the symptomatic hemorrhage rate was higher in the group of the LIT patients (9.5% vs 3% ; $p = 0.046$). The outcome was influenced by the site of the occlusion, being better in the anterior than in the vertebrobasilar circulation. Overall, the results of clinical series report that the efficacy of LIT in the anterior circle varies from 30% to 70% and that the clinical outcome depends on the degree of recanalization; similar results are reported for the vertebrobasilar circulation.

Although these results are encouraging, LIT has some limitations:

Difficult recruitment of patients within the limits of the therapeutic window, which appears still too short.

Increased incidence of hemorrhagic complications compared with systemic thrombolysis (10% versus 6.4%).

The clinical results depend on the arterial recanalization rate (a complete recanalization is obtained in only 30–40% of cases) and the reperfusion time.

When the flow has been only partially restored, reocclusion can occur.

For these reasons, industry and clinical research have been oriented towards the project on new treatment modalities in order to enhance the effects of LIT. The main fields of interest are mechanical recanalization (by means of aspiration or fragmentation of the clot) and the association of LIT and systemic thrombolysis to improve the recanalization time and rate.

Mechanical thrombolysis is performed to reduce the thrombus burden and to obtain a faster recanalization, sometimes even immediate. This approach has also the potential advantage to reduce the need of thrombolytic drugs and so to decrease the symptomatic hemorrhage rate. Therefore, a mechanical treatment can be performed even after 6 hours (depending on the series, within 8 hours). The most evaluated mechanical device is the Merci system, which allows to catch and extract the clot inside a guide catheter. This device has been evaluated in two randomized trials alone or in conjunction with pharmacologic LIT. In the last, the multimerci trial, 164 patients were enrolled and the recanalization rate was 54% with merci alone and 69% with merci and rt-PA; the favourable outcome (m-RS 0–2) was 39%. Interestingly, in patients treated with the new generation Merci device clinical results were improved; that underlines the continuous improvement of these devices. Other mechanical devices are available, but most of them have not evaluated in clinical radomized trials. A recent trial concerns the new device Penumbra, composed by an aspiration system and a thrombectomy device. Preliminary results are good, since recanalization rate (TIMI 2–3) was 85 %.

An other mechanical approach is intracranial angioplasty, that can now be more safely performed than in the past thanks to high compliance balloons. In a series of PTA of the middle cerebral artery, a recanalization rate of 91% and m-RS of 73% were reported.

Recently, new attention has been oriented towards primary clot stenting, with or without simultaneous anti-GP IIb-IIIa injection. Actually this must be considered a bailout procedure but results are very promising.

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Indications, Techniques, Catheters for Mechanics Disobstruction. The Stents

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Indications to mechanical thrombolysis are mainly represented by an acute arterial occlusion with a high thrombus load (T siphon, Basilar artery) in a patient presenting out of the necessary time window (3–6 hrs) or with a wake-up stroke or after unsuccessful iv thrombolysis (bridging therapy). The most common techniques are constituted by clot suction with large bore microcatheter (21–35), clot retrival devices (Merci, IN TIME), clot fragmentation and aspiration (Penumbra) and soft angioplasty and stenting.

Our experience is mainly derived from the use of angioplasty and stenting in combination with asystemic glycoprotein (gp) IIb/IIIa inhibitor Tirofiban) in patients with acute basilar occlusion .

Outcome in acute ischemic stroke due to basilar artery (BA) occlusion remains poor with high mortality or severe disability, despite the proliferation of numerous endovascular techniques. In patients with stroke due to BA occlusion a wider time window acute intervention is allowed, because of the poor prognosis and the progression of symptoms. We assessed the hypothesis that an intra-arterial approach with primary stenting combined with systemic glycoprotein (gp) IIb/IIIa inhibitors is feasible and might lead to high recanalization rates. We retrospectively reviewed 23 consecutive patients with acute BA occlusion, treated with intra-arterial approach at the Careggi Hospital (Florence, Italy) from February 2004 to May 2008. We evaluated the recanalization rate using the Thrombolysis in Myocardial Infarction (TIMI) score and 3 month outcome using the modified Rankin scale (mRS) in patients treated with primary basilar stenting and gp IIb/IIIa inhibitor tirofiban, compared with intra-arterial thrombolysis with urokinase and/or mechanical disruption.

Nine patients (45% male, mean age 62 ± 16 years, median NIHSS 27) were treated with intracranial stenting and gp IIb/IIIa inhibitors and 14 patients (78% male, mean age 70 ± 15 years, median NIHSS 26) were treated with intra-arterial urokinase and/or mechanical disruption. Eight out of 9 (89%) patients treated with stenting had recanalization of BA (TIMI 2–3), versus 10/14 (71%) of patients treated with urokinase. Complete recanalization (TIMI 3) was achieved in 67% of patients treated with stent versus 14% of subjects treated with urokinase. Good outcome (mRS 0–3) rate in the stenting group was similar to the urokinase group (33% versus 28%, respectively). Mortality rate was higher in the stenting goup (44% versus 36%). One symptomatic hemorrhage was observed in the urokinase group.

Conclusions In our series, the approach with systemic administration of gp IIb/IIIa antagonists and placement of intracranial stent appears to be feasible and safe, reducing the use of thrombolytic agents. The high recanalization rate obtained with this procedure makes this approach promising. More data are needed to confirm the efficacy of this treatment.

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National Organization of Stroke Assistance

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Regarding all the interventions directed to the reduction of death and disability following a stroke, it was demonstrated that a early recovery in a dedicated unit, a Stroke Unit, determines an absolute reduction of the risk of dead/dependency of 5.6%; practically for every 1000 patients admitted in Stroke Unit, 56 avoid died/dependency.

In order to make a correct evaluation of the "stroke question", it is important to know the data of prevalence and incidence in western countries.

Prevalence increases with age. In international population-based studies, prevalence reaches values between 4,61 and 7,33 for 100 inhabitants in the subjects older than 65 years.

In Italy available data are from the *Italian Longitudinal Study on Aging* (ILSA) (1), that refers to a population between 65 and 84 years. Among this population the prevalence rate is a 6,5% (IC_{95}: 5,8–7,2), with an higher prevalence rate in male (7,4%; IC_{95}: 6,3–8,5) than the female (5,9%; IC_{95}: 4,9–6,9).

In other European population-based studies with a similar methodological approach, the incidence rate

was 8, 72 per 1·000 (IC_{95}: 7, 47–10, 06) in subjects between 65 and 84 years.

These data reveal that we are in front of a real "stoke epidemia" and that it needs structural and coordinated interventions both at regional and national level. Considering even the severity of strokes (110,000 strokes per year and 230,000 those with disability from previous stroke) it has become indispensable to make an operative reorganization and to promote the idea that stroke is a curable medical emergency. It is also necessary to stimulate the prompt beginning of a correct secondary prevention.

On the epidemiological data shown, that characterize stroke like one of the main causes of dead, the following interventions should be adopted:

Prevention in the general population

– Health education programs

– Programs to aware of the stroke question the General Medicine Doctors

– Emanation of specific regional guidelines. Useful for technical, methodological, and organizational support for the Local Sanitary Companies, based on the national guidelines (SPREAD).

Prevention in high risk individuals

– To improve the identification of individuals at greater cardiovascular risk

– To guarantee the therapeutic continuity to the high risk patients both with pharmacological and non-pharmacological strategies, according to the international guidelines.

– To improve the accessibilty to the early intensive units and then to the follow-up and post event programs.

Improvement of the organizational efficiency and effectiveness

– To help the early admission, in specialized units possibly, of the stroke patients in order to facilitate the prompt institution of specific

therapies such as pharmacological or sugical re-vascolarization in ischemic stroke or neurosurgical evaluation in the hemorragic.

All this is possible by the institution of the Stroke Unit that synthetizes how much was previously debated.

A Stoke Unit is:

1. a ward that admit patients with acute stroke (within 48 h)
2. presence of beds dedicated exclusively to the cure of patients with acute stroke (at least 80%)
3. staff (doctors and nurses) dedicated exclusively to the cure of the patients with stroke (at least a doctor or nurses occupied for 80% of their working hours).

From the experiences matured up to now in international and national contest, characterizing points for a SU are:

– multi professional integration
– early rehabilitation
– staff education
– particular attention to the communication with the patients, their relatives and with the doctors of general medicine.
– engagement to guarantee a continuity in the cure and the attendace.

The chance to have a continuous monitoring of vitals sign (Blood pressure, heart rate, temperature) leads to a better surveillance of the patient in the acute phase and characterizes the intesive-subintensive type of stroke unit.

The stroke unit must be integrated with all the other units that are involved with the management of the patient during his acute phase. It must also be opened to the territory of competence, through the collaboration with the general medicine doctors and with Local the Sanitary Company and the Districts to the aim to guarantee the *dimissioni protette* and the programs of rehabilitation and reinsertion of the patient.

The implementation of the subintensive dedicated units (Stroke Unit) represent a part of a more wide process that tends to guarantee the best management for the patients and the therapeutic continuity.

This must be carry out even by the integration with the territory, the rehabilitation structures, the ambulatorial activity of follow-up and secondary prevention.

The objective is to realize the standardization and the adaptiation of the regional welfare levels as well as the correct distribution of the human and technological sources in order to answer in the right way to the Stroke Emergency.

(1) The Italian Longitudinal Study on Aging Working Group. Prevalence of chronic diseases in older Italians: comparing self-reported and clinical diagnoses. *Int J Epidemiol* 1997; **26**: 995–1002.

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