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Stroke and Atherosclerosis

Atherosclerosis, an Immuno-Mediated Disease

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Atherosclerosis is a chronic inflammatory disease resulting from the interaction between modified lipoprotein (LDL), monocyte-derived macrophages and cellular elements of the arterial wall, such as endothelial cells (ECs) and smooth muscle cells (SMCs) [1]. Evidence from human and experimental studies as well as the recent studies on transgenic and gene-targeted mice support a major role of the immune system in the atherosclerosis [2].

The initiating events of the atherosclerotic lesions is the accumulation of LDL in the subendothelial space. Accumulation of LDL in the intima is greater when levels of plasma LDL are raised and it is facilitated by local (increased endothelial permeability) and systemic (hypertension, smoking, diabetes, elevated homocysteine plasma levels) factors.

LDL diffuses passively through EC junctions, and its retention in the vessel wall seems to involve interaction between the LDL constituent apolipoprotein B (apo B) and matrix proteoglycans. If not removed; proteoglycan- and protein-bound LDL particles easily undergo minimal oxidation (mLDL) or oxidation (oxLDL), because the cells of arterial wall are consistently secreting oxidative waste products into subendothelial space. High-density lipoprotein (HDL) carries out an important protective action in removing the excess cholesterol from vessel wall. Moreover, HDL prevents for some time LDL oxidation, removes the biologically active oxidized phospholipid from mildly oxidized LDL via PAF-acetylhydrolase, and inhibits the production of lipoperoxides and thiobarbituric acid reactive substances (TARBs) via the enzyme paraoxonase. mLDL and much more oxLDL trigger an inflammatory response of ECs by inducing the expression of adhesion molecules (P- and E- selectine, VCAM-1), chemokines (monocyte chemoattractant protein (MCP)-1), macrophage colony stimulating factor (M-CSF), cytokines (TNF-α). Different categories of chemokines may participate in the various phases of the inflammatory response in the recruitment of distinct leukocyte classes to the atheroma. Endothelial MCP-1 plays a primary role in the recruitment of circulating leukocytes because it binds chemokine receptor CCR-2 that is constitutively expressed on the monocytes. For this reason, monocytes are selectively attracted, they adhere to the ECs and migrate along MCP-1 gradient into the subendothelium, where they undergo differentiation to macrophages under the influence of M-CSF. Monocyte-derivated macrophages recognize and uptake modified LDL by means of numerous scavenger receptors (SRA I and II, CD36, CD68, MARCO, SR-PSOX) forming foam cells. The uptake of mLDL and oxLDL by macrophages is initially induced by TNF-α produced by the activated ECs, but during the development of the atherosclerotic lesions and in the mature plaque the expression of the macrophage receptors and the LDL lipid uptake are differently regulated by various cytokines. For example TNF-α, IL-6 and INF-γ down regulate scavenger receptor SRA I, whereas IL-4 upregulates CD36, and lectinlike receptor (LOX-1) is controlled by TNF-α and transforming growth factor (TGF)-β [3]. The macrophages degrade the components of oxLDL and process them for antigen presentation and simultaneously undergo to activation producing cytokines, proteolytic enzymes, growth factors and tissue factors (TF). During LDL oxidation or degradation, neo-antigens may be formed and, therefore, new acute immuno-mediated inflammatory reactions may occur in the time. For these reasons the macrophages and the lymphocytes are central for the development and progression of the atherosclerotic plaques.

If the LDL concentration remains elevated in the plasma or in the subendothelial space, the inflammatory process persists in the intima and atherosclerosis lesion develops. The initial and most minimal changes of the intimal space (Type I lesion, according Stary) [4] consist of only microscopically and chemically detectable lipid deposits with isolated group of macrophages and foam cells. Although several adhesion molecules (E-selectin, VCAM) may attract also lymphocytes in addition to monocytes, the lymphocyte recruitment is particularly promoted by a "trio" of endothelial chemokines (IP-10, Mig and I-Tac) that selectively attract T and B cells bearing the CXC R3 receptor. Rare lymphocytes may be found in type I lesion, whereas they are clearly evident in type II lesion (fatty streaks). In the mature stable plaques, T cells constitute approximately 10% to 20% of the cell population, whereas B lymphocytes are very rare and tend to localize forming infiltrates in the adventitia and periadventitial connective tissues. In addition to T cells and macrophages, atherosclerotic lesions contain another immune effector cell, the mast-cells, that may have an important role in the acute coronary syndrome because they accumulate at sites of plaque rupture and produce enzymes which may degrade the extracellular matrix. Most of the T cells in atherosclerotic lesions are CD4/CD8 able to recognize protein antigens presented to them by macrophages, dendritic cells and ECs following the activation by INF-γ (DR+1 ECs). Both T cells and macrophages of the plaque are activated, i.e. they express HLA-DR molecules, and produce cytokines, chemokines and other active factors. In high proportion T cells of the plaques are memory cells and, hence, are provided with a prompt and intense reaction to the antigens. Plaque T cells have properties of Th-1 subtype and secrete both auto-stimulatory cytokines (IL-12 and IL-18), and inflammatory cytokines (INF-γ, IL-2, TNF-α and β) which cause activation of macrophages and vascular cells, especially of the ECs, that become able to participate in the cellular immunity as antigen-presenting cells. T cells with functional profile of Th2 are rare in the plaques, but are important since elaborate inhibitory cytokines (IL-4, IL-5 and IL-10)

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of the Th1 pathway [5]. Fatty streaks may completely regress [4] if LDL plasma concentration decreases, HDL level is high in plasma and risk factors are corrected, otherwise the atherosclerotic lesions progress to type III lesion (preatheroma) and, then, to atheroma (type IV lesion) with proliferation and migration of SMCs until the advanced lesion (type V to VIII). The cytokines and other active factors, such as growth factors and proteolytic enzymes produced by macrophages and T cells have profound effects on ECs, SMCs and fibrogenesis and, as a consequence on the structural architecture of the plaques [2, 5]. Thus, growth factors such as FGF-2, PDGF produced by macrophages and heparin-binding growth factor released by T cells promote the proliferation of SMCs and the macrophage derivated FGF-1 can stimulate the growth of ECs resulting in a strengthening of the plaque. For this purpose, TGF-β produced by the macrophages and SMCs , but mainly by a third T helper cell (Th3), is particularly important because strongly promotes the synthesis of interstitial collagen [5]. In contrast, pro-inflammatory cytokines, such as TNF-α and INF-γ tend to inhibit vascular cell proliferation. In this context, INF-γ plays a major role because powerfully inhibits collagen synthesis by SMCs and stimulates macrophages to produce inflammatory cytokines, such as TNF-α, IL-6, tissue factor and matrix metalloproteinase, thus weakening the structure of the plaque, facilitating its rupture and thrombus formation. Notably, INF-γ and IL-2 are synthesized by Th1 lymphocytes whenever they are involved in a new acute immune reaction. Individual patients, who for genetic or environmental reasons tend to form neoantigens during LDL degradation, more easily may produce an immune reaction within the plaque with consequent release of INF-γ and other inflammatory cytokines [2]. Thus, the probability of acute ischemic, often fatal, coronary events depends on the amount and kind of antigens (neoantigens) produced in the degradation of LDL, on the ratio between stimulatory and inhibitory cytokines (Th1/Th2 cell ratio) and by the substantial presence of Th3 helper in the plaque.

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Stroke Epidemiology in North Eastern Italy

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The World Health Organization MONICA Project was established in the early-mid 1980s in many Centres around the world to MONItor trends in CArdiovascular diseases (coronary heart disease – CHD- event registration is obligatory, stroke optional), and to relate these to risk factor changes in the population over a ten year period. It was set up to explain the diverse trends in cardiovascular disease mortality which were observed from the 1970s onwards. There are total of 32 MONICA Collaborating Centres in 21 countries. 15 Centres in 9 countries monitored both CHD and stroke. The total population age 25–64 years being monitored is ten million men and women. In Italy the Area Friuli (north-east) participated in CHD and stroke monitoring. In the MONICA Project stroke is defined as rapidly developed clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death), with no apparent cause other than a vascular origin. In every Collaborating Centre all the suspected events in the community (out of hospital and in hospital) were reviewed and validated according to the MONICA Protocol with external quality control. In Friuli from 1984 to 1993 4124 strokes were registered, of which 1432 were fatal within 28 days from symptom onset. In men about 6% of non fatal strokes were attributed to subarachnoid haemorrhage, 18% to intracerebral haemorrhage, 75% to brain infarctions and 2% to acute but ill-defined cerebrovascular disease; the figures for women were respectively 16%, 18%, 63% and 3%. The age standardized event rates of all stroke events (i.e. first and recurrent) were 131 per 100 000 age group 35–64 in men and 61 per 100 000 in women, without significant variations throughout the ten years under surveillance. The age standardized incidence rate of first ever stroke events per 100 000 age group 35–64 in Friuli was 112 in men and 53 in women, with minor variations in the ten years monitored. In Friuli the age standardized validated stroke mortality per 100 000 age group 35–64 in men dropped from 50 in 1984 to 28 in 1993 and in women from 26 in 1984 to 19 in 1993. Consequently the percent case fatality of all strokes decreased significantly from 38% to 21% in men and from 45% to 32% in women. Considering the percent case fatality of first ever stroke, it decreased from 34% to 18% in men and from 43% to 26% in women in the same time period. These data, related to "premature" stroke, i.e. that occurring before 65 years of age, clearly show a stable trend in stroke incidence and attack rate from the mid 1980s to the mid 1990s, as well a defined decrease in case fatality. It is difficult to attribute this finding to a better stroke care as in case of CHD acute care, because we did not measure the disease severity and the individual treatment of risk factors. Of all the established stroke risk factors only age, sex, smoking, hypertension, hypercholesterolemia and obesity were measured in three independent surveys at the beginning, in the middle and at the end of the MONICA surveillance period. With this design, an ecological analysis was possible, comparing trends in stroke with trends in risk factors, considering the different populations as units. Considering all the above-mentioned risk factors together in a score, this trend was related to stroke trend after a lag phase of at least four years, particularly in women. Of the various risk factors hypertension was the most important. This means that risk factors should be treated for at least four years before having an effect at the population level. The MONICA-Friuli stroke register, though the only one in Southern Europe has major limitations because it does not include older age groups where stroke is more frequent and of course it does not represent the whole country. However, based also to this experience, eight Italian areas – Friuli, Brianza, Veneto, Modena, Firenze, Lazio, Napoli and Caltanissetta, developed a simplified CHD and stroke register system, merging death certificate data with hospital discharge data and validating a proportion of the suspected cases according to the MONICA protocol. In particular for the stroke registration medication and procedures before, during and after the

event were added, as well as severity indexes, according to the Northern Sweden proposal.

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Acute Stroke: Diagnostic and Therapeutical Pathways

Acute Ischemic Stroke: Diagnostic-Therapeutic Procedures. The Point of View of Neurologists

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The organization of a Stroke Unit inside the Emergency Department (EDSU) made necessary the definition of diagnostic-therapeutic procedures for acute stroke patients, which represent the local application of national guidelines [1]. We may differentiate them as emergent procedures, aimed at giving tailored revascularization therapies, and urgent procedures aimed at defining the underlying ethiopathogenic mechanism to assign the most appropriate secondary prevention therapy.

Emergent Diagnostic-Therapeutic Procedures

On admission to the Emergency Department, a detailed neurological assessment is made by means of the NIHSS score in order to quantify the severity of neurological deficit, while no differentiation of stroke subtype is attempted since this is not reliable on simple clinical grounds [2]. Whatever the degree of neurological deficit, patients undergo CT to differentiate cerebral ischemia from parenchymal haemorrhage, tumour or other focal lesions. In case of cerebral haemorrhage a neurosurgical consultancy is required and, if there is not a surgical indication, the patient is admitted in the EDSU. Ischemic stroke patients with very severe deficit (stuporous or comatose) at hospital entry, after consultancy with the resuscitation staff, are admitted in the EDSU in order to stabilize their conditions and perform the examinations necessary for ethiopathogenic diagnosis and secondary prevention (see below).

If the neurological deficit is slight to moderately severe (NIHSS score between 6 and 24), the clinical picture is suggestive for a carotid territory stroke, the delay between onset of symptoms and clinical observation is less than 3 hours, and CT shows no or very limited early signs, the patient undergoes extra- and intra-cranial Doppler flow study, eventually supplemented, in case of doubts, by MR or CT angiography. The next step is emergent therapy which, in case of symptomatic internal carotid artery (ICA) occlusion and patency of the ipsilateral middle cerebral artery (MCA), may be carotid endarterectomy. Instead, in case of ICA patency or non significant ICA plaques, the choice is i.v. rt-PA irrespective of the demonstration of symptomatic MCA occlusion by TCD, considering the low sensitivity of TCD in detecting distal MCA branch occlusions. However, in case of MCA patency at TCD and rapid clinical improvement we restrain from giving thrombolysis.

If the neurological examination suggests a diagnosis of posterior circulation stroke and ultrasounds, eventually completed by MR or CT angiography, detect a basilar artery occlusion i.a. thrombolysis or, alternatively, i.v. heparin are given.

When sinus venous thrombosis is diagnosed by clinical and instrumental examinations, i.v. heparin is given (with a target aPTT of 1.5–2 times baseline values) together with warfarin (target INR 2 to 3).

Urgent Diagnostic-Therapeutic Procedures

These apply not only to all acute ischemic stroke patients but also to TIAs, whom we do not discharge immediately given the high risk of having a stroke in the following 48 hours [3]. After entry CT, to which also TIA patients are submitted to exclude other possible causes of a transient neurological deficit, a Doppler flow study is performed which allows us to differentiate four subgroups:

1. patients with definite large artery stroke, as those having a symptomatic carotid or basilar artery severe stenosis or occlusion, whose treatment has already been discussed above;
2. patients with probable large artery stroke, as those with complicated (i.e. ulcerated) plaques determining a 40% to 60% stenosis of ICA ipsilateral to the affected hemisphere.
3. patients with possible large artery stroke, as those with non complicated carotid plaques determining a 40% to 60% stenosis.
4. patients without large artery stroke, as those with small non stenosing carotid plaques or without plaques.

In the groups 2 (after discussion with cardiologists), 3 and 4 we proceed with cardiological examinations, in order to look for cardiac sources of emboli.

In patients with chronic atrial fibrillation (CAF) we start oral anticoagulants if there are not contraindications, while when anticoagulation may be risky we perform transesophageal echocardiography (TEE) in order to evaluate the presence of intra-cardiac thrombi. Patients, without CAF but with past medical history of cardiopathy and older than 45 years, undergo first transthoracic echocardiography

and, if no cardiac condition at risk of embolization is found, they undergo TEE. TEE is the first choice examination in patients with past medical history of cardiopathy and younger than 45 years and in all those without past medical history of cardiopathy irrespective of age. In case a definite cardiac source of emboli is detected oral anticoagulant therapy is started, while if no cardiac source is found an haematological screening is performed to look for pro-thrombotic states eventually completed with genetic research. Moreover, surgical consultancy is again required for patients with probable large artery stroke.

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Blood Pressure Management

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Background and Purpose: Elevated blood pressure (BP) may be found in three quarters of patients with acute ischemic stroke at presentation, about half of which have a history of hypertension. At the hospital admission systolic BP (SBP) is higher than 220 mmHg in more of 10% of patients [1].

The influence of arterial BP values in the first days of acute ischemic stroke on cerebral damage and on functional recovery is unknown. Rapid decrease of BP may be unfavourable. In fact the ischemic penumbra surrounding the profoundly ischemic core may recover over time and any decrease in BP may promote irreparable injury of the tissue at risk. Moreover, the blood flow distal to a severe intra or exrtracranial arterial stenosis may further decrease and predispose to thrombus propagation [2]. On the other hand, untreated elevated BP may precipitate secondary hemorrhagic infarction and worsen perifocal oedema. Most studies, although not all, have found that high blood pressure, whether measured as casual or 24-hour BP monitoring, in the acute phase of stroke is associated with a poor outcome [3, 4]. Lowering BP is clear indicated in the presence of concomitant disease as myocardial ischemia, significant congestive heart failure and aortic dissection. We carried out a study in patients hospitalised for acute stroke to evaluate the behaviour of BP in the first four days from the acute event in absence of antihypertensive therapy.

Methods: For this purpose, 33 patients with first ischemic stroke (12 M; 21 F; 71.9 ± 12.3 years) were submitted to 24-hour BP monitoring (4 and 3 recording per hour in day- and night-time, respectively; SpaceLab 90207) within 1 day of the cerebral event and 4 days thereafter. The cuff was applied on the non-paretic arm. Cerebral CT scans were obtained at the admission and between the 3rd and 7th day after the index event. Patients with atrial fibrillation (to avoid inaccurate BP measurement) or with a mandatory need of antihypertensive treatment, according to the American Heart Association Statement [5], were excluded. 24-hour BP monitoring is useful to abolish the white-coat effect and reduce the variability among different operators; moreover we can get useful information about diurnal and nocturnal BP variations and heart rate.

Table 1

	24 h SBP	24 h DBP	Dayt. SBP	Dayt. DBP	Night-t. SBP	Night-t. DBP
1st day	145 ± 18	82 ± 10	147 ± 18	83 ± 10	144 ± 21	80 ± 11
4th day	139 ± 17*	79 ± 8	140 ± 17*	81 ± 8	139 ± 24	77 ± 11

*$p \leq 0.05$.

Table 2

	24 h SBP		24 h DBP	
	Hp+	Hp−	Hp+	Hp−
1st day	152 ± 13	141 ± 20	83 ± 8	81 ± 9
4th day	150 ± 14	131 ± 15*	84 ± 8	76 ± 8**

*$p \leq 0.05$; **$p \leq 0.02$.

Results: About 40% of patients had a history of hypertension and 1/3 of totality was on antihypertensive treatment before stroke. 27% had a major stroke, according to the Canadian Stroke Scale; 27% had lacunar infarct on CT, 58% had non lacunar infarct and 15% had "negative" CT. The mean interval between symptom onset and first BP monitoring was 16 hours while the mean interval between symptom onset and 2nd BP monitoring was 118 hours.

Table 1 shows that SBP was significantly lower on the fourth day in comparison to the first day of monitoring, while the reduction of diastolic BP (DBP) was not statistically significant. No significant differences were observed between the two days of monitoring concerning heart rate and BP variability, evaluated as standard deviation of SBP and DBP.

Then we studied two groups of patients, with and without a history of hypertension before stroke. Table 2 shows that SBP and DBP were significantly lower in the 2nd monitoring only in patients without a history of hypertension (Hp−), while in previously hypertensive patients (Hp+) BP did not significantly decrease during the first 4 days after a stroke.

Conclusions: These results indicate that in the first days of acute ischemic stroke BP spontaneously decreases in patients without a history of previous hypertension; moreover there are no significant modification of heart rate and BP variability.

In our clinical practice we treat hypertension in the acute phases of ischemic stroke only in previously hypertensive patients with minor stroke, especially lacunar stroke. Preferentially we use the angiotensin-converting enzyme inhibitor perindopril because it did not reduce cerebral blood flow in experimental setting [6]. We favour a smooth return to pre-existing BP levels; subsequently long-term BP management had to be considered in every stroke patient according to PROGRESS trial [7].

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Diagnostic – Therapeutic Pathways in Stroke Management: The Role of the Cardiologist

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The need for a multidisciplinary evaluation of patients with stroke has been firmly established in recent years. In this framework the role of the cardiologist is of utmost relevance because of the multiple interactions between cardiovascular and cerebrovascular disease [1–4].

There are two major reasons for the cardiologist to look after patients with transient ischemic attacks (TIA) or stroke. First of all, TIA or ischemic stroke may be cardioembolic in nearly one fourth of cases. Secondly, more than one half of cerebrovascular patients may have coexisting coronary artery disease (CAD) and the risk of coronary events in the long-term follow-up exceeds the risk of cerebrovascular recurrences. Thus the search for cardiac sources of embolism and for coexisting CAD should be performed in every patient with cerebral ischemia.

Cardioembolic Stroke

Nearly 20–25% of all ischemic strokes are cardioembolic; nonvalvular atrial fibrillation (AF) accounts for about 50% of cardioembolic strokes [5]. Echocardiography allows the detection of potential cardiac sources of embolism in many cases of cryptogenic strokes which account for up to 40% of the strokes in young adults.

The cardiac lesions more frequently detected in patients with TIA or stroke include: (1) lesions at high embolic risk: ventricular thrombi (detectable in acute myocardial infarction (MI) and dilatative cardiomyopathies), left atrial appendage thrombi (detectable in patients with AF, sick sinus syndrome and atrial flutter), endocarditic vegetations, rheumatic mitral valve disease, thrombosis of prosthetic heart valves, cardiac tumors; (2) lesions at low or uncertain embolic risk: mitral valve prolapse, mitral annular calcification, aortic valve calcification or calcified aortic valve stenosis, aortic plaques, patent foramen ovale, atrial septal aneurysm. The dilemma of whether to label a minor potential cardiac source of embolism as the cause of a stroke was common in the past with mitral valve prolapse, and nowadays it is common with patent foramen ovale.

Echocardiography is the technique of choice for the confirmation of cardiac sources of embolism and for the detection of occult cardiac lesions in patients with normal clinical examination. Transthoracic echocardiography (TTE) has been shown to be effective in detecting potential cardiac sources of embolism in many patients with history and clinical evidence of cardiac disease. Conversely, in patients without overt cardiac disease the yield of TTE was only 1.5% (range 0–6%). An important improvement in the search for cardioembolic sources has been achieved with transesophageal echocardiography (TEE). The search for potential cardiac sources of stroke actually represents one of the major indications for TEE in most Institutions. The cardiac lesions more frequently detected by TEE in patients with ischemic stroke include: left atrial thrombus, atrial septal aneurysm, patent foramen ovale, spontaneous echo contrast, valvular strands and vegetations, and aortic plaques. The causal relationship between cardiac lesion and stroke should be assessed in the individual patient. Cardiac ultrafast CT, and magnetic resonance imaging are supplemental techniques that can be used when TEE studies are non diagnostic. Holter monitoring should be reserved for those patients with suspected paroxysmal AF or sick sinus syndrome detectable in about 4% of cerebrovascular patients with normal clinical examination.

Specific treatment for the prevention of cardioembolic stroke include long-term anticoagulant therapy in patients with AF and 6-month or long-term therapy in patients with post-MI severe left ventricular dysfunction [5, 6]. The precise role of percutaneous transcatheter occlusion in patients with patent foramen ovale is still debated. Finally, percutaneous left atrial appendage transcatheter occlusion (PLAATO), in patients with AF not eligible for anticoagulant therapy, is a promising technique under investigation in ongoing clinical studies.

Coexisting Coronary Artery Disease

The early and late prognosis of patients with cerebral ischemia is critically influenced by the coexistence of CAD [3]. MI and sudden death are the leading long-term causes of death in patients with cerebrovascular disease. One third of patients with TIA, stroke, or asymptomatic carotid disease has history of previous MI or angina pectoris.

Cerebrovascular patients with carotid lesions have a significant risk of coronary events during the follow-up. After a TIA or stroke the risk of MI or coronary death is 2–2.5-fold the occurrence of stroke or cerebrovascular death. Even in patients with asymptomatic carotid bruits the prevalence rate of coronary death is 3-fold the cerebrovascular mortality, and the risk of coronary events in the follow-up correlates with the degree of carotid stenosis. Finally, also in patients undergoing carotid endarterectomy, MI is the leading cause of early and late morbidity and mortality.

All these data show that cardiac events often occur in patients with symptomatic or asymptomatic carotid disease. TIA may be considered a possible harbinger of future MI or coronary death. A routine cardiologic evaluation of cerebrovascular patients could allow to identify a high-risk subgroup to submit to a more aggressive approach.

A noninvasive evaluation including exercise ECG testing followed, if abnormal, by myocardial scintigraphy is a reliable protocol for identifying and staging CAD in these patients; as alternative to exercise, dipyridamole myocardial scintigraphy or echocardiography are warranted [3, 7]. Patients at high risk include those with strongly positive exercise testing or large perfusion defects at myocardial scintigraphy or multiple transient asynergic segments at dipyridamole

echocardiography. Patients at high risk should be submitted to coronary angiography for identifying the severity of the CAD and planning the best monitoring and management.

Beside the coexistence of symptomatic CAD in about one third of patients, a silent CAD is detectable in about one fourth of cerebrovascular patients. Several studies, including our experience, employing myocardial perfusion scintigraphy have demonstrated a prevalence of 24–41% of perfusion defect in patients with TIA or minor stroke without cardiac symptoms.

Whenever a coexisting, even silent, CAD is detected in a patient with stroke, a vigorous treatment of CAD is warranted. In addition to antiplatelet treatment, which is effective for preventing both cerebrovascular and coronary events, statins, betablockers, and ACE-inhibitors are effective therapies, beside aggressive risk factors modification, for the specific prevention of coronary events. Coronary revascularization by coronary artery bypass graft or percutaneous coronary interventions are indicated in cerebrovascular patients with advanced CAD at coronary angiography and significant angina or severe inducible myocardial ischemia, as well as heart failure or left ventricular dysfunction.

When indications to both carotid and coronary revascularization is established, the choice of staged or combined operations is determined by assessment of the relative severity of carotid and cardiac risk factors and according to the preference of the diverse Institutions. However, simultaneous operations should be considered for patients with unstable angina and for those with left main CAD, or multivessel coronary lesions without adequate collateral circulation, or in the presence of poor left ventricular function. Preliminary carotid angioplasty followed by coronary-artery bypass graft is another possible alternative for these patients.

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Diagnostic Assessment in Surgical Treatment of Carotid Stenosis

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When evaluating a patient who is expected to undergo reconstructive carotid surgery, one must consider that carotid stenosis is a part of a diffuse vascular disease, involving cardiac and peripheral vessels; thereafter, preoperative evaluation should comprehend not only accurate assessment of carotid artery, intracranial vessels and cerebral parenchyma status, but also careful detection of cardiac disease and associated risk factors for atherosclerosis, which can influence early and long term results of surgical intervention.

Duplex scanning (DUS) is now universally accepted as the first choice instrumental examination for detection of significative carotid stenosis and indication for surgical intervention: several studies comparing duplex and angiography showed a predictive positive value for DUS of 97% [1], with higher sensitivity and specificity than angiography in plaque's morphology assessment [2].

The role of DUS is basical in evaluation not only of degree of stenosis, but also of quality of carotid lesions: echogenicity and composition of the plaque, surface characteristics are probably associated with different risks of embolization and consequent cerebrovascular symptoms [3], and this fact can be important in detection of high-risk asymptomatic patients, who could benefit from prophylactic surgical intervention.

The introduction and large diffusion of non invasive imaging methods, such as magnetic resonance angiography (MRA) and computed tomography angiography (CTA), allowed, in last years, to significantly reduce the need for invasive evaluation of extra and intracranial vessels' evaluation [4]. At the moment [5, 6], it is accepted that a validated DUS associated with non invasive intra and extracranial evaluation is sufficient for preoperative assessment of patients candidated to carotid endarterectomy. Angiography should be performed only in the presence of disagreement between DUS and CTA (or MRA) or between clinical presentation and non invasive imaging methods. Preoperative study of cerebral parenchyma with CTA scan or MR imaging remains indicated in patients undergoing carotid endarterectomy, both in symptomatic and asymptomatic patients [7]. Moreover, the presence of large cerebral lesions detected at CT scan is one of the major contraindication to urgent surgical intervention in patients with unstable neurological status [8]. The role of carotid surgery in the presence of instable neurological symptoms is still controversial. One must distinguish between patients with crescendo TIA or stroke in evolution and critical carotid stenosis and patients with acute stroke and carotid artery occlusion. In the presence of crescendo TIA or stroke in evolution, once the presence of critical carotid stenosis is detected, immediate study of cerebral parenchyma should be performed. The presence of intracranial haemorrhage or ischemic lesion with large perilesional oedema is a contraindication to urgent surgery; when ischemic lesion is limited (<1.5 cm) [9] or absent, carotid endarterectomy could be performed, on condition that middle cerebral artery (evaluated by transcranial Doppler or angiography) is still patent. Results in reported series are fairly satisfactory [8, 9].

In the presence of unstable neurological status (mild/moderate neurological deficit) with duplex finding of occluded internal carotid

artery, imaging of cerebral parenchyma should be immediately performed: if negative, or in the presence of limited ischemic infarction (<1.5 cm), patency of intracranial internal carotid artery should be assessed by transcranial Doppler, CTA, MRA or angiography [10]. Surgical intervention can be attempted only under these conditions, and reported results are encouraging.

An Italian multicentric study concerning surgical treatment of acute neurological patients (STACI) is currently on the way, aiming at claryfying indications and results in this subset of high risk patients.

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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 thromboendarterectomy 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 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-MR and angio-CT, also if all these methodics presents some limits to assess the degree of stenosis and characterize the pathologic arterial walls. Recent dynamic contrast-enhanced CT and MR imaging techniques such as the Perfusion-Weighted CT and Perfusion-Weighted MR imaging, associated with Diffusion-Weighted MR imaging or MR Spectroscopy, arouse great interest helping predict clinical outcome at very early time points and allowing the identification of optimal candidates for therapeutic interventions, including thrombolysis (i.e., 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 (thrombolysis, stenting) or in uncertain cases.

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.

Management of Patients with Carotid Stenosis: The Angiologist's Point of View

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Carotid atherosclerosis is one of the main risk factors for ischemic stroke. The annual risk of ipsilateral stroke for asymptomatic, albeit severe stenoses is as low as 1 to 2%, but increases to 13% in patients with recent appropriate focal neurological deficits. However the risk decreases after the first 2–3 years from the symptomatic episode, dropping again to 3%.

Echo-color Doppler ultrasonography is the diagnostic method of choice, being highly accurate, noninvasive and low-cost. Carotid angiography still represents the gold standard, however, less invasive techniques as RM angiography and Angio-CAT are becoming increasingly common. Carotid endarterectomy is strongly recommended for severe symptomatic while for the moderate symptomatic, as well as for the severe asymptomatic ones the benefit in terms of stroke risk reduction is modest and surgery should be restricted to selected cases in surgical centers of high experience.

Apart from surgery, in all patients with carotid atherosclerosis correction of cardiovascular risk factors is mandatory. Antiplatelet therapy (ASA alone or with dypiridamole, ticlopidine) is effective in secondary prophylaxis of athero-thrombotic stroke; its use in asymptomatic carotid stenoses can be recommended, even if more because of a plausible rationale than of clinical trial-based evidences.

Risk Factors of Stroke

High Blood Pressure, Renin-Angiotensin System and Stroke

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The contribution of the renin-angiotensin system (RAS) to the pathogenesis of vascular complications in patients with high blood pressure was first suggested 30 years ago by Brunner et al. that reported, in a retrospective analysis, a higher incidence of stroke and heart attack in high-renin hypertensive patients compared with normal and low-renin subjects [1]. Eventually, a growing body of evidences from experimental and clinical studies demonstrated that the RAS activation has a detrimental impact on arterial wall. In particular, in vitro studies showed that angiotensin II may be directly or indirectly responsible for vascular lesions by inducing vascular smooth muscle cells hypertrophy and proliferation, enhancing the release of norepinephrine and epinephrine at nerve endings, and increasing the synthesis and release of vasoconstrictive factor such as Endothelin-1. The elevated blood pressure and RAS activation may also accelerate vascular atherosclerosis. Indeed, it has been shown that carotid and aortic atherosclerosis in the Watanabe heritable hyperlipemic rabbit were increased by one-kidney, one-clip hypertension and cardiovascular mortality and stroke rate were higher in stroke-prone SHR when fed a high-sodium diet, which cause a paradoxical rise in plasma renin activity. Some interesting data come also from the investigations of RAS polymorphisms. In particular, it has been reported that the presence of DD genotype of ACE gene in hypertensive patients is a risk factor for stroke and a recent meta-analysis reported that the D allele of ACE gene is not related to hypertension but seemed to be associated with high risk of atherosclerotic complications, including coronary heart disease and stroke. Interestingly, the presence of the DD genotype and/or the D allele of ACE gene resulted significantly higher in patients with cerebral white matter lesion, a subclinical form of ischemic brain damage, than that observed in patients without brain lesions. On the other end, significantly higher plasma levels of ACE were found in patients with carotid intimal-medial thickening compared with control subjects. From the clinical point of view, it has been shown that renovascular hypertension, regardless of its etiology, is associated with more detrimental effects on carotid arteries than primary hypertension even in presence of similar hemodynamic load, possibly because of activation of RAS [2]. The availability of pharmacological agents that act inhibiting the RAS such as ACE-inhibitors (ACE-I) and angiotensin II type 1 receptors blockers (ARBs) further helped as to better understand the role of RAS in the pathogenesis of cerebrovascular complication in patients with hypertension. Pretreatment of SHR with candesartan or captopril showed to decrease the infarct area and to normalize cerebral artery intima-media thickness, leading to increased arterial compliance and reduced cerebral blood flow decrease during ischemia at the periphery of the lesion, more effectively than a calcium channel blocker. Moreover, in hypertensive patients, the ACE-I perindopril showed to improve cerebral blood flow index better than acebutolol, which suggest a more significant improvement in cerebral perfusion [3]. Positive results on cerebrovascular protection by RAS inhibition were also confirmed in large clinical trials. In the PROGRESS, a blood pressure-lowering regime based on perindopril reduced the risk of stroke by 28% among both hypertensive and nonhypertensive individuals with a history of cerebrovascular disease [4]. In the LIFE study, antihypertensive therapy with losartan reduced the risk of stroke more than atenolol, in hypertensive patients with left ventricular hypertrophy [5]. Finely, in the SCOPE study, candesartan therapy reduced the risk of non-fatal stroke by 28% in elderly people with mild hypertension [6]. In conclusion, the results of experimental and clinical studies clearly demonstrate the importance of RAS activation in the hypertensive stroke pathology. Due to the financial impact on health care system and long-term debilitating effects of stroke in the hypertensive patients, continue improvement of therapy of high blood pressure is vital to reduce the global burden of hypertensive vascular complications.

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Dyslipidaemia and Stroke

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The association between total serum cholesterol concentration and coronary artery disease is well established, but the relation between stroke and cholesterol remains elusive. Epidemiological studies in Japanese [1] and Japanese Americans [2] failed to associate cerebral infarction with raised cholesterol but found an inverse relation with the incidence of intracerebral haemorrhage and a meta-analysis of the prospective follow-up of 450,000 patients within 45 separate cohorts over an average period of 16 years detected no relation between cholesterol concentration and the overall incidence of stroke [3].

It is therefore likely that cholesterol influences certain types of stroke and any effect is likely to be diluted if strokes are not divided into appropriate diagnostic grouping. Meta-analysis of published trials of lipid lowering treatment and incidence of stroke are fraught with potential bias and pitfalls, but few trials support the hypothesis that lowering cholesterol concentration effectively reduces the incidence of stroke; for example in the WOSCOPS [6] Study treatment with pravastatin reduced cholesterol concentration and the primary incidence of coronary events but not stroke, but in the 4 S Study [5] and more recently in the Heart Protection Study [7] simvastatin treatment as secondary prevention of coronary heart disease offered a significantly reduced number of cerebrovascular events.

Indeed Matsamura et al. [4] to evaluate whether thoracic aortic plaques together with dyslipidaemia are related to ischemic stroke and to which of the subtypes of stroke showed that severe plaques in the proximal aorta together with dyslipidaemia are seen more frequently in patients with atherothrombotic stroke.

On this way Horenstein et al. [8] showed that cholesterol is a risk factor for nonhaemorrhagic stroke in women <55 years of age and is more strongly associated with mortality in black women <55 years of age than in white women.

The apparent paradox regarding the not clear association between LDL and/or HDL levels and stroke and stroke risk lowering action of the statins can be explained on the one hand by the heterogeneity of strokes and on the other hand by the specific characteristics of stroke. Exists, infact, a strong indication for a relationship between blood lipid prophiles and subtypes of stroke pathogenetically related to atherosclerosis as like the LAAS TOAST subtype [8, 9, 10].

Indeed Engstrom et al. [11] explored whether the cholesterol-related incidence of stroke and myocardial infarction is modified by plasma markers of inflammation (*inflammation-sensitive plasma proteins: ISP*) (*fibrinogen*, *alpha-1 antitrypsin*, *haptoglobin*, *ceruloplasmin and orosomucoid*) in a large population based cohort showing that only hypercholesterolemia associated with high ISP levels have a significantly higher risk of ischemic stroke, while normocholesterolemia and hypercholesterolemia with normal ISP levels have a overlapping no significant association with ischemic stroke risk. Genes contributing to interindividual variation in lipid levels may play a role in the etiology of stroke, for this reason Morrison et al. [12] examined the association between polymorphism in the lipoprotein lipase (LPL) and apolipoprotein E (APOE) genes and stroke in the Atherosclerosis Risk in Communities (ARIC) Study showing that only LPL S447X polymorphism is significantly associated with subclinical cerebral infarction and incident clinical ischemic stroke in men from a middle-aged American population and how this association does not appear to be mediated by triglyceride, HDL and LDL-cholesterol levels or additional risk factors.

In conclusion, although dyslipidaemia and stroke association appears yet not fully ascertained, a bound of experimental and epidemiologic studies have contributed to underline that this relation is probably valid only for the atherosclerotic stroke subtypes and only for the association with an axillary inflammatory plasma prophile as confirmed by benefits offered by the secondary prevention trials using statins in cerebrovascular higher risk patients probably through the pleiotropic actions of the statins.

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C Reactive Protein, Antiphospholipid Antibodies and Homocysteine

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Several data demonstrate that inflammation plays an important role in the pathophysiology of ischemic stroke. Elevated blood levels of inflammatory and hemostatic markers are associated with increased cardiovascular risk in healthy subjects and in patients with coronary artery disease (CAD) and ischemic stroke. Recently, it has been demonstrated that elevated C-reactive protein (CRP) levels independently predict the risk of future stroke and transient ischemic attack. From a pathophysiological perspective, these data support the hypothesis that patients who respond to stroke with marked activation of the inflammatory system may be at risk for more intense activation of coronary triggering events. Moreover, these results can improve the prediction of vascular risk in patients with ischemic stroke and may lead to a better clinical identification of patients who might benefit from an aggressive secondary prevention and for whom the cost-to-benefit ratio for long-therapy use of new antiplatelets agents would be improved. Furthermore, it was demonstrated that CRP level measured within 12 hours after symptom onset of an acute ischemic stroke is not independently related to long-term prognosis. In contrast, a CRP increase between 12 and 24 hours after symptom onset predicts an unfavourable outcome and is associated with an increase incidence of cerebrovascular and cardiovascular events.

Transient ischemic attacks and strokes are the most common types of arterial thromboses reported in antiphospholipid antibodies syndrome (APS). The association of antiphospholipid antibodies (aPL) with stroke is most clearly shown in studies of stroke in the young (below age 50). Studies of all strokes have had conflicting results with some case-control studies showing a strong association (34% vs. 11%) with aPL. In a prospective nested case-control study, anti-β2-glycoprotein-I predicted later stroke risk at 15 years (with less of an association at year 20). It is not reasonable to suggest that all patients with a first ischemic stroke be screened for aPL. Currently available information allows us to suggest screening for aPL in selected subgroups of patients. Stroke patients under the age of 40 years should have aPL determinations performed as part of the evaluation for stroke etiology. Patients of any age with unexplained stroke likewise should be screened for the presence of aPL. Any stroke patient with first or recurrent stroke who has some other clinical (SLE, livedo reticularis, recurrent fetal loss, valvular heart disease) or laboratory features (prolonged aPTT, thrombocytopenia, hemolytic anemia Coombs positive) should also be screened for the presence of aPL.

A mild hyperhomocysteinemia is present with a prevalence between 12% and 47% of patients with coronary artery disease, ischemic stroke or peripheral artery disease. In a meta-analysis on 9 studies, odd ratio for ischemic stroke was 2.5 (95% IC 2.0–3.0). The strongest evidence of a relation between homocysteine (Hcy) and risk of cerebrovascular disease has been given by 6 prospective studies with a follow-up between 1.4 and 12.8 years on 830 cases and 1872 controls. The vascular risk showed to be dose-dependent in relation to both fasting and post-methionine Hcy levels and statistically independent of traditional cardiovascular risk factors even if it was reported a multiple effect in presence of smoking and hypertension.

In a subgroup of patients from ARIC study, intima media thickness was associated with high levels of homocysteine. Moreover, analysis of the Framingham study showed that the severity of carotid stenosis was inversely associated with the dietary intake of folic acid and vitamin B6. Several studies, either case-control or prospective, demonstrated the presence of elevated Hcy levels in patients with history of transient ischemic attack and/or stroke. In the Caerphilly study, a prospective study on 2254 males (range 50–64 years), Hcy levels within the fifth quintile were associated with a significative risk (OR = 2.5 CI 1.0–6.2) in the subgroup of subjects with stroke below age 65. In addition to these results, a recent study indicated that mild hyperhomocysteinemia is the only variable able to identify patients with juvenile ischemic stroke. Elevated levels of Hcy seem to significantly affect the extent of aortic ateroma, evaluated with a transesophagus echo, in patients with previous ischemic stroke. One of the major cause of premature ischemic stroke is the artery dissection. Recently, it was demonstrated that not only hyperHcy but also MTHFR polymorphism is an independent risk factor for the dissection. Finally, preliminary data suggest that hyperHcy is a risk factor for the occurrence of cerebrovascular events (TIA/stroke) in patients with atrial fibrillation. On the basis of these results on the association between Hcy and cerebrovascular disease, several intervention trials are ongoing attempting to determine whether lowering Hcy levels with vitamin supplementation will reduce the recurrence of stroke.

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Estrogen and Stroke

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In western countries 1 woman out of 6 dies of stroke. The growing age of population increases the risk of mortality. Beyond age (non modifiable risk factor) the main factors that have been linked to the development of stroke in woman are: hypertension, the most important risk factor, diabetes, dyslipidemia and smoking. The relationship between estrogen and stroke has long been recognized as an important association; several studies have been stressed to this topic. These studies could be dissected out on the basis of the study designed (observational cohort or randomized studies) or on the basis of estrogen treated patients (primary or secondary prevention studies). These

studies are hardly comparable because of the different type of route of HRT administration. Nevertheless observational studies show that estrogen prevent stroke (20-30% decrease); while randomized studies show that estrogen donot influence the incidence of stroke. The latter published randomized study of primary prevention known as WHI, has been recently interrupted because of an increase of stroke in women treated with HRT. This enhance has been attributed to estrogen pro-inflammatory and pro-thrombotic action. On the other hand, all data of the most important and randomized study have been referred to estrogen oral assumption. Preliminary data of our group indicate a lack of negative influence of estrogen on incidence of stroke. However our results appear to hold true for transdermal assumption. Hence an hypothetical action could be linked to the kind of molecule and to the route of HRT administration. New randomized studies are needed to define the role of estrogen in cardio and cerebro-vascular protection.

Stroke Risk and Stroke Diagnosis: Sonographic and Neuroimaging Techniques

Transcranial Color-Coded Duplex Ultrasonography – Use of Echo Contrast Agents in the Evaluation of Cerebrovascular Disease

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Transcranial color-coded duplex ultrasonography (TCCS) enables the visualization of basal cerebral arteries through color-coding the flow velocity information. TCCS was first applied in children. The development of new high-resolution ultrasonic systems made it possible to examine the intracranial arteries and veins in adults as well (Furuhata, 1989; Bogdahn et al., 1990). The purpose of this presentation is to demonstrate the technique for examining intracranial arteries, veins and cerebral parenchyma, and to present typical pathological findings in occlusive disease, in vascular malformations, cerebral venous thrombosis as well as in cerebral parenchyma disorders. Additionally, the advantages of echo contrast agents in the evaluation of cerebrovascular disease will be shown.

The *arteries of the circle of Willis* can be identified by their anatomic location with respect to the brain stem structures and by determination of the flow direction. For the imaging of *intracranial veins*, the equipment must be adjusted to a low flow setting; that is, the pulse repetition frequency has to be set at its lowest value, the color box has to be as small as possible, and the frame rate and wall filter have to be adjusted (Bartels, 1999).

It is technically relatively easy to detect a *stenosis in the proximal segment of the arteries of the Circle of Willis*. These arteries can be imaged the best with the transtemporal insonation in the mesencephalic axial plane. Data concerning the sensitivity and specificity of TCCS in *stenosis of middle cerebral artery (MCA)* remain limited. Furthermore, no criteria for the quantification of intracranial stenosis by TCCS are available. The classification is based on conventional TCD studies: In the case of the stenosis of the middle cerebral artery a peak systolic flow velocity of over 160 cm/s, or mean value over 90 cm/s, is considered pathological. A difference in mean flow velocity of at least 30 cm between the two sides is also indicative of a stenosis. The *degree of stenosis* is estimated on the basis of the changes of the Doppler spectrum (increased angle-corrected blood flow velocities and spectral broadening in the site of the stenosis, flow disturbances upstream and downstream from the lesion, reduced maximum and mean flow velocities distal to the stenosis). TCCS provides information on the localization of the stenosis. Using frequency-dependent color-coding, the site of the stenosis can be more easily recognized due to the aliasing phenomenon. Additionally, the thickened vessel wall in the area of the stenosis can be imaged in B-mode due to its higher echogenicity (Seidel et al. 1995).

Differentiating between a stenosis and a *vasospasm* can sometimes be problematic. In the case of a stenosis the aliasing phenomenon is usually visible in a circumscribed, short section of the vessel, corresponding to the extension of the stenotic segment, whereas with a vasospasm several vessels are often affected. Increased flow velocities can also be registered in the case of obstructive lesions in the contralateral hemisphere or in extracranial carotid disease due to a *compensatory increase in blood flow through collateralization*. Diagnostic errors can be avoided by considering the findings with all arteries supplying the brain. Of particular clinical relevance is an *occlusion of the middle cerebral artery*. It can arise due to a local thrombosis in an atherosclerotic lesion, or in the case of e.g., vasculitis, moyamoya disease, and coagulopathy. Most often, however it is caused by embolism, with either arterial or cardiac sources for the emboli. An early diagnosis in patients with cerebral ischemia is crucial for the therapeutic strategy – especially in the decision for a thrombolysis.

Sonographic diagnosis of *occlusion* of a cerebral artery can be made when a color-coded signal cannot be obtained at depths of insonation corresponding to that artery, although neighboring arteries can be imaged well. Criteria for the sonographic diagnosis of MCA occlusion in the axial plane include lack of detectable flow in the MCA, a good visualization of the ipsilateral posterior cerebral artery (PCA), and detection of the collateral flow.

In patients with acute stroke contrast enhancement is valuable, especially in those patients whose baseline scans are not of good quality. In such a situation it is important for further diagnostic steps and for therapy to be able to determine whether failure to visualize a cerebral vessel is due to methodological problems or to an occlusion of a cerebral artery. Using *echo-contrast agents* (Levovist, Sonovue) it is possible to obtain more detailed information about the anatomical course of the cerebral arteries. Additionally, new techniques such as use of echo contrast agents for the ultrasonic assessment of a *cerebral parenchyma* will be presented. The potential of the different techniques to visualize cerebral contrast enhancement in different brain areas (such as harmonic imaging, cerebral perfusion techniques) will be discussed.

Conclusion: Color-coded duplex ultrasonography is increasingly accepted as a valuable method in neurovascular diagnostics. In the hands of an *experienced examiner*, it is a reliable tool in the evaluation of cerebrovascular diseases. The main limitation of TCCS, like that of conventional TCD, is the need for an adequate acoustic window which can be overcome with echo contrast agents.

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Intima-Media Thickening of Carotid Artery and Arterial Compliance

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Introduction: Intima-media thickening (IMT) of carotid artery, assessed by non-invasive ultrasonographic B-mode is proposed as marker for atherosclerosis [1]. Its measure is largely employed in observational and interventional epidemiological studies as intermediate or proxy cardiovascular ischemic end-points. Increased IMT is closely associated with known and less well-demonstrated cardiovascular risk factors, with higher prevalence of coronary ischemic accidents, stroke, peripheral artery diseases and, generally, atherosclerosis elsewhere in the arterial system. Recently, Cardiovascular Health Study, GENIC and Rotterdam study have demonstrated that Carotid-IMT was a powerful indicator of incident coronary and cerebral ischemic events. So, high resolution B-mode evaluation of supraaortic vascular arteries is fundamental in the work-up of TIA-Stroke patients and asymptomatic patients.

Methods: Despite the general agreement concerning IMT-carotid definition, the variability of its measurement, between 0.75 to 0.97 [2], is still too elevated for an index with such significant predictive value and for a measure that varies so little annually. The reasons of this variability are related to equipment, ultrasonographic scanning, image recording and storage, but mostly to measuring "in se". The CCA is well insonated by the ultrasonic beam, is easily recognized and easier to identify than the bifurcation or the carotid artery. Moreover, the IMT predictive ischemic risk measured at the CCA is virtually the same as the one measured at the BIF or CI. The CCA far-wall is considered a better measuring target for practical and ultrasonographic reasons: the spatial location of an interface can be better determined when the impedence increases from a less dense element (blood) to a denser structure (intima-layer edge).

IMT VITA Project: The VITA Project is an epidemiological investigation on 15,055 subjects aged 18–65 and enrolled from 1993 to 1997 in Vicenza, Italy (Rodeghiero F). A sub-sample of these subjects were screened to evaluate the genetic and behavioural risk factors for carotid atherosclerosis and cardiovascular events, and to determine the normal values of IMT-CCA in a general-population. This sub-sample is formed by 4,279 Caucasian subjects (2,324 F and 1,955 M) with an enrolment-age = or >40 yrs. From January 2000 to January 2002, 2513 subjects aged 44–72 were enrolled, 1382 females and 1131 males with a median age of 54 years.

Two trained neurologists (B.C., M.R.) performed the ultrasonographic exam with a 7.5 MHz probe-frequency Ecocee SSA-34OA TOSHIBA system. Subjects were examined in the supine position: CCA, BIF, IC, EC were bilaterally insonated with longitudinal (anterior, lateral, posterior) and transverse scans. The plaque was defined as localized focal echo structure encroaching into the vessel lumen widenings of the arterial wall of >1.5 mm.

All subjects had IMT measurements of the CCA far-wall, at least 10 mm of continuous boundary between intima-media and media-adventitia clearly distinguishable and free of plaque, faraway from bifurcation with a digital-acquisition/measurement-software (M'ath, Metris, France). A total of 100 measures in mean were automatically performed on the right and left far-walls and the mean value was considered. All subjects had at least two stored CCA-digitalized-images and, when plaques were found, a videotape was recorded and described with a standardized questionnaire. The images of the all subjects with a plaque and a random sample (10%) of the general population were reviewed in a central reading centre (P.P.) using the same software. Intra and inter-reproducibility have been reported in other studies using the same method for IMT measurement [3]. Anthropometric, laboratory measurements, blood pressure and a standardized questionnaire were obtained. The median CCA-IMT was 0.65 mm. There was an evident age-related increase of CCA-IMT, that resulted in significantly different reference ranges for age (upper 97.5 percentile and 90% CI): age 45–50 (492 subjects): 0.76 (0.74–0.77); age 50–55 (853 s.): 0.82 (0.81–0.84); age 55–60 (831 s.): 0.87 (0.85–0.92); age > 60 (337 s.): 0.90 (0.86–0.93).

The prevalence of atherosclerotic plaques was 19.1% (7.1%, 13.0%, 23.8% and 32.6%). The multivariate analysis of Risk factors for CCA-IMT >97.5 percentiles or plaque is described in Table 1.

The male-gender and hypertension (>160 mm Hg) are closely related to a CC-IMT above the age- adjusted reference limit, whereas male-gender, hypertension, dyslipidemias, smoking are associated with a high probability of having plaques. In conclusion, no major differences are apparent in median IMT between our study and those concerning populations at higher cardiovascular-risk. The presence of plaque is strongly related to major cardiovascular risk factors.

Arterial Compliance: The study of functional alterations of the conduit arteries provide an interesting element in carotid atherosclerosis prevention. Arterial compliance is defined by the ratio between volume and pressure variation:

$$C = \triangle V/\triangle P$$

The reciprocal of compliance is the elastic modulus, an index of arterial stiffness. Both measurements must be made at a given

Table 1

Risk factor	IMT > 97.5		Plaque	
	OR	P	OR	P
Male-gender	2.0	0.001	1.5	<0.001
Triglycerides > 200 mg%	1.0	NS	2.0	<0.001
HDL-Cl < 50 mg%	0.66	0.05	0.83	NS
T-Chol. > 200 mg%	1.3	NS	1.8	0.001
BMI > 25	1.1	NS	1.2	NS
Smoking	1.4	0.05	2.2	<0.001
SBP > 160 mmHg	3.2	<0.001	2.1	<0.001
Antihypertensive drugs	1.0	NS	1.9	<0.001

pressure. Another index is the stiffness index β, given by the equation:

$$\beta = \frac{\{\log_e(Ps - Pd)\}D_d}{(Ds - Dd)}$$

Recently new echo-Doppler techniques have been developed to evaluate viscoelastic properties and thickness of carotid arteries. Study of these functional parameters may provide further information in addition to conventional cardiovascular risk factors and carotid IMT [4].

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CT-Angiography of the Carotid Artery: First Results with a Novel 16-Slice-Spiral-CT Scanner

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Purpose: To evaluate a novel multislice CT system (16-slice-spiral-CT scanner) for the diagnosis of carotid artery stenosis.

Material and Methods: Twenty patients with symptomatic atherosclerotic disease of the carotid arteries were examined with a 16-slice-spiral-CT scanner. Collimation was 16 × 0.75 mm, table speed 36 mm/s (pitch of 1.5), rotation time 0.5 s, tube current was 160 eff.mAs at 120 kV. 60 ml of contrast material was injected with a power injector followed by a saline flush. The start delay was measured with the test bolus method. Interactive multiplanar reformation (iMPR) and thin slab MIP as well as volume rendering were used for image evaluation and presentation. Correlation with Magnetic Resonance Angiography (3D-TOF and CE-MRA) was obtained in each patient.

Results: Scan time was 9 s for a range of 300 mm. This allowed imaging the whole length of the carotid artery (aortic arch to circle of Willis) in a true arterial phase. Pulsation artefacts did not impair the evaluation of the vessels at the level of the aortic arch. Overall image quality of both "source images" and 3D-reconstructions was excellent, due to a reduced voxel size of 0.03 mm^3. Image evaluation and postprocessing (iMPR, MIP) was done within 15 min. iMPR was highly accurate for demonstrating plaque morphology and determining the percentage of the stenosis.

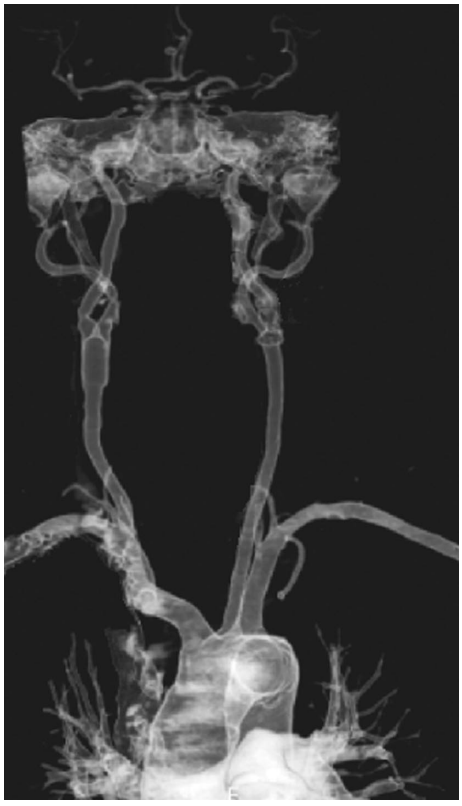

Figure: VRT of the carotid arteries.

Conclusion: For the first time, true arterial phase images of the entire carotid artery with high spatial resolution could be acquired with Spiral-CT. This method offers the potential to replace catheter angiography in the evaluation of carotid artery stenosis and is a fast and cost-effective alternative to MRA.

Hemodynamic Monitoring of the Brain During Carotid Endarterectomy

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Carotid endarterectomy (CEA) is recognized today as the treatment of choice for selected patients with symptomatic and severe extracranial internal carotid artery stenosis. Stroke, myocardial infarction, and death are its major complications. A subtle cognitive decline persisting for several weeks after surgery has been described recently. The incidence of brain infarction ranged between 5% and 7% in the large CEA trials, but it is higher at some centers where the procedure is performed infrequently. Complication rates also vary among surgeons. Impaired perfusion and embolism are the most common causes of perioperative brain infarction.

Transcranial Doppler ultrasound (TCD) monitoring reveals that CEA can be divided into phases characterized by differing degrees of

hemodynamic impairment and brain embolism. The middle cerebral artery on the side of CEA is usually monitored. In most patients, the peak-systolic flow velocity drops to 50% to 75% of preoperative values at cross-clamping, the hemodynamic litmus-test of the operation. Changes in flow velocity parallel changes in cerebral blood flow. In 5% to 15% of cases, the peak-systolic velocity drops to less than 15% of baseline. Patients in this subgroup are suspected to be at a high risk for impaired perfusion and brain ischemia. The variability in the response to clamping is usually ascribed to differences between patients regarding available collateral blood flow channels. Successful shunting reverses the flow velocity decline, with a rebound to 50% to 120% of preoperative values.

Although brain microembolism is ubiquitous during CEA, it has a high incidence at particular phases of the operation. Dissection, shunting, and internal carotid artery closure are high-risk periods. The two-minute interval following clamp release is a particularly active phase for microembolism, and the latter can also persist during the 12-hour period immediately following the operation. More than 25% of all perioperative brain infarcts may occur during the postoperative period. Both gaseous bubbles and particulate microemboli occur at clamp release, but microemboli during the dissection phase and immediate postoperative period are thought to consist mostly of particulate material. Microembolism during the dissection and postoperative phases has been associated with asymptomatic brain infarction, with small and subcortical lesions seen on magnetic resonance imaging. In addition, during the immediate postoperative phase, it is associated with clinically detectable cognitive impairment and brain infarction.

Thus, more than 10 years of TCD monitoring has shown that CEA is not a black box, and that the different phases of the operation present different challenges and opportunities for therapeutic intervention. These observations have been used to improve the selection of patients for shunting and to treat microembolism with antithrombotic agents, such as dextran-40 and a platelet glycoprotein IIB/IIIA receptor antagonist, during the immediate postoperative phase of the operation.

The number of prospective studies establishing the efficacy of TCD monitoring in reducing the incidence of brain infarction remains limited. Based on data from several published studies, an 85% or more drop in the middle cerebral artery peak-systolic velocity at cross-clamping is considered an acceptable criterion for shunting at several medical centers. More than 25 microemboli per 10 minute interval or more than 50 microemboli per hour during the immediate postoperative period may be considered a sufficient reason for treatment with dextran-40. These criteria are considered tentative, however, and the need for appropriately designed investigations to establish definitive TCD criteria for therapeutic intervention is recognized.

Transcranial Doppler Imaging According to Evidence Based Medicine

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In the last several years Transcranial Doppler examination (TCD) has turned out to be one of the most increasingly useful tool in the field of exploration of intracranial vessels. Even though it remains a matter of debate the relationship between cerebral blood flow and the flow velocities of the circle of Willis measured by TCD, this technique remains one of the most important non invasive methods for assessing and monitoring intracranial cerebral hemodynamics. Identification of cerebral arteries is based on the anatomical approach, the angulation of the probe, the depth of the insonation, the direction of the blood flow and the anatomical relationship between intracranial vessels.

Established application of Transcranial Doppler Sonography in the clinical and experimental setting are reported below:

- Diagnosis of intracranial occlusive disease
- Auxiliary test for extracranial occlusive disease
- Evaluation of the hemodynamic effects of extracranial occlusive disease on intracranial blood flow
- Detection and identification of arteriovenous malformations
- Preoperative compression tests for the evaluation of the functional capacities of the circle of Willis
- Detection of the cardiac right-to-left shunt (patent foramen ovale and paradoxical embolism)
- Monitoring and follow-up of vasospasm in subarachnoid hemorrhage and migraine
- Monitoring and follow-up of spontaneous or pharmacological ricanalization of occluded vessels
- Evaluation of collateral pathways after occluding interventions
- Monitoring during neuroradiological interventions
- Monitoring during carotid endarterectomy
- Monitoring during cardiac surgery
- Evaluation of brain death
- Evaluation of vasomotor reactivity with CO_2 or with vasoactive drugs
- Stimulation of visual cortex
- Neuropsychologic tasks for hemispheric dominance

A recent paper on the role of NeuroSonology in cerebral ischemia reported that TCD will become in the future the diagnostic technique of choice in the early phase of cerebral ischemia. The authors suggest the three major potential values of TCD in the acute phase of cerebral infarction:

- A diagnostic value in the early identification of stenoses and occlusions of cerebral arteries with contributions to the etiologic diagnosis and the pathophysiology of stroke
- A prognostic value with prompt informations on markers of stroke progression
- A role in therapeutic decision-making particularly in the selection of patients for thrombolytic treatment

A significant improvement in the assessment of intracranial hemodynamics has been obtained with the introduction of Transcranial Color Coded Doppler Sonography (TCCS) that allows the identification of a wide variety of cerebrovascular diseases such as cerebral infarcts and hematomas, arteriosclerotic vascular changes, arteriovenous malformations and aneurysms.

With this technique it is also possible to obtain images of parenchymal abnormalities in patients with tumors or degenerative disorders of the central nervous system. TCCS permits the identification of intracranial vessels using real time localization of vascular and parenchymal alterations by color imaging superimposed on the white and black B-mode images.

The main advantage of Transcranial Color Coded Imaging of the brain vessels is its ability to permit angle-corrected determination of

Doppler flow velocities. Comparison between conventional TCD and TCCS reported a good correlation between intracranial hemodynamic parameters with a 10 to 15% improvement of flow velocities on TCCS that allowed an improved recording quality and interexaminer reproducibility and a higher detection rate of anatomically difficult localizations.

Transpulmonary stable ultrasound contrast agents improve the quality of Doppler signal and the intensity of transcranial imaging allowing a wide variety of clinical applications.

TCCS and contrast agents can identify and further assess by Doppler sampling the intracranial venous system with clear definition of the inferior sagittal and straight sinuses, the inferior cerebral vein and the vein of Galen. This technique will probably be in the future of utmost importance in monitoring cerebral venous thrombosis.

TCCS with contrast enhancement will also play a fundamental role in the identification of aneurysms and in the postoperative and postinterventional follow-up of patients with arteriovenous malformations.

Due to interactions of ultrasound waves with brain tissue, TCCS may be important in the evaluation of brain tumor size, in the differentiation of tumor components and in the identification of peritumoral tissue. The detection of vascularization of brain tumors with contrast enhanced TCCS has shown that this technique will provide further informations about the biology of different tumors so that it will be possible to have a more precise characterization of the lesion allowing to distinguish between radionecrosis, tumor progression or recurrence.

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Brain CT-Scan in Acute Stroke

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Despite the sophisticated information derived from the routinary use of MRI in cerebro-vascular pathology, the CT scan remain anyhow the first investigation of choice in the acute stroke.

CT study is available in every emergency care unit and may be rapidly performed in few minutes for standard imaging. The main questions, in this type of patients, are immediately resolved by CT scan: is the ictal insult hemorrhagic or ischemic? are there indirect findings related to recent ischemic stroke? is it possible to determine the vascular interested territory, related to the clinical findings? Precocious, iperacute ischemic signs are the iperdensity of the thrombosed vessel (most frequently the middle cerebral artery or its main branches), the loss of white/gray matter gradient density (lenticular sign), an early parenchimal hypodensity, the sulci effacement.

Moreover, the improvement of CT techniques, particularly of spiral CT angiography, may directly identificate the occluded vessel in ischemic stroke, the "guilty" aneurism in subaracnoid hemorrhage, the thrombosed basilar artery in a comatous patient, while software implementations allow cerebral perfusional studies, adding further useful pathophysiological information.

The Role of Emission Tomography in the Study of Brain Function

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Emission tomographic methods (single photon emission computerised tomography (SPECT) and positron emission tomography (PET)) allow in vivo measurements of multiple parameters of regional cerebral physiology, such as blood flow, oxidative and glucose metabolism. In addition they are unique in evaluation the multiple neurotransmitter/neuroreceptor systems of the human brain. These potentialities will become more and more important as the field of research moves from the system to the cellular and molecular levels of investigation.

Functional neuroimaging studies will also complement other methods in clinical and research protocols. In parallel with methods for the *in vivo* study of brain anatomy (CT and MRI), the assessment of the functioning of the human brain is applied both in patients and in normal subjects. Anatomo-clinical and functional imaging studies are used to estimate the effects of neurological and psychiatric diseases.

The two main aims of research are:

a. *theoretical/speculative*, in the field of Cognitive Neuroscience, to clarify the in vivo functional correlates of the mental activity.
b. *applied studies*, to increase the understanding of biological and clinical aspects of neurological and psychiatric diseases, to provide useful information for prevention and early diagnosis programs, and for pharmacological and rehabilitative treatments.

Main research fields include:

a. *the in-depth study of single cases or comparable group* of patients with cognitive deficits, using the tools of cognitive neuropsychology, combined with functional imaging methods, such as 18F-FDG PET. These are mainly applied to the study of patients with dementia and stroke in chronic phase. In particular, the observed changes in perfusion/metabolism have been correlated with the behavioural modifications measured in patients with neuropsychological testing (Perani et al. 1993).
Recent studies have shown that vascular risk factor play a role in the development of dementia. Long-standing hypertension may lead to the development of white matter lesions and dementia by promoting hyalinisation of blood vessels walls and localised atherosclerosis that lead to a disconnection of subcortical-cortical

association pathways and the development of dementia. It is important to evaluate the role of functional neuroimaging techniques to study the early correlates of cognitive impairment in the hypertensive patients to be used in clinical trials aiming to evaluate the potential of antihypertensive drugs in the prevention of the cerebrovascular complication of hypertension.

b. *the study of the functional recovery after stroke*. Functional neuroimaging methods (in particular, positron emission tomography (PET)) have been shown to provide relevant contributions to the *in vivo* study of recovery mechanisms in neurological patients. Two different approaches have been used: measurement of regional cerebral perfusion or metabolism at rest, before and after recovery, or activation studies, in which the measurement of brain perfusion is performed while the recovered patients are engaged in the actual performance of a task. Previous studies of recovery from cognitive disorders due to cerebrovascular lesions have shown its correlation with regression of functional impairment in anatomically undamaged brain areas (diaschisis), which is easily identifiable with functional imaging. These methods can be used also to evaluate the effects of rehabilitation and of pharmacological treatments. One limitation of the studies of recovery of neuropsychological functions using PET or SPECT steady-state techniques is the lack of a direct correlation between regional functional changes and specific behaviour. Activation studies are more adequate for a fine-grained correlation of modifications in pattern of cerebral activation and behavioural recovery. The variation of rCBF in a test-retest paradigm while the patients were performing specific cognitive tasks has been reported. PET activation studies have been performed in patients who had recovered from motor impairments (Weiller et al. 1993), aphasia (Weiller et al. 1995) and unilateral neglect (Pizzamiglio et al. 1998). These studies have reported an extensive functional re-organisation and the crucial cerebral activations in cortical regions similar to those observed in normal subjects, as well as of regions in the contralateral, undamaged hemisphere.

c. *the in-vivo study of neural correlates of mental activity*. PET studies have shown the close coupling among cerebral blood flow, metabolism and cerebral function not only after exposure to simple sensory stimuli or during simple motor activities, but also with more complex mental tasks. The results so far achieved have provided the mapping of the functional circuits subserving cognitive and sensorimotor functions, such as attention, language, memory and visual recognition (see for review Perani and Cappa 1998). In addition, cognitive activation studies have been addressed to the areas of language and memory, in bilingual subjects and in dyslexic patients.

d. *neuropharmacological studies by tomographic imaging techniques* to measure the distribution and regional function of various molecular components that is at the basis of the neuronal communication like receptors, membrane carriers, neurotransmitters and enzymes. The central nervous system controls behavioural and humoral processes by modulating the transfer of information through complex neurochemical interaction. These interactions occur through different neurotransmitter systems and functions to maintain homeostasis and to control each different cognitive or behavioural process in physiological condition or their alteration during pathologies. A new strategy of PET based psychopharmacology is to develop tools that can be used to non-invasively measure changes of neurotransmitters interaction in neurological and psychiatric diseases. In order to understand the function of a particular neuronal circuit and the relative transmission systems that are involved, studies have been be carried out in absence of a pharmacological treatment, after stimulating with active drugs the transmission system of interest. PET methods represent a unique tool for the study of the neurochemistry of the brain in normal and in disease and for the characterisation of pharmacokinetic and pharmacodynamic properties of active drugs. Recent findings on the sensitivity of [^{11}C]raclopride D2 dopamine receptors binding to changes in extracellular dopamine concentration, suggest the use of this tracer as a new tool for the in vivo PET measurement of the modulation of dopaminergic system by pharmacological or behavioural stimulation. This method has been used to study the modulation of dopaminergic system by serotoninergic or GABAergic drugs such as benzodiazepine, vigabatrin or SSRI inhibitors and the activity of dopaminergic system in psychotic patients after amphetamine challenge (see for review Moresco et al. 2001).

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Ultrasound Perfusion Imaging of the Adult Human Brain

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In this review, methodological aspects of cerebral perfusion imaging with ultrasound signal enhancing agents will be described.

By means of harmonic imaging technology (conventional harmonic and pulse-inversion harmonic imaging) and non-harmonic imaging technology (contrast burst and time-variance imaging), human cerebral perfusion can be depicted as a two-dimensional scan. The three major principles of perfusion measurement by ultrasound are analysis of the bolus kinetics and during contrast infusion analysis of the refill as well as the destruction kinetics of contrast agents in the brain parenchyma.

Using the bolus method, hypoperfused areas in stroke patients can be visualised and parameter images of wash-in and wash-out curves can be generated off-line. Clinical examples will be presented.

The recently developed theory on the refill kinetics and the destruction kinetics of UCA enable us to calculate quantitative parameters for the description of the cerebral microcirculation, being less affected by the depth dependence of the contrast effect. These parameters, too, can be visualised as parameter images.

The ultrasound methods described in this review represent new minimal-invasive bedside techniques for analysing brain perfusion, which extend the diagnostic potential of conventional ultrasound technology for the investigation of the cerebral macrocirculation.

Ultrasound Examination Techniques in Patients with Stroke

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The advent of cerebral computerized tomography and the use of cardiac and cerebrovascular ultrasound techniques, in patients with cerebrovascular accidents, have allowed for distinguishing and accurately classifying the two main stroke etiologies (thrombosis and hemorrhage). These techniques have enhanced our understanding of the different mechanisms involved in acute brain ischemia (atherothrombosis and cerebral embolism) [1, 2]. Ischemia accounts for approximately 75% of all strokes [2]. Based on the NINCDS report [2], 17 percent of cerebral brain infarcts can be attributed to carotid artery disease; 28% are lacunar, 15 percent are cardio-embolic and the rest are most probably due to embolisms of unknown origin. While CT scanning allows for distinguishing between ischemic and lacunar infarction, ultrasound techniques are used to identify the site of the obstruction and to search for all possible embolic sources.

Carotid and Vertebral Arteries

When the proximal internal carotid artery is sonographically patent and the conventional Doppler shows a dampened signal with a high resistance velocity profile, the distal internal carotid artery is most probably occluded. A proximal occlusion can be directly demonstrated when the vascular lumen appears to be totally occupied by echogenic material: if no Doppler signal is present occlusion is total. Pre-occlusion can be diagnosed when a Doppler signal is still detectable within a long thin residual lumen ("string sign").

In those patients with previous cerebrovascular events and greater than 70% stenosis, carotid surgery, instead of medical treatment should be carried out [3]. Although angiography is considered the gold standard to assess disease severity, the carotid duplex is currently the most widely used diagnostic procedure for grading carotid stenosis. In experienced hands, the ultrasound technique is more than 90% accurate [4]. Its results are well correlated with both angiography [5] and pathological findings [6]. Thus, carotid surgery is being undertaken based solely on duplex values [7]. The transcranial Doppler (TCD) detects the intracranial effects of hemodynamic carotid stenosis and can be used to validate the results of the carotid duplex with a 95% sensitivity level [8]. Invasive angiography is now only indicated in selected cases. Since the carotid duplex and transcranial color-coded sonography (TCCS) are routinely performed in all patients with carotid stenosis prior to surgery, the number of angiographies in our department has significantly dropped, but without any change in surgical complications.

Transcranial Doppler

During acute stroke, TCD can be used to detect intra and extracranial disease and to sequentially monitor the patency of cerebral arteries [9]. TCD can reveal a focal stenosis and/or a blockage of a cerebral vessel; it can exclude the presence of subarachnoid hemorrhage. In combination with the carotid duplex, transcranial examination can demonstrate occlusion of a carotid artery. At TCD follow-up, intracranial flow changes can provide useful prognostic information: after reperfusion, limited flow velocity most probably indicates a negative outcome [9]. In recent years, the original limitations of TCD (low signal to noise ratio, inadequate acoustic window, poor visualization of the posterior circulation) have been overcome by the use of transcranial color-coded sonography (TCCS), especially when new contrast agents are used in combination with power imaging techniques [10]. TCCS is more sensitive than TCD in detecting middle cerebral artery occlusions and is better suited than the latter in following up any non-invasive demonstration of early recanalization, after thrombolytic therapy [11].

Echocardiography and Ultrasound Evaluation of the Aortic Arch

Aortic and cardiac two-dimensional sonography can demonstrate thrombotic formations in the left cardiac chambers and detect thick unstable plaques in the ascending aorta: these may be responsible for embolic events [12, 13]. If other sources of embolic events have been excluded, the finding of a patent foramen ovalis by 2D sonography may indicate a paradoxical embolism as a pathogenetic mechanism.

In the stroke patient, the combined use of cardiac and cerebrovascular ultrasound examinations provides a unique tool for effectively seeking and identifying the possible causes of a cerebral ischemic event, both in an acute setting and in those subjects with previous cerebral events.

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Stroke and Cerebral Ischemia: Challenging Cases

Different Diagnostic Hypothesis in a Case of Stroke

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An 80-year-old woman was admitted in the Florence University Hospital on October 11th 2002 because of angina at rest and a positive stress-echo test (inducible ischemia in the circumflex artery area). Her risk factors were previous history of smoking, hypertension, hypercholesterolemia, familiarity for vascular disease, a history of CAD (unstable angina, previous AMI, previous CABG) and TIA (left hemiparesis) and a slightly reduced EF (49%). She also had a mitral prosthetic valve (Starr Edwards). On October 12th the patient underwent PTCA with double stenting of a dominant right coronary artery and started ticlopidine treatment [1] and oral anticoagulants administration (warfarin and heparin until the INR was in range) [2]; the INR was 1.4. On October 15th while attempting to stand up she fell down, without showing any major traumatic lesion; after several hours a big hematoma appeared in the right groin; the blood pressure dropped from 130/70 to 90/50 mm Hg and the hemoglobin concentration decreased from 12.4 to 8.3 g/dl in 24 hours. She received blood transfusions and was rehydrated. A CT scan demonstrated an hemorrhage from a branch of the right profound femoral artery, that was repaired, during arteriography, with multiple spiral embolizations. On October 16th at 8.00 am the INR was 5 vitamin K was administrated. In the evening the patient appeared to be confused and after several hours developed a sudden monoparesis of the left arm with hyperreflexia of the left leg, a positive ipsilateral Babinski sign, and no defect of cranial nerve function. At 5.00 pm the INR was 4.5. Because of the high INR, the association of warfarin therapy to GP IIb-IIIa antagonists antiplatelets and a recent trauma, a differential diagnosis between ischemic and hemorrhagic stroke was necessary. A CT scan ruled out hemorrhagic lesions. The possible causes of ischemic stroke were then considered: the cardioembolic source, since she had a mechanical Starr Edwards valve; an embolic source from a carotid atherosclerotic plaque, given the association with CAD; a border-zone ischemia, given the recent acute anemia and hypotension in a chronically hypertensive patient, hence with a right-shifted cerebral autoregulation curve [3, 4, 5, 6, 7]. The TEE did not show thrombi or smoke-effect in the left atrium. The carotids showed extensive atherosclerotic disease with calcific plaques less than 5 mm thick – that implies a low embolic risk – without significant stenosis. During the following days the patient gradually recovered from the monoparesis. The most reliable diagnosis seems to be lacunar stroke due to hypovolemia with anemia and hypotension in a chronically hypertensive patient. A second CT scan did not show cortical ischemic lesions, confirming our diagnosis. Another problem to discuss was the safety of the association of anticoagulants and antiplatelets [8, 9, 10, 11]. Finally we underscore the clinical query of the treatment of patient with non significative carotid stenosis, symptomatic or asymptomatic, and the identification of the "true symptomatic" patients [12, 13].

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Transcranial Color-Coded Doppler (TCCD) is a Sensitive and Specific Test to Determine Thrombolysis-Eligible Patients with Acute Stroke

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One challenge of contemporary ischemic stroke therapy is to reverse the neurological deficit by reopening intracranial vessels with thrombolytic agents, in fact in 1996 the US Food and Drug

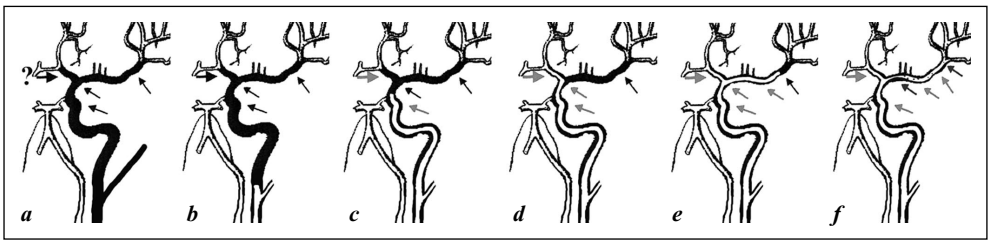

Figure 1: ***a*** Carotid common artery and internal carotid and middle cerebral artery occlusion. ***b*** Carotid internal artery and middle cerebral artery and anterior cerebral artery occlusion. ***c*** T occlusion. ***d*** Middle cerebral artery occlusion. ***e*** M2 of middle cerebral artery occlusion. ***f*** intracranial stenosis of the middle cerebral artery M1.

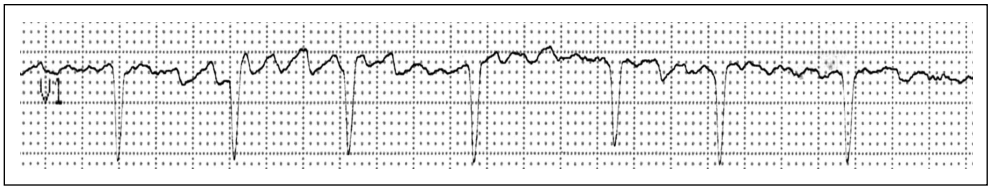

Figure 2: Atrial fibrillation.

Administration approved the intravenous recombinant tissue plasminogen activator (rTPA) in acute stroke on the basis of the NINDS (The National Institute of Neurological Disorders and Stroke) trial data [1, 2]. Neurovascular imaging is essential to the development of acute stroke therapies [3] because there is a great heterogeneity in the pathophysiology of ischemic stroke. Rapid identification of the location and severity of arterial obstruction provides important information that aids in the triage of acute stroke patients. TCCD is a noninvasive, nonionizing and relative rapid method of assessing anatomic and hemodynamic patterns of cerebral circulation [1], in fact it allows real-time assessment of the flow velocity, pulsatility and microembolic signals [3]. Recently TCCD has been evaluated in detail and validated in the setting of acute ischemia [4]. TCCD has been reported to have a sensitivity of 87.5% a specificity of 88.6%, positive predictive value of 87.5% and negative predictive value of 88.6% compared with angiography in patients with occlusion and stenosis of cerebral vessels [3]. The TCCD is a useful test in the emergency stroke department for evaluating thrombolysis eligible patients, for monitoring the vessels recanalization after rTPA therapy, for evaluating the presence of cerebral collateral circulation and the cerebral re-perfusion by-means the densitometry study [1]. There are several sites of intracranial artery occlusions that may benefit in different way to thrombolytic therapy. In particular the middle cerebral artery present different site of occlusive stenosis: the T occlusion (middle and anterior arteries and C1 tract of carotid syphon) has presented a partial response to thrombolysis, while the occlusion of MCA in presence of patent anterior cerebral artery and carotid syphon as well as the distal occlusion of MCA in the M2 tract have major benefit from thrombolytic therapy. Moreover, the contemporary occlusion of internal carotid artery and MCA responded to rTPA with a difficult recanalization and a high cerebral hemorrhagic risk (fig. 1). Among the thrombolysis-eligible subjects even patients with atrial fibrillation are included independently from the intracranial occlusion site (fig. 2).

However, thrombolysis cannot sufficiently treat the embolizing carotid focus, since the stenosing plaque remains. The combination of thrombolysis and thrombendarterectomy offers the possibility to treat embolus and focus simultaneously. The TCCD is useful to asses the presence of intracranial occlusions or stenosis in patients with stroke in evolution or crescendo transient ischemic attacks (cTIAs) before the surgical therapy. In fact, the emergency carotid endarterectomy (CEA) may be indicated in carotid related progressive stroke and cTIAs due to an occlusive thrombus in internal carotid artery [5].

In our Stroke Unit 16 patients with acute stroke were treated: 14 patients were submitted to endovenous rTPA therapy and 1 patient was treated with intraarterial thrombolysis in the last one CEA was indicated. All patients presented a complete recovery without bleeding complication. All patients treated with thrombolysis presented an MCA occlusion and received rTPA within 3 hours from the onset of neurological deficits in a dose of 0.9 mg/kg. Moreover, with serial TCCD we have observed that the time window for the recanalization ranged between 4 and 12 hours and the fast recanalization might be considered a positive prognostic factor for a good outcome.

In summary TCCD is both sensitive and specific in determining arterial occlusion and stenosis in acute cerebral ischemia. Moreover this method is noninvasive and relatively fast diagnostic for selecting thrombolysis-eligible patients and for monitoring the recanalization and resumption of flow that is correlated to the patient prognosis.

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Angioplasty and Stenting of the Carotid Arteries in Patients with Cerebral Ischemic Stroke

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Among all the neurologic diseases of adult life the cerebrovascular ones clearly rank first in frequency and importance. The effects of acute internal carotid occlusion on brain tissue vary, depending upon the location and extension of the thrombus (intracranial carotid bifurcation) in relation to available collateral flow and anastomotic channels as well as the presence of concomitant cerebral embolism. There are two mechanisms by which strokes arise from an acute occlusion of the internal carotid artery. First an embolus arising from the thrombosis above the occlusion may cause a stroke in any of the tributary vessels of the internal carotid artery and their branches (artery-to-artery embolism). Second, internal carotid artery occlusion may lead to ischemia in the region of lowest perfusion between branch vessels (watershed or border-zone infarct). The clinical picture may be extremely pleomorphic ranging from mild transitory focal deficits (TIAs) to a severe impairment of consciousness. The therapeutic options (endovascular or surgical) of acute internal carotid occlusion should take into account the results of both anatomic (morphologic imaging) and functional (perfusion) studies. Whenever a cerebral ischemic stroke from acute internal carotid occlusion occurs, the main goal is to reestablish as soon as possible the patency of intracranial vessels by means of intra-arterial fibrinolysis improving cerebral perfusion and enhancing the collateral flow. In case of an isolated cerebral hemisphere due to unavailability of collateral circulation disobstruction of the occluded internal carotid artery should be attempted first by whatever mean is available (mechanical clot removal devices, PTA and/or intra-arterial fibrinolysis). Once cerebral flow and tissue perfusion are improved by partial or complete restoration of vessel patency, the natural fibrinolytic pathways are enhanced by the arrival of fresh plasminogen whereas platelet aggregation and coagulation phenomena are obstacled hindering "in loco" new clot generation. Furthermore restoration of an adequate cerebral flow improves the anticoagulant response of the endothelium hampering the deposition of fibrin clots at level of the microcirculation ("no reflow phenomenon"). Intra-arterial fibrinolysis followed by angioplasty (PTA) and/or stenting of carotid arteries are aimed to facilitate all the aforementioned mechanisms limiting the extent of tissue necrosis in the infarcted territory. We report intra-arterial fibrinolysis and subsequent PTA and stenting in two patients with cerebral embolic ischemic stroke from acute occlusion of the internal carotid artery. In one patient acute thrombotic occlusion of the internal carotid artery occurred on an atherosclerotic hemodynamically significant stenosis and in the other patient on a spontaneous dissection at level of the petrous portion of the internal carotid artery. In both cases locoregional administration of 800,000 or 1,200,000 IU of Urokinase (UK) respectively through the microcatheter restored internal carotid lumen patency. The latter was followed in one case by successful PTA at the origin of the internal carotid artery and subsequent, fibrinolysis plus PTA of a clot at level of the M1 tract of the ispilateral middle cerebral artery. In the other case internal carotid flow restoration was followed by deployment of two consecutive overlapped stents in the dissected tract. In both our cases after procedure completion systemic anticoagulation (heparin) was continued for 72 hrs (APTT 2–3 times the baseline value) while instituting antiplatelet therapy (Ticlopidine and ASA). Alternatively a more rapid antiplatelet therapy may be obtained by intravenous administration of monoclonal antibodies to platelet GPIIb/IIIa receptors (abciximab Reopro; Eli Lillyand Co, Indianapolis, IN). This agent inhibits the binding of fibrinogen to platelets and thus inhibits platelet aggregation. Intravenously administered abciximab is a short acting agent with an initial half-life of 10 min and a second-phase half-life of 30 min. Platelet function gradually recovers during a period of 48 hrs. The rationale for the administration of abciximab is to avoid systemic heparinization that is known to cause together with intra-arterial fibrinolysis a higher rate of hemorrhagic complications of the infarcted cerebral area due to reperfusion. Reports on the iv administration of GPIIb/IIa inhibitors after intra-arterial fibrinolysis seems to guarantee an high rate of success in restoring vessel patency without a significant increase in the number of hemorrhagic complications. However it is noteworthy that in both our cases the association of intra-arterial fibrinolysis and anticoagulant-antiplatelet therapy did not determine hemorrhagic complications. Angioplasty and stenting of the carotid arteries represent new therapeutic options in patients with acute carotid occlusion and cerebral ischemic stroke. Their employ associated to intra-arterial fibrinolysis (thromboembolic ictus) may urge to change the postprocedural therapeutic protocol in favor of antiplatelet rather than anticoagulant drugs. However, the consequences of such hypothesis are not fully understood and the experience of neuroradiologists as well as the progress of endovascular devices (protection devices) and new drugs are necessary to decrease the intra-periprocedural risk and improve the clinical management and outcome of patients.

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Reversible Early CT Scan Signs of Cerebral Ischemia After Endovascular Carotid Stenting

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Early CT signs of ischemic stroke, due to an increase in tissue water content, are commonly attributed to cytotoxic edema and development of irreversible injury [1], therefore they are considered prognostically favorable. Jaillard et al [2] comparing early CT signs with DWI – PWIMRI demonstrated that early signs of cerebral ischemia at CT may represent a reversible process.

We describe a case of a 73 year old male hypertensive and hypercholesterolemic with a history of a previous left carotid TIA. The patient was admitted to the Interventional Cardiology Department of our hospital to be submitted to an endovascular treatment with positioning of a stent device in the left internal carotid artery, which revealed to be significantly stenotic at Doppler ultrasonography. In order to enhance the safety of carotid stenting procedure a new occlusive device (Parodi Anti-Embolization Catheter, PAEC), with an occlusion balloon attached to the outside of the catheter at the distal end was utilized; the characteristics of this device allow to create a reversal of flow from the internal carotid artery before and during stent deployment and post-dilatation. During the procedure the balloon was inflated twice for a few seconds and the patient after 20 seconds became aphasic and unresponsive; both times balloon deflation ripristined normal patient conditions. Thirty seconds after stent dilatation with balloon still inflated, the patient again became unresponsive, aphasic and right sided hemiparetic, balloon was promptly deflated without resolution of symptoms. An angiogram with selective injection of 10 cc iodinated contrast media in both common carotid arteries did not reveal occlusion of major and distal cortical branches. A CT scan performed half an hour after onset of symptoms demonstrated the presence of diffuse hyperdensity of the cerebral fronto-parietal-occipital cortex, corresponding to the left carotid artery territory (fig. 1). The diffuse hyperdensity, related to the presence of the contrast media, was associated with cortical sulci effacement of the left hemisphere. The patient was treated with steroids and mannitol. The day after the patient was responsive but still aphasic and right sided hemiparetic. A second CT scan revealed reduction of the previous described contrast hyperdensity and sulci effacement. Thirty-six hours later neurologic evaluation revealed hemiparesis reduction and almost complete resolution of aphasia. CT scan revealed normal cortex density with normal difference in cortex and white matter contrast resolution. Magnetic Resonance Imaging, performed in order to better define the entity of cerebral ischemic damage, revealed the presence of small ischemic lesions located in the subcortical white matter and excluded the presence of left hemispheric ischemic infarction (fig. 2). The patient presented complete resolution of symptoms after one week from the procedure.

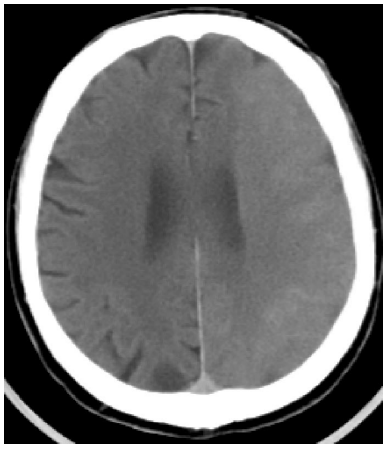

Figure 1: CT scan performed 30 minutes after onset of symptoms. Diffuse left hemispheric cortical-subcortical hyperdensity associated to sulci effacement.

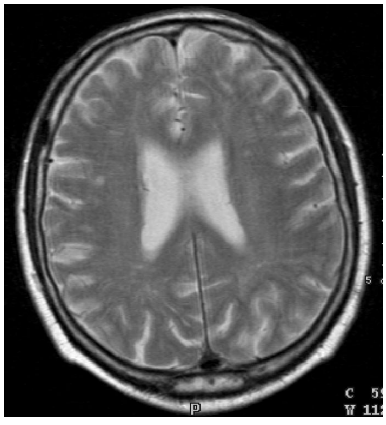

Figure 2: MR.T2WI. Small ischemic subcortical ischemic lesions with no evidence of left hemispheric infarction.

This case demonstrates a reversible alteration on CT in the territory of the left internal carotid artery in a patient with a prolonged ischemia of the same vascular territory. We can postulate that the acute effacement of the left hemispheric sulci and relative hyperdensity could be related to an hyperhemic acute condition with increase of left hemispheric blood volume, after the transitory hypoperfusion due to balloon occlusion. The presence of the cortical hyperdensity during the first 36 hours after the onset of ischemia should be related to some minor impairment of capillary and or arteriolar vessels endothelium. These vessels were presumably chronically dilated in a patient with a long-standing left hemispheric hypoperfusion.

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Carotid Surgery and Interventional Procedures for Stroke Prevention

Evidence Based Treatment: Carotid Endarterectomy

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To achieve prophylaxis of ischemic stroke, carotid surgery should be safe, durable and effective. Appropriate indications, careful preoperative evaluation, safe intraoperative cerebral monitoring and protection, precise intraoperative quality control, low perioperative complication rates and long-term evaluation of results are all key-factors in making carotid endarterectomy (CEA) an effective procedure in stroke prevention.

Indications for surgery are today well established as a result of international randomised trials: NASCET [1] and ECST [2] trials have demonstrated the effectiveness of CEA in stroke prevention in patients with symptomatic >70% carotid stenoses with respect to medical treatment alone; also in patients with moderate (50 to 69%) symptomatic carotid stenosis, CEA was demonstrated to be superior to best medical treatment. In patients with symptomatic <50% carotid stenosis, surgery is not recommended.

The indications for surgery in patients with asymptomatic carotid stenosis are more controversial: the only published randomized trial was ACAS trial [3], which demonstrated the effectiveness of surgery in stroke prevention in patients with >60% carotid stenosis when surgical risk is maintained under 3%; this was also the recommendation of AHA Guidelines on stroke prevention [4].

However, even if the mild advantage of surgery in asymptomatic patients is well accepted, the need for identification of high-risk asymptomatic patients is recognised by Cochrane Study Group [5] recent metanalysis. At the moment, two randomised trials, ACSRS and ACST, are on the way, aiming at the identification of asymptomatic patients at higher risk of stroke, who can obtain more advantage from surgery than from conservative treatment.

There is no evidence in Literature concerning ideal preoperative diagnostic evaluation; at the moment, first level diagnostic instrument is duplex scanning; most studies in Literature suggest that the combination of duplex scanning and non invasive complementary imaging (CTA, MRA) is the gold standard in planning surgical intervention. The use of angiography is now limited to patients with more complex lesions or when results of duplex and CTA (or MRA) disagree [6].

The choice of anaesthesiological approach, of surgical technique and of appropriate cerebral monitoring and protection is basically for CEA to be successful; in fact, most neurological complications of carotid surgery happen in perioperative moment.

However, there is again no evidence concerning the best intraoperative option: there are no differences in terms of stroke, death and cardiovascular complications between local and general anaesthesia [7]. Similar results are obtained when comparing different surgical techniques (primary closure, patch closure, eversion) [8] and different cerebral protection methods (routine shunt, no shunt, selective use of shunt on the basis of cerebral monitoring) [9, 10].

In postoperative period, it is important to perform a long-term surveillance program with duplex scanning, to identify the presence of significative restenosis and to monitor the evolution of contralateral carotid artery lesions. There is no evidence concerning the ideal timing and frequence of postoperative controls. At the moment, considering that symptomatic restenosis is relatively uncommon and there is no correlation between restenosis and ipsilateral symptoms [11], it is universally accepted to perform a "mild intensity" control program (1, 6, 12 months and then annually), with more frequent controls in patients at high risk of restenosis or with severe contralateral stenosis.

In last years, the use of endovascular techniques has been proposed also in patients with carotid stenosis. There are several published series in Literature, however most of these studies included few patients, with no randomization and poor statistical analysis.

There is only one published randomized trial, CAVATAS trial which demonstrated better results for carotid stenting but was severely criticized for the unacceptable complication rates both in surgical and endovascular group.

At the moment, there is no evidence supporting the effectiveness of carotid artery stenting in stroke prevention.

Finally, available evidences in carotid surgery can be resumed in four key-points:

1. Surgery is the treatment of choice in patients with symptomatic severe or moderate stenosis.
2. Surgery is effective in stroke prevention in patients with severe asymptomatic stenosis when surgical risk is lower than 3%. There is the need for identifying high-risk subset of asymptomatic patients.
3. The choice of appropriate technical strategies is highly dependent on experience of single surgical group.
4. The effectiveness of alternative approaches should be validated against surgical gold standard.

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Carotid Angioplasty and Stenting with and without Cerebral Protection Devices in a Consecutive Series of 461 Patients

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Background: Carotid angioplasty and stenting is now accepted as a less invasive technique which provides an attractive alternative for many patients, particularly those with significant co-morbidities. The primary endpoint of this study was to evaluate the procedural success rate and early neurological complications (during the procedure and the hospital stay) in 461 consecutive patients enrolled to undergo an endovascular treatment of carotid critical stenosis, and to evaluate the impact of cerebral protection devices analyzing the differences between protected and non-protected procedures.

Methods: From June 1997 to May 2002 a total of 461 consecutive patients (347 males and 114 females, mean age 70.09 ± 7.7) underwent percutaneous angioplasty and/or stenting of the extracranial carotid artery. In the first 126 patients (group A – 27.33%) the carotid angioplasty and stenting procedure was performed without cerebral protection devices. In the second 335 patients (group B – 72.66%) the endovascular procedure was conducted under cerebral protection, by using several types of devices.

The used cerebral protection devices were: Angioguard Filter (167 patients, 49.85%); Trap Filter (56 patients, 16.71%); Mednova Neuroshield (41 patients, 12.23%); Epi Filter (31 patients, 9.25%); PercuSurge Occlusive Balloon (25 patients, 7.46%); Arteria Parodi Device (7 patients, 2.08%); Moma Device (7 patients, 2.08%); Medicorp Occlusive Balloon (1 patient, 0.29%).

Results: Percutaneous procedure was effective in 459/461 patients (99.56%).

In one case (0.21%) the endovascular treatment was ineffective because of spiral dissection of LICA (major asymptomatic complication) distal to the stenosis site due to PercuSurge occlusive balloon vessel injury. In one case (0.21%) despite the good angiographic final result, the endovascular procedure was ineffective because of the 0.014 wire of the Angioguard system remained trapped in the proximal edge of a Palmaz P205 stent placed in the common carotid artery. The system was easily retrieved via surgical cut-down of the carotid artery.

No death occurred in either group. The overall symptomatic complication rate in group A (126 patients treated without cerebral protection) was 3.96%: 3 minor strokes (2.38%); one TIA (0.79%) and one intracranial hemorrhage (0.79%).

The overall symptomatic complication rate in group B (335 patients treated with cerebral protection devices) was 4.14%: one major stroke (0.29%) (a retinal artery embolus occurred 6 hours after the procedure); 4 minor strokes (1.19%); 2 TIA (0.59%), 2 visual field deficit (0.59%), 4 intracranial hemorrhage (1.19%); one arterial wall fissuration during the stent post dilatation phase (0.29%).

The embolic complications were 4 (3.17%) in the group A and 91 (2.66%) in the group B.

Considering the population treated by using cerebral protection devices (group B 335 patients), in 131 cases (39.10%) macroscopically visible plaque debris was captured and retrieved. Embolic debris composition: cholesterol crystals, fibrin material, atheromatous plaque, macrophage foam cells.

Conclusions: Our data suggest that percutaneous dilatation and stenting of the carotid artery protected by cerebral protection devices is feasible and effective. In our consecutive series the use of the cerebral protection systems allowed us in 131 cases (39.10%) to capture macroscopically visible plaque debris, but the percentage of embolic complication is more or less equal in the two groups (3.17% in the group A and 2.66% in the group B). The use of protection devices is not complication free. The majority of embolic complication are late events.

Carotid Embolism without Evidence of Hemodynamic Stenosis: Management

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Stroke is the third leading cause of death and a principal cause of long-term disability in much of the industrialized world [1], with stenotic atheromatous plaques of the carotid bifurcation as one of the important risk factors.

Recent trial results have shown that carotid endarterectomy (CEA) can reduce the risk of stroke among patients with severe carotid stenosis [2, 9].

A dilemma still remains the management of patients with moderate carotid stenosis and recurrent neurologic symptoms, when no other cause (arch aortic disease, cardiac valvular or rhythm disorder, recent myocardial infarction, intracerebral or subarachnoid hemorrhage, lacunar infarct) could be identified.

One of the mechanism involved could obviously be the atheroembolization, which depends on the plaque morphology.

In support of embolization as the etiology of most strokes, few infarcts are in the watershed areas, microemboli can be detected in the middle cerebral artery, and restenosis of hemodynamic severity are much less likely to be associated with stroke [10].

Several investigators have studied the correlation of carotid plaque morphology and cerebrovascular symptoms [5]: this relationship might be as critical as severity of stenosis in determination of ischemic neurologic events and therefore, it has to be considered in the selection of patients for surgical evaluation. [5].

Plaque rupture is a key mechanism underlying acute events as it comes true from research performed in recent years [8].

High-resolution ultrasonography has been widely used for this purpose and its ability to characterize carotid plaques is considered a major advantage over arteriography. Ulcerated, echolucent and heterogenous plaques with a soft core may represent unstable plaques at high risk for embolism [3, 8].

Histological studies of the plaques have showed that the echolucent plaques are associated with an increased lipid content and are more vulnerable to rupture; on the contrary, echogenic plaques consist mainly of fibrin and collagen which makes them more stable [8, 12].

Besides, many studies shown that the progression of the stenosis is higher in heterogenous plaques and pulse pressure and HDL are found to be the key risk factors; this observations can help us identify more accurately the patients at greater risk for the development of cerebrovascular symptoms [7, 12].

For such reasons and according to many authors, the unstable plaque may be another parameter, not only the degree of stenosis, to consider when making a decision as to whether or not proceed with surgery [7, 11].

Our Experience: Over a 5-year period between September 1997 and September 2002, 1008 CEAs were performed. Indications for operation were asymptomatic carotid stenosis in 593 (58.8%) and symptomatic carotid stenosis in 415 (41.1%). Among the symptomatic patients, we have treated 41 with moderate stenosis (50–69% of stenosis). In these group the CEA was performed in the presence of neurologic symptoms without another evident (cardiac, neurological) disease: 35 (85.3%) had history of transient ischemic attacks (TIAs) and 6 (14.6%) history of established stroke. 30 CEAs (73.1%) were performed in males, median age of 68 years (range 50–69), 38 (92.6%) in hypertensive, 8 (19.5%) in diabetics and 10 (24.3%) in patients with CAD. The contralateral carotid artery was occluded in 5 patients (12%). Local anaesthesia was used in 37 (90%) out of the 41 surgical procedures, while the remaining 4 (9.7%) were performed under general anesthesia. The post operative period was uneventful.

Conclusion: Factors other than degree of stenosis are also important in determining high-risk carotid plaque. Symptomatic patients with moderate stenosis due to unstable plaque, had a high incidence of stroke and progression of degree of stenosis. In these cases the carotid endarterectomy might be beneficial in the prevention of stroke [5, 6].

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Thrombo-Embolic Carotid Disease with no Hemodynamic Lesions

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Stroke is the second most common cause of death world-wide, exceeded only by heart disease. Results of large randomized trials, such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) have demonstrated the superiority of a combination of carotid endarterectomy (CEA) and best medical management over medical therapy alone in providing protection against stroke in selected symptomatic patients [1, 2]. Although a comparison of the results was complicated by the fact that they had measured the degree of stenosis differently on the pre-randomization angiogram, the two trials were in agreement as concerns the benefits of CEA for symptomatic patients with an internal carotid artery (ICA) stenosis greater than 50%. In patients with a moderate (50% to 69%) ICA stenosis, however, the benefit of CEA was less significant than in patients with severe (70% or greater) ICA stenosis [1–5]. Finally, symptomatic patients with mild (less than 50%) stenosis did not benefit from CEA. In fact, in ECST, no benefit of CEA was demonstrated among patients with ipsilateral ICA stenosis of less than 30% [2]; among the NASCET patients with an ICA stenosis of less than 50%, there was no significant difference in the risk of ipsilateral stroke between patients who underwent CEA and those who were only treated medically [1]. From the data in these trials, it is clear that patients at lowest risk of stroke are the least likely, while those at highest risk of stroke are the most likely to benefit from CEA. Since the benefit of CEA in patients with moderate stenosis was significant but relatively small, this has raised the question of whether it is appropriate to perform CEA in such cases.

Among patients with moderate symptomatic ICA disease, cerebrovascular symptoms must be attributed to the carotid lesion only when no other cause (cardiac valvular or rhythm disorder, recent myocardial infarction, intracerebral or subarachnoid hemorrhage, lacunar infarction) can be identified.

An observational study on data collected from the NASCET revealed that a fair proportion of the cases of ipsilateral stroke in symptomatic patients with moderate ICA stenosis were cardioembolic or lacunar in origin (12% and 28%, respectively) [6]. Specifically, among patients with other than lacunar stroke (large-artery disease is commonly associated with disease of the intracranial small vessels – the site of lesions causing lacunar stroke!), the risk of stroke in patients on medical therapy was reduced by CEA from 24.9% to 9.7% at 3 years, an absolute risk reduction of 15.2%. Among patients with "probable" lacunar stroke at entry, the risk of subsequent stroke dropped from 25.5% to only 16.5%, an absolute risk reduction of 9.0%. As there is no evidence to suggest that these patients should

be denied the CEA, the lower benefit must be weighed in any decision about CEA [3–5].

The best-known risk factor for the onset of cerebrovascular events is high-grade ICA stenosis [1, 2]. However, since a significant number of patients with severe ICA stenosis may remain asymptomatic, factors other than the degree of stenosis may play a crucial part in inducing cerebrovascular symptoms. Carotid plaque can cause cerebrovascular ischemic symptoms either by hypoperfusion secondary to the ICA stenosis, or by embolization secondary to plaque disruption, so the ultrasonic morphology of the plaque may be as critical as the severity of the stenosis in determining the incidence of cerebrovascular symptoms [7]. Patients with echolucent plaques are associated with a higher frequency of cerebrovascular symptoms and a significantly higher risk of future neurological events than patients with echogenic plaques. Echolucent plaque has a higher lipid content, which makes it more vulnerable to rupture, whereas echogenic plaque consists mainly of fibrin and collagen and is consequently more stable and less likely to trigger ischemic events [7, 8].

Among patients with only moderate stenosis [1], the best results after CEA were observed for stenoses nearest the upper limit, in men, in patients 75 years of age and older, with a recent history (in the last 3 months) of non-disabling stroke rather than transient ischemic attacks (TIAs) as the qualifying event, with hemispheric rather than retinal symptoms, and with angiographically-detected intracranial atherosclerotic disease (tandem lesions). On the other hand, women with few risk factors, patients with retinal, not hemispheric events, and those presenting with TIA rather than non-disabling stroke, with no intracranial disease, are generally best treated with medical care alone [1].

In conclusion, because some patients with a symptomatic 50% to 69% stenosis stand to benefit from CEA, several factors should be considered in deciding whether to treat a given patient surgically, including any presence of risk factors for stroke and local surgical expertise (at a centre where surgeons can perform CEA with a perioperative stroke or death rate of less than 2%). Once the risks and benefits have been explained to patients, the final decision depends on whether they are willing to accept the early risk and nuisance of the CEA in the hope of the long-term benefit.

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Guidelines for Treatment of Carotid Pathology

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Relying on the most important trials in literature and on the Italian Guidelines for Stroke (SPREAD) [1], in order to examine the latest indications to therapy in case of carotid atherosclerotic lesion, we are distinguishing patients as for symptomatic and asymptomatic for cerebral ischemia, and applying to the NASCET [2] and ECST [3] evaluation criteria for carotid stenosis.

Echo-Doppler examination of supra-aortic vessels is recommended in patients with transient ischemic attack (TIA) or recent stroke for the pathophysiologic work-up, and in asymptomatic subjects with a high carotid stenosis prevalence (e.g. with peripheral arteriopathy or well-documented coronary artery disease, and in subjects over 65 years with multiple vascular risk factors).

Carotid endarterectomy (CE) is recommended in case of symptomatic carotid stenosis (SCS) >70% (NASCET method), but CE is contraindicated for SCS <50%. In patients with SCS between 50% and 70% CE is indicated only in case of recent ischemia, non ocular symptoms, ulcerated plaque, not very old age, male sex and absence of diabetes. Surgical indications are relative in case of asymptomatic patients with carotid stenosis >60% (NASCET method), under the assumption that the perioperative major complications are less than 3% and with respect to life perspectives of patient.

As far as it concerns the pre-operative examination for the diagnosis of carotid stenosis, yet sovraortic vessels' angiography is still gold standard diagnostic technique, for being used in most important trials, echo-doppler examination can be assumed to be satisfactory enough, if it validated by comparison with angiographies or surgical findings. Complementary Magnetic Resonance Imaging (MRI) 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 MRI, or when MRI 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 computed tomography (CT) 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-randomised 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.

Regarding to traditional open CE or by eversion both techniques can be indicated with the same amount of major perioperative complications <3%. The use of patch is surely indicated in case of hypoplasic internal carotid artery.

At present percutaneous transluminal angioplasty (PTA) or primary stenting of carotid stenosis is not considered safe and long term results are necessary, together with randomised controlled trials of comparison with CE, 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 centres 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 haemorrhagic cerebral lesions through CT 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 patency of the cerebral middle artery can surely offer a better prognosis.

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

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The Medical Treatment of Patients with Stroke

Stroke Management: The Antithrombotic Therapy

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Ischemic stroke is the third leading cause of death and one of the most common causes disability, affecting an estimated 700,000 people annually in the United States [1], and about 7% of all patients with a history of TIA or stroke will have a recurrent event each year [2]. Strategies targeted to the secondary prevention of stroke are likely to be more cost effective than primary prevention strategies, the absolute risk reductions are substantially higher and therefore the number needed to treat is lower in relation to the high risk. Antiplatelet agents are the mainstays of ischemic stroke prevention. Aspirin remains the best-studied and most commonly used antiplatelet medication, and it is widely considered the front-line medication for the prevention of ischemic stroke. The therapies recommended for initial therapy include aspirin (50–325 mg) daily, the combination of aspirin (25 mg) and extended-release dipyridamole (200 mg) b.i.d., or clopidogrel (75 mg) daily. Ticlopidine 250 mg b.i.d. is approved for stroke prevention but is not the first-line therapy [3]. Clinicians facing new antiplatelet agents are often uncertain regarding optimal treatment strategies for their patients. While aspirin remains the treatment of choice in many circles, some clinicians have begun to adopt drugs such as clopidogrel as front-line agents for stroke prevention. Although newer antiplatelet agents such as ticlopidine and clopidogrel appear to be as effective as aspirin in stroke prevention, they are also substantially more costly. Aspirin has also been shown to be efficacious in the secondary prevention of stroke in patients with atrial fibrillation. However, these patients are best treated with warfarin unless there are specific contraindications to this medication [4] enrolled patients within three months of their TIA or minor stroke. Subjects were randomized to receive adjusted-dose warfarin (international normalized ratio 2.5–4), aspirin 300 mg/d, or placebo. Strokes occurred at 12% per year in the placebo group, at 10% per year in the aspirin group, and only 4% per year in the warfarin group. The AHA also recommends aspirin (50–325 mg/d) for patients who do not tolerate warfarin. The "Antiplatelet Trialists' Collaboration" since 1988 has performed metanalyses over all clinical trials performed with antiplatelet drugs (aspirin, sulphinpyrazone, dipyridamole) in patients with stroke, TIA, unstable angina and myocardial infarction. The first metanalysis collected results from 25 clinical trials with about 30,000 patients, showing a 25% reduction of cardiovascular events (stroke, myocardial infarction, vascular death) and a 15% reduction of vascular deaths in relation to antiplatelet treatment [5]. In particular, the authors found a 27% decrease in non-fatal stroke. A new metanalysis published from the same Group in 1994 [6], considered 145 studies with 100,000 patients and the results were similar with a 22% reduction of vascular events, 23% of non-fatal stroke and 17% of death rate. Drugs, at present, useful as antiplatelets are aspirin, dipyridamole, ticlopidine, indobufen, clopidogrel, triflusal.

In 2002 [7] the Antiplatelet Trialists' Collaboration performed the last metanalysis that showed that aspirin (or another oral antiplatelet drug) is protective in most types of patient at increased risk of occlusive vascular events, including those with an acute myocardial infarction, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischemia, peripheral arterial disease, or atrial fibrillation. Low dose aspirin (75–150 mg daily) is an effective antiplatelet regimen for long term use, but in acute settings an initial loading dose of at least 150 mg aspirin may be required. Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances, but more research into this strategy is needed. In particular, in patients with a history of stroke or transient ischemic attack (18,270 patients) the antiplatelet therapy resulted in 36 fewer serious vascular events per 1000 patients. This benefit reflects a large and highly significant reduction in non-fatal stroke (25 fewer/1000; $P < 0.0001$), along with a smaller but still significant reduction in non-fatal myocardial infarction (6 fewer/1000; $P = 0.0009$). Although the reduction in vascular mortality of 7 per 1000 was only marginally significant ($P = 0.04$), the highly significant reductions in non-fatal vascular events and in all cause mortality (15 fewer deaths/1000; $P = 0.002$) strongly reinforce the conclusion that prolonged antiplatelet therapy reduces the risk of death in such patients. These benefits clearly exceeded the estimated excess risk of bleeding of about 1–2 additional major extracranial bleeds per 1000 patients per year. Figure 1 shows the benefit of antiplatelet treatment in patients with stroke in this metanalysis [7].

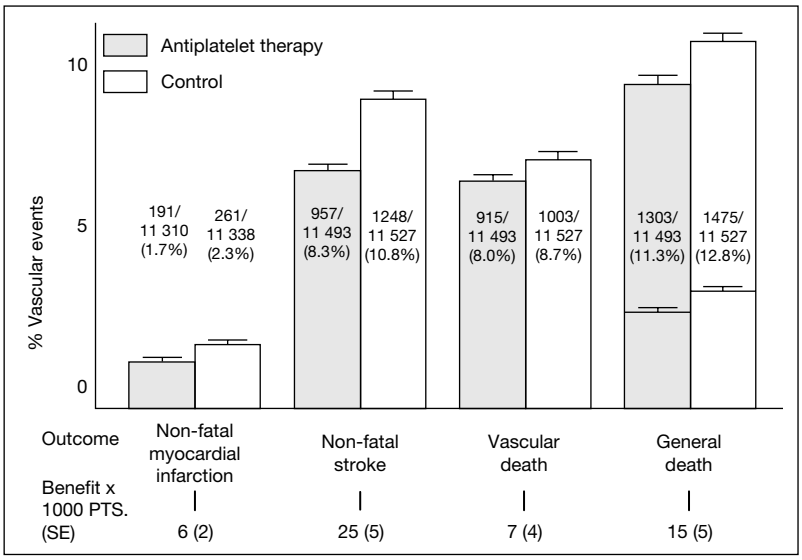

Figure 1: Absolute benefit of antiplatelet therapy in patients with previous stroke or TIA.

Table 1: Stratification of non-rheumatic atrial fibrillation subjects by biannual stroke risk (JAMA 2002)

Biannual stroke risk, %	Patient features	2001 ACCP recommendations	Number needed to treat to prevent 1 stroke
Low (approximately 2)	Aged <65 y, no major risk factors	Aspirin	227 (132–2500)
Low moderate (approximately 3)	Aged 65–75 y, no major risk factors	Aspirin or warfarin (target INR, 2–3)	Aspirin: 152 (88–1667) Warfarin: 54 (46–69)
High moderate (approximately 5)	Aged 65–75 y, no major risk factors but with either diabetes mellitus or coronary artery disease	Warfarin (target INR, 2–3)	32 (28–42)
High (approximately 12)	Aged <75 y, with hypertension, left ventricular dysfunction, or both or aged >75 y without other risk factors	Warfarin (target INR, 2–3)	14 (12–17)
Very high (approximately 20)	Aged >75 y, with hypertension, left ventricular dysfunction, or both or any age and prior stroke, TIA, or systemic embolism	Warfarin (target INR, 2–3)	8 (7–10)

Antithrombotic treatment for patients with atrial fibrillation: Patients with atrial fibrillation and history of stroke have a very high risk of a new stroke, about 20% biannual risk (table 1) [8]. Four randomized trials provided information on antithrombotic strategies for the secondary prevention of stroke in survivors of TIA or stroke [4, 9–11]. The data from these trials indicate a substantial benefit with adjusted-dose warfarin (RR reduction 68% vs. placebo, RR reduction 71% vs. low-dose warfarin plus placebo) and a smaller but significant benefit with aspirin (RR reduction 17–29% vs. placebo).

Secondary prevention of ischemic stroke with antiplatelet therapy: A systematic review of 4 trials found that thienopyridines are modestly more effective than aspirin in decreasing the risk of the combined endpoint of stroke, myocardial infarction or vascular death in patients with high risk of a vascular event [12]. In patients with a history of stroke, thienopyridines decreased the relative risk of stroke by 13% above that aspirin [12]. Furthermore thienopyridines decrease the risk of gastrointestinal bleedings but increase the risk of rash and diarrhoea, and the incidence of neutropenia (in particular with ticlopidine).

The Antiplatelet Trialists' Collaboration did not show significant benefit from adding dipyridamole over the use of aspirin alone [7], but in an individual randomized trial found the additional of extended-release dipyridamole to aspirin significantly decreased the risk of death [10].

RCTs have found that prolonged antiplatelet treatment is beneficial for people with a prior (presumed ischemic) stroke or TIA, unless there is a clear contraindication. No clear evidence exist that any other antiplatelet regimen is superior to medium dose aspirin (75–325 mg daily) in the prevention of vascular events. Aspirin 75 mg daily is as effective as higher doses in the long term prevention of vascular events, but it remains unclear whether doses lower than 75 mg daily are sufficient. RCTs have found that clopidogrel or the combination of aspirin and dipyridamole are safe and effective alternatives to medium dose aspirin.

Table 2: (**a**) Strength of recommendations and (**b**) recommendations for secondary prevention

a	
Level I (Grade A)	Data from randomized, controlled trials with low false-positive and false-negative errors
Level II (Grade B)	Data from randomized, controlled trials with high false-positive or false-negative errors
Level III (Grade C)	Data from nonrandomized, concurrent cohort studies
Level IV (Grade C)	Data from nonrandomized cohort studies using historical controls
Level V (Grade C)	Data from anecdotal case series
b	
R7.1 (Grade A)	In patients with TIA or non-cardioembolic ischemic stroke, antiplatelet therapy with aspirin (100–325 mg/day) *is recommended*.
R7.2 (Grade A)	In patients with TIA or non-cardioembolic ischemic stroke, the association of aspirin (50 mg/day) and dipyridamole (400 mg/day) *is recommended*.
R7.3 (Grade A)	In patients with TIA or ischemic stroke, when aspirin is not well tolerated or is ineffective, antiplatelet therapy with ticlopidine (500 mg/day) *is recommended*, monitoring for haematological complications in the first three months.
R7.4 (Grade C)	In patients with emboligenic cardiopathies or valvulopathies and a cardioembolic stroke or TIA, oral anticoagulant therapy *is recommended*, maintaining the INR between 2 and 3.
R7.5 (Grade C)	In patients with hypercholesterolemia and TIA or ischemic stroke due to supra-aortic vessel atherosclerosis, hypocholesterolemic therapy with statins *is recommended* because it has been shown to prevent stroke and acute myocardial infarct.
S7.1	In case of TIA or ischemic stroke, there is no evidence in favour of the effectiveness of oral anticoagulant therapy maintaining the INR between 2 and 3.
R7.6 (Grade A)	In patients with ischemic stroke or non-cardioembolic TIA, oral anticoagulant therapy, maintaining the INR between 3 and 4.5, *is not recommended* for its higher cerebral hemorrhagic risk.
R7.7 (Grade A)	In patients with non-valvular atrial fibrillation and an embolic stroke or TIA, oral anticoagulant therapy *is recommended*, maintaining the INR between 2 and 3.5.
R7.8 (Grade A)	In case of embolic stroke or TIA in patients with non-valvular atrial fibrillation and contraindications to oral anticoagulant therapy, antiplatelet therapy with aspirin (325 mg/day) *is recommended*.
R7.9 (Grade B)	In case of embolic stroke or TIA in patients with non-valvular atrial fibrillation and contraindications to oral anticoagulant therapy and aspirin, treatment with indobufen (100–200 mg b.i.d.) *is recommended*.
R7.10 (Grade A)	In case of embolic stroke or TIA in patients affected by dilatative cardiomyopathy isolated or associated with non-valvular atrial fibrillation or with an intraventricular thrombus, oral anticoagulant therapy *is recommended*, maintaining the INR between 2 and 3.
R7.11a (Grade C)	In patients with ischemic stroke or TIA proved to be due to a patent foramen ovalis, antiplatelet therapy with aspirin (325 mg/day) *is recommended*.
R7.11b (Grade C)	In patients with ischemic stroke or TIA proved to be due to a patent foramen ovalis and the presence of septal aneurysm or deep venous thrombosis, oral anticoagulant therapy *is recommended* maintaining the INR between 2 and 3.
R7.11c (Grade C)	In case of stroke recurrence while on oral anticoagulant therapy, in patients with ischemic stroke or TIA proved to be due to a patent foramen ovalis, surgical cardiac correction *is recommended*.
R7.12 (Grade C)	In case of stroke recurrence, in patients with cardiac valvular prostheses who are on proper oral anticoagulant therapy, the association of oral anticoagulant and dipyridamole (400 mg/day) or aspirin (100 mg/day) *is recommended*.

Italian Guidelines: SPREAD (Stroke Prevention and Educational Awareness Diffusion): Table 2 reports the recommendations derived from the SPREAD Collaborative Group [13] synthesize the current approach to this therapy. The recommendations have been formulated considering the evidence found in the Cochrane Database of Systematic Reviews and electronic medical literature databases (e.g. MEDLINE), as well as data from both Italian and international research directly available to the experts involved in the guidelines formulation. Documented consensus on still-developing subjects has been also considered, specifying its peculiarity. The strength of evidence was graded according to a 3-grade rating (Table 2).

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Atrial Fibrillation and Risk for Stroke

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Introduction

Atrial fibrillation (AF) is the most frequent sustained tachyarrhythmia observed in clinical practice and is associated with substantial morbidity and mortality [1]. It is estimated that 2.2 million adults in the United States have intermittent or chronic AF [2]. It has a prevalence from 0.2 to 0.9% in different age groups in the general population, and an incidence that reaches 4% in patients older than 60 years, and up to 15% in those older than 70 years [3, 4].

Furthermore, the number of AF cases may be underestimated because of the exclusion of unrecognized, asymptomatic AF. In the Cardiovascular Health Study, 12% of AF cases were diagnosed solely by annual electrocardiographic screening and presumably were asymptomatic [5].

These data are constantly worsening because of the changing demographics in the industrialized world, moving to an increasing proportion of the population older than 60 years [5, 6]. Other factors involved in this increasing prevalence of AF are the improvements in survival after myocardial infarction and the improved performance of cardiothoracic surgeries [7], which are associated with a high rate of postoperative AF. In myocardial infarction survivors, the increase in AF over time was dramatic; the prevalence of AF increased from 4.9% to 17.4% between 1968 and 1989 [8].

Moreover the impact of AF on the health care cost cannot be forgiven, how a prospective cohort study of hospitalized Medicare patients with and without AF suggested [9]. In this study the total Medicare spending was 9–23% greater in men and 10–11% greater in women with AF compared with those without AF.

Aside from its symptomatic effects (palpitations, dyspnea, dizziness, and sometimes, angina and syncope), AF is associated with an adverse long-term prognosis due, besides to an impaired hemodynamic function, to an increased risk of systemic thromboembolism, and especially of stroke [10].

Atrial Fibrillation and Risk for Stroke

It is estimated that 15% of strokes occur in the setting of AF [11]. Whereas the age-adjusted incidence of stroke approximately doubled with coronary artery disease, trebled with hypertension, and quadrupled in the presence of congestive heart failure, AF conferred nearly 5-fold risk of stroke [12].

Stroke in the setting of AF was nearly twice as likely to be fatal compared with stroke from other causes [13]. Survivors of stroke who had AF had longer hospital stays [14], increased disability [13, 14], and more likely to have recurrent strokes [13].

AF may even contribute to dementia. In a prospective study, dementia was twice as common in presence of AF, even after adjustment for other dementia risk factors [15]. A possible mechanism by which AF contributes to dementia is through “silent infarcts”. Data from the Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) trial show that 15% of the trial sample with a normal neurologic exam had occult strokes on baseline computerized tomography scan. It is possible that conditions associated with AF, like hypertension, could have been the cause of the infarcts, but over half of the silent infarcts were consistent with emboli [16].

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Acute Stroke Therapy

Stroke Unit and Stroke Team

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Stroke Units considered as an organizational model that allows to reduce of about 20% the risk of death/residual disability in Stroke patients. Existing evidence indicates that the best results are achieved by Stroke Units that combine the most effective medical treatment with early rehabilitation. The Study Group for Cerebrovascular Diseases of the Italian Neurological Society has achieved a consensus about the different modalities of stroke care organization, indicating the standards and evaluating advantages and disadvantages for each model. Intensive Stroke Unit have to be limited to patient who need cardiorespiratory assistance. These patients constitute about 10% of total strokes, namely those with extensive hemispheric lesions, brain stem lesions and with and without involvement of multiple cranial nerves.

This type of stroke unit has high costs, the access is limited and there is a need of selecting cases. This model can allow advanced experimental trials in the very severe stroke patient. Semi-intensive stroke units are destined to every patients with stroke without selection by age or severity.

It permits an adequate diagnosis and treatment for stroke type and the continuity of treatment between the very early phase and the sub-acute phase of the disease. This type of stroke unit is that proposed as the most effective one by the collaborative systematic reviews. In hospital where there is no possibility to implement a stroke Unit, an expert Stroke Team, can be set up. In this case a team of professionals, including neurologists, physiotherapists and nurses, is called by whatsoever department of the hospital to monitor clinical and functional conditions of stroke patients. There are data which show that in comparison with management in stroke Units mortality dependency and institutionalization are higher. Optimization of stroke Units seem the best choice for every hospital, following examples coming from several European Countries, including Sweden, Austria and, partly, Italy and Great Britain.

The Use of Transcranial Doppler During Thrombolysis in Acute Ischemic Stroke

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Different from the situation in the chronic phase of stroke, in the acute stage more than 60% of patients will present with an intracranial vessel occlusion [1]. In this situation, transcranial Doppler and color-coded duplex sonography provide a fast, cost effective, and non invasive bed-side technique with a high sensitivity and specificity [2, 3] for diagnosing intracranial vessel pathology.

The knowledge of the vascular status in this situation may allow for a more effective selection of patients for reperfusion strategies, particularly when intra-arterial thrombolysis is under consideration. In the PROACT trial [4], in only 38% of patients undergoing diagnostic angiography an occlusion was confirmed. In a recent study on perfusion (PWI) and diffusion (DWI) weighed MRI within 6 h after stroke onset [5] a relevant PWI/DWI mismatch was present in 120 of 139 patients examined. Vessel occlusion was demonstrated in 90% of patients, so that the vascular status has a high predictive value for a PWI/DWI mismatch and may also be of relevance for selecting patients for intravenous thrombolysis.

Transcranial ultrasound (TU) is an ideal technique to monitor the recanalization process during thrombolysis in close intervals. Reported 24 h recanalization rates of 50 to 60% [6, 7] comply well with those found by other imaging techniques [5]. The functional outcome after thrombolysis is closely related to the hemodynamic situation expressed as Doppler flow grades [8]. TU was able to demonstrate a recanalization time window of <6 h after stroke onset, where recanalization has a positive effect on the functional outcome [7, 8]. Recanalization beyond 6 h after stroke onset probably has no longer a beneficial effect on the patients deficits.

Diagnostic ultrasound itself has a thrombolytic effect. This has come into focus with reports on dramatic early recovery and increased recanalization rates when continuous TCD monitoring is applied during thrombolysis [9, 10]. However, in vitro experiments suggest, that low-frequency ultrasound may be even more effective in clot dissolution than high-frequency diagnostic ultrasound [11] and clinical studies with low-frequency probes are currently undertaken. Hopes are justified, that TU may transit from a purely diagnostic to a therapeutic tool.

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Interventional Radiology in the Ischemic Cerebrovascular Pathology

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Interventional neuroradiology techniques will be used more and more frequently in the various clinical presentations of the ischemic cerebral pathology.

Emergency Treatment of Stroke Patients

Intraarterial thrombolysis represents one of these techniques and will be used in conjunction with others depending on the type and location of the intracerebral lesion and on the time delay since the onset of symptoms.

1. Intracerebral hemorrhage should be excluded and setting the meeting point at the CT unit for Stroke patients remains the simplest way to save time.
2. Non hemorrhagic cases should have an angiogram that gives information on two points : 1) extension of the ischemic area (digitized parenchmography gives this information as precisely as perfusion MR), 2) involvement of the lenticulostriate arteries (these terminal arteries have more than 40% chances of rupture when revascularized after the 6th hour). Non thrombolysis of lenticulostriate cases after the 6th hour has presently eliminated, in our experience, the risk secondary intraparenchymatous hemorrhage. Other location cases have been treated up to the 12th hour.
3. Several techniques of retrieval of an intracerebral or cervical clot are presently available. They are more or less sophisticated including simple aspiration, lasso retriever or mechanic retriever types. On short series they all have had encouraging results.
4. Angioplasty and stentings will be also used more and more frequently on emergency in order to treat intracerebral and cervical arterial stenoses related to atherosclerotic plaque or dissection and to prevent from an hemodynamic or embolic recurrence.
5. Carotid occlusion treatment represents a technical therapeutic challenge that is valuable considering the poor prognosis of most of the stroke cases related to this anatomical entity.

Treatment of Transient Ischemic Symptoms

Angioplasty and stenting of cervical and intracerebral stenoses related to atheroma or other causes are more and more accepted. Atherosclerotic stenoses at the carotid bifurcation should be treated using a cerebral protection system because of the risk of cerebral embolic complications. These protection systems are either a temporary occlusion of the carotid artery or a filter. New dedicated stents and less traumatic approaches are currently developed. Combined stenting of other stenotic cervical or intracerebral arteries in the same session is an other advantage of the endovascular approach that should become, in our opinion, the future standard in this type of pathology and particularly at the level of the carotid bifurcation.

Treatment of Asymptomatic Stenoses

Endovascular treatment is in our opinion indicated when there is an obvious ulceration of the atheromatous plaque at the carotid bifurcation in order to modify the turbulences and consequently cure the ulceration preventing the patient from an embolic stroke. The treatment is also indicated when it is possible to demonstrate radiographically that the cerebral flow distal to one or several cervical stenoses is significantly altered on standard or enhanced (Diamox) investigations. The systematic use of psychometric testings before and after endovascular techniques has showed obvious improvements that widely open the chronic cerebral ischemia field.

Carotid Disease and the Risk of Stroke in Patients with Acute Coronary Syndromes Undergoing Primary Coronary Angioplasty

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Present epidemiologic data indicate that the prevalence of stroke in patients with acute myocardial infarction (AMI) is 2.5% in the general population and 1% in patients younger than 75 years. Several randomized studies have provided some evidence on the main risk factors for stroke: previous cerebrovascular accidents, diabetes, atrial fibrillation, aging, congestive heart failure, greater than 100 bpm heart rate, infarct site and extension, emergency IABP [1, 2]. The occurrence of stroke in patients with AMI severely worsens the patient prognosis, by increasing absolute in-hospital mortality by 33% and the long term mortality by nearly 16% (45.9% vs. 12.6% and 27.9% vs. 11.7% respectively), without mentioning the severe long-term consequences among survivors and their social cost [3].

The epidemiology and pathophysiology of ischemic stroke are significantly different compared to the hemorrhagic stroke. Hemorrhagic stroke is a well known complication of the fibrinolytic therapy, especially during the 24 hour period after starting the treatment, the incidence varying from 0.07% to 1.5% [4]; the prevalence of ischemic stroke is similar (0.1%–1.3%) but the mechanisms involved are different: cardioembolic events, “in situ” thrombosis due to the activation of the coagulation system, hemodynamic effects of low cardiac output [4]. The incidence of ischemic stroke ranges

between 1.7 to 3.2% in patients receiving fibrinolytic treatment while the incidence of hemorrhagic stroke is unrelevant [3].

The stroke prevalence during coronary interventional procedures is very low, the estimated prevalence is around 0.38%, equally distributed between ischemic and hemorrhagic stroke (49% vs. 46%) [5]. According to a metanalysis of four different randomized trials the incidence of stroke in patients with acute coronary syndromes undergoing coronary angioplasty and treated with conventional therapy plus GP IIb/IIIa inhibitors was 0.36% with no difference between the treatment and the placebo group.

The extension and severity of coronary disease is greater in patients with associated atherosclerotic disease of the carotid or femoral arteries [7]. In patients with multivessel disease undergoing primary PTCA that subsequently exhibit an indication to surgical revascularization, the association with carotid disease worsens the prognosis, indeed the post-surgical rate of stroke increases from 2% in the general population to 4.9% in patients with carotid disease [8].

In acute coronary syndromes, after treating the culprit lesion, the following revascularization strategy in patients with multivessel disease should be carefully take in consideration a prognostic risk evaluation a based on the associated atherosclerotic disease, especially in the cerebrovascular compartment.

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Principal Medical (Non-Neurological) Complications in Patients with Acute Stroke

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Despite continued advances in prevention and treatment, stroke remains the third cause of death (after coronary heart disease and all cancers), and the leading cause of disability in advanced age. Strategies available for stroke management have grown impressively during the last decade, and since it has become clear that specific treatment (namely thrombolysis) needs to be applied in a narrow therapeutic window, stroke units (SU) have been established as intensive or non-intensive care units in many hospital sites.

Unfortunately, such specific treatments are beneficial only in a selected portions of stroke patients. Nevertheless, the usefulness of SU has been demonstrated in all patients, in terms of mortality, length of institutionalization, rate of complications and functional outcome. This means that most of these patients benefit from being managed and cured from a more general standpoint. As a matter of fact, the incidence of stroke and the limited number of SU keep the rate of hospitalization in Internal Medicine Departments relatively high.

As a rule, stroke patients present a wide spectrum of different diseases and ask for a multidisciplinary approach [1]. Many diseases pre-exist when stroke ensues, and possibly facilitate its occurrence; such are arterial hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, chronic obstructive lung disease, chronic alcoholic liver disease (the latter as for hemorrhagic stroke) [2–5]. Other diseases complicate the acute course of stroke and affect mortality in the short term and functional outcome in the long term; such are pneumonia, urinary tract infections, fever from any cause, water metabolism disturbances, venous thrombus-embolism [6]. It has been estimated that 95% of stroke patients have at least another disease while in hospital, and that 51% of the deaths that occur 3 months after a stroke can be attributed to medical complications [7].

Thus, a complex array of medical (apart from neurological) problems needs to be faced in stroke patients, and common disorders require special considerations. Arterial hypertension needs to be treated judiciously, in order not to derange brain flow to critical areas [8]. Hyperglycemia, due to poorly controlled diabetes, affects unfavorably the clinical outcome [9], but brisk reductions of glycemia, as well as the use of hypotonic solutions (e.g., dextrose 5%) facilitate brain edema, and should be avoided. Atrial fibrillation may cause embolic stroke, but other arrhythmias accompany hemispheric stroke; although they appear to have little influence on the course of the disease, they add to the clinical burden in stroke patients [10]. Venous thrombus-embolism is a major concern in stroke and requires systematic pharmacological or non-pharmacological profilaxis.

Although rare, various medical diseases other than atherosclerosis and related cardiovascular disorders may cause ischemic stroke and need to be considered in the differential diagnosis, especially in younger people and female gender; such are LES, APA/LAC syndrome, other caogulopathies, sickle cell anemia, vasculitides.

Such a wide range of actual or potential problems in stroke makes it clear that an internist is a legitimate (if not essential) component of the team dedicated to the patients in the acute phase of stroke, in any clinical setting.

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Vascular Dementia

Epidemiology of Dementia

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Dementia is one of the most disabling health conditions in the elderly [1]. Dementing disorders are responsible for the 8.7% of the 161.2 million Disability-Adjusted Life Years lost as a consequence of noncommunicable disorders in people aged 60 years and over. The heavy impact on the health care systems is strictly related to the aging process occurring in both developing and developed countries. The world population aged 60 and over was 488 million in 1990 and will be about 1363 million in 2030, with an increase of 180% [2].

Public health needs objective information on the magnitude of the problems, and accurate epidemiological data are essential for an adequate planning of health care services, and for resources allocation. Population-based studies, in particular, apart from estimating the dimension of the problem, may provide insight into the pathogenic mechanisms of dementia, and enable the identification of the risk and protective factors that may prevent or delay the onset of the disease.

A large number of studies on the frequency of dementia have been carried out in industrialized countries, reporting roughly similar rates. The average prevalence for subjects aged 65 years and over is about 5–6% [3, 4]. The prevalence doubles approximately with every 5 years of age, determining an almost exponential increase, at least between the age 65–84 years. The age-specific prevalence rates range from about 1% in subjects 65–69 years of age, to 40% in age-group 85–89 years. The annual incidence rate of dementia is estimated to be about 10 per 1000 in people aged over 65 years, ranging from 2–8 per 1000 in subjects aged 65–69 years, to 30 per 1000 and more in subjects aged 80 and over [5, 6].

The majority of the epidemiological studies aimed at the estimation of Alzheimer's disease (AD) and vascular dementia (VaD) rates, the most common types of dementia in industrialized countries. AD is reported as the most frequent dementing disorder in United States, in Canada and in Europe, accounting for the 50–80% of dementia cases. VaD is the second cause of dementia, with relative proportions ranging from 9% to 50% in the different surveys. In Italy, the only data available on a national basis are from the Italian Longitudinal Study on Aging (ILSA), a multicentre population-based study involving 5600 subjects in eight municipalities in northern, central and southern regions of the country. Results from the ILSA Study indicate a prevalence for total dementia of 6.4%. Average incidence rates per 1000 were 12.47 for dementia, 6.55 for AD and 3.30 for VaD. AD represented 52.7% of cases, and vascular dementia 26.8% of cases [6].

Based on above epidemiological data, the available estimates indicate that approximately 3,286,000 persons in the European Union have dementia, and about 824,000 new cases will develop in a year [4, 5]. According to the findings from the ILSA Study, in Italy, one of the oldest countries in the world, currently 680,000 older persons have dementia, and about 150,000 new cases of dementia are expected each year, while in 2020 a total of 213,000 incident cases can be expected in the Italian elderly population [6].

Considering the heavy impact of dementia, the focus of research is currently moving towards conditions as cognitive impairment without overt dementia, that might possibly precede the onset of the disease [7, 8]. While the occurrence of dementia in an aged population is estimated to be around 1% per year, the annual conversion to dementia in subjects with cognitive impairment may vary from 4% to 10%. Research on frequency and outcome cognitive impairment may give insight into the pathogenic mechanisms of dementia.

In view of the reported high figures on the global burden of dementing disorders, the search for strategies aimed at preventing or delaying the onset of dementia has to be considered among the major objectives of medical research.

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Neuroimaging of Dementia

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The first issue to be addressed by neuroimaging techniques in patients presenting with cognitive decline is to ascertain or exclude treatable causes of dementia. These include several conditions as subdural hematoma, normal pressure hydrocephalus and tumors which are curable with neurosurgical treatment. For this purpose plain and contrast enhanced Computed Tomography (CT) generally suffices, although the same information can be obtained with conventional T1 and T2 weighted Magnetic Resonance (MR) imaging.

In the majority of the patients presenting with progressive cognitive decline no treatable cause is found and differential diagnosis has to be pursued among the most common causes of dementia. These include Alzheimer's Disease (AD), Multi-Infarct Dementia (MID), Fronto-Temporal Dementia (FTD), Creutzfeld-Jacob Disease (CJD), Cortico-Basal Degeneration (CBD) and Lewy Body Disease (LBD). The neuroimaging techniques employed for this task in a clinical setting usually include CT, conventional MRI and perfusion Single Photon Emission Computed Tomography (SPECT).

In particular, CT and conventional MRI can demonstrate different patterns of regional atrophy in AD, FTD and CBD which in AD and FTD are variably combined with areas of white matter changes detected as hyodensity on CT or increased signal on T2 weighted MRI [1,2]. Similar white matter changes however can be frequently found in elderly subjects often with history of arterial hypertension and subtle or mild cognitive decline. These white matter changes termed Leuko-Araiosis (LA) are completely non-specific. In patients with MID a variable combination of multiple subcortical lacunes, cortical infarcts and LA is observed. In patients with advanced CJD MRI can demonstrate symmetric increased signal in the basal ganglia in T2 weighted images. Perfusion SPECT generally shows a symmetric pattern of reduced cerebral blood flow in the fronto-parietal-temporal regions in AD, an asymmetric reduction of flow in the fronto-temporal regions in FTD, patchy areas of reduced flow in MID and a typical symmetric occipital flow reduction in LBD.

Recent hardware and software developments has renewed interest in the potentials of MRI in the assessment of dementia in a clinical research setting.

In particular, three dimensional thin slice acquisition enables accurate estimation of the volumes of regions of interest which are selectively involved in the neurodegeneration process, i.e. of the hippocampus in AD [3]; perfusion studies with intravenous paramagnetic contrast agents and rapid echo-planar imaging sequences can demonstrate with better spatial resolution than SPECT the cerebral blood flow patterns reported above [4]; proton MR spectroscopy can demonstrate reduce concentration of the neuronal marker N-acetyl aspartate with a distribution matching that of neuronal degeneration in AD [5, 6].

The most recent MRI studies focused on application of diffusion-weighted and Magnetization Transfer (MT), MRI in the investigation of normal aging [7, 8] and dementia. These techniques can provide an indirect measure of biophysical integrity of the cerebral white and gray matter and are characterized by high spatial resolution and reproducibility. Analysis of region of interest and of lobar or whole brain histograms reveals increased diffusion and reduced MT in AD which are correlate with performance of the patients on neuropsychological testing [9, 10]. Moreover diffusion changes (increased apparent diffusion coefficients and reduced fractional anisotropy) can be documented not only in areas of LA but also in normal appearing white matter in patients with LA [11, 12].

The quantitative study with diffusion histograms would be more sensitive to progression of the process underlying LA than visual evaluation of the areas of increased signal on T2 [13].

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Transcranial Doppler and Assessment of Cerebral Vasomotor Reactivity in Vascular Dementia

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Vascular dementia (VD) is one of the common devastating sequels after stroke. The role of the cerebral hemodynamic status in the occurrence and progression of VD is still uncertain. Transcranial Doppler

sonography (TCD) has become widely used in assessing cerebral vasomotor reactivity (VMR) which provides information regarding cerebral autoregulation and collateral circulation. VMR is defined as a shift between cerebral blood flow (CBF) or cerebral blood flow velocity (BFV) before and after administration of a potent vasodilatory stimulus test. Surprisingly, VMR was more frequently calculated in patients with dementia of Alzheimer type (AD) than in patients with VD [1–3]. Nagata et al. [1,2] found preserved VMR in AD and controls. Stoppe et al. [3] revealed significantly reduced VMR in the patients with AD as compared with controls and these findings were well correlated with increasing cognitive impairment. Some studies were performed in order to distinguish between AD and VD by assessment of VMR [4]. Matteis et al. [4] used TCD and apnea test for evaluation of VMR in 10 patients with VD, 10 patients with AD and 20 healthy matched controls. VMR to apnea was significantly lower in the VD group compared with to the other 2 groups. These data suggest that impaired VMR could be an additional criterion for discriminating between VD and AD patients. CO (2) test was performed in the TCD study for assessment of VMR in patients with CADASIL [5]. 29 CADASIL individuals were compared with equal number of age-and sex-matched control subjects. CO (2) reactivity was significantly was reduced in CADASIL patients. Moreover, VMR was lower in disabled compared with non-disabled CADASIL individuals. The reduced CO (2) reactivity suggests functional impairment of VMR probably related to vascular smooth muscle cell dysfunction. Takahashi et al. [6] studied VMR to CO (2) in patients with dementia due to multiple infarction in the territory of the perforating artery. 11 patients were demented and 16 patients were with multiple infarctions without dementia. Only patients with cerebral infarction located in the perforating territories were included in this study. VMR was found lower in demented patients with multiple infarctions. We conducted a prospective study in order to determine the value of VMR as a parameter to predict cognitive decline in patients after ischemic stroke [7]. VMR was assessed using TCD and the Diamox test (1 g acetazolamide i.v.). All patients underwent carotid Doppler to exclude severe carotid occlusive disease as a factor which might affect VMR. Bilateral, multiple lacunar infarcts were confirmed by CT and/or MRI in all patients. The patients were divided into those with dementia based on DSM-IV criteria and the MMSE scale and those without dementia. 10 patients with dementia and 7 patients without dementia were comparable in terms of common vascular risk factors and timing after ischemic stroke (3–36 months). The mean VMR% was 33.3 ± 21.5% for demented patients and 43.7 ± 29.8% for patients without dementia. There was no statistically significant difference between the VMR of the two groups ($P = 0.2$). Our data suggested a non significant trend to worse VMR in VD. The objective of our second study on this topic was to assess and compare VMR in VD patients with multiple lacunar infarcts and single large vessel strokes [8]. Seventeen patients with VD were included in this study and were divided into those with multi-infarct dementia (10 patients) and single infarct dementia (7 patients). Following the Diamox test, the BFVs in the middle cerebral arteries among the patients as a whole increased from 78 ± 26.8 to 104 ± 34.5 cm/s, while the VMR% showed a 30 ± 12.5% increase. The mean VMR% was 33.3 ± 21.5% for group 1 and 30 ± 19.5% for group 2 (P = NS). Our data revealed a similar VMR in patients with multi-infarct and single infarct types of VD. While multi-infarct and single infarct types of VD are clearly different in terms of bilaterality or strategic lesions we found comparable VMR patterns of patients with VD. In conclusion, all studies were limited in terms of small number of patients and larger studies are needed to further evaluate the role of VMR in VD.

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Antihypertensive Treatment and the Prevention of Dementia

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After the double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial ended in February 1997, randomized patients were offered active study medication for a further period of observation [1]. One of the goals of the extended follow-up was to refine the estimates of the long-term effects of antihypertensive therapy on the incidence of dementia.

Eligible patients had no dementia and were at least 60 years old. Their systolic blood pressure at entry was 160 to 219 mm Hg, with diastolic blood pressure below 95 mm Hg. Antihypertensive therapy was started immediately after randomization in the active-treatment group, but only after termination of the double-blind trial in the control patients. Treatment consisted of nitrendipine (10–40 mg/d), with the possible addition of enalapril (5–20 mg/d), hydrochlorothiazide (12.5–25 mg/d), or both add-on drugs.

Median follow-up increased from 2.0 years in the double-blind trial to 3.9 years overall. The incidence of dementia doubled from 32 to 64 cases, 41 of whom had Alzheimer's disease. Throughout follow-up systolic/diastolic pressure was 7.0/3.2 mm Hg higher in 1417 control patients than in 1485 subjects randomized to active treatment. At the last examination, the blood pressure difference still was 4.2/2.9 mm Hg; 48.1%, 26.4% and 11.4% of the control patients were taking nitrendipine, enalapril and/or hydrochlorothiazide, whereas in the active-treatment group these proportions were 70.2%, 35.4% and 18.4%, respectively. Compared with control, long-term antihypertensive therapy reduced the risk of dementia by 55%, from 7.4 to 3.3 cases per 1000 patient-years (43 *vs* 21 cases, $P < .001$). After adjustment for

sex, age, education, and entry blood pressure, the relative hazard rate associated with the use of nitrendipine was 0.38 (95% confidence interval, 0.23–0.64; $P < .001$). Treatment of 1000 patients for 5 years can prevent 20 cases of dementia (95% confidence interval, 7–33).

The question whether blood pressure lowering treatment can prevent vascular and neurodegenerative dementia has also been addressed in other placebo-controlled trials [2–5]. Treatment based on thiazides [2–3], ß-blockers [2–3], the ACEI perindopril given in monotherapy [4], or the ARB candesartan [5] failed to protect against cognitive impairment and dementia. In contrast, the extended follow-up of Syst-Eur patients [1] reinforces the evidence that blood pressure lowering therapy initiated with a long-acting dihydropyridine protects against dementia in older patients with systolic hypertension.

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Treatment of Vascular Dementias

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Vascular cognitive impairment is the second most common form of mental deterioration in the elderly after the degenerative dementias. A number of drugs have been tested with the aim of improving or slowing cognitive decline. Most of these trials have yielded unsatisfactory results. VaD encompasses several different clinical-pathological subtypes, understanding the pathophysiological mechanisms that cause cognitive impairment is an essential step for choosing proper treatment strategies. The treatments in VaD can be divided into three broad categories: preventive, aiming to improve cognitive function, and symptomatic.

Preventive Treatment

Antithrombotic therapies: A small placebo-controlled trial showed that aspirin had a beneficial effect on cognitive performances of multi-infarct dementia patients. A group of the Cochrane Collaboration reviewed the evidence on the effects of aspirin in vascular dementia, they concluded that there is very limited evidence that aspirin is effective in treating patients with a diagnosis of VaD and further research is needed.

Intervention for risk factors control: The Syst-Eur Trial demonstrated that the control of systolic hypertension in the elderly reduced the incidence of dementia. The SHEP trial, using a thiazide diuretic and a beta-blocker, failed to demonstrate a protective effect of antihypertensive treatment against dementia. The PROGRESS Study aimed to test the hypothesis that blood pressure reduction obtained by using the ACE-inhibitor perindopril would reduce the incidence of dementia among patients with cerebrovascular disease. The main outcome of the study, stroke recurrence, showed a significant effect of perindopril associated with indapamide in Multi-infarct dementia in reducing the risk of stroke.

There is evidence to suggest a relation between lipids and vascular changes involved in VaD. The precise mechanisms by which lipid abnormalities are associated with dementia are at present poorly understood. Very preliminary data exist on the effect of HMGCoA reductase inhibitors (statins) and other lipid-lowering agents in regard of dementia.

Therapy of Vascular Dementia

Ergot alkaloids: The possible beneficial effect of these compounds seems to rely on their vasodilatory action, mediated by α-1-receptor antagonism, and on a number of effects on the cerebral parenchyma mediated by modulation of nitric oxide synthase, dopaminergic and cholinergic effects, increased O_2 utilization and cell glucose uptake, leading to augmented resistance of neuronal and glial cells to ischemia. Hydergine is the prototype of this class of drugs, another agent of this class is nicergoline.

Xanthine-derivatives: The prototypes of xanthine-derivatives family of drugs are pentoxifylline and propentofylline. Among the mechanisms of action of this compound are: reduction of phosphodiesterase activity, adenosine antagonism, reduction of Ca^{2+} intracellular influx. At the parenchyma level, they have neuroprotective effects. Denbufylline, another xanthine derivative, has been evaluated in the treatment of cognitive dysfunction without effect in improve cognitive dysfunction.

Calcium-antagonists: Nimodipine a dihydropyridinic calcium-antagonists have a double action on vascular bed and brain parenchyma. In the experimental animal, they reduce age-related microvascular changes and, acting on L-type Ca^{2+} receptors and nitric oxide metabolism, have a vasodilatory effect with improvement of blood supply in hypoperfused areas. Calcium-antagonists also reduce pathological Ca^{2+} intracellular influx and nitric oxide-free radicals interaction via the block of NMDA-mediated nitric oxide synthase induction. Some preliminary studies carried out with nimodipine, taking into account VaD subtypes and aiming to reduce heterogeneity of the target population, have provided encouraging results. Cyclandelate is another vasoactive calcium channel blocker tested on patient with cognitive decline.

NMDA receptor antagonist: Memantine, a low-affinity, voltage dependent, non-competitive NMDA receptor antagonist, has raised expectations in both symptomatic and neuroprotective treatment of dementia.

Posatirelin and Ginkgo Biloba extract: Posatirelin, a TRH-analogue that interferes with cholinergic and monoaminergic systems, has been preliminarily shown to have beneficial effect on patients suffering from probable VaD. EGb761 is a particular extract of Ginkgo the main effect seems to be related to its antioxidant properties as

scavengers for free radicals with possible beneficial effects on excessive lipid peroxidation and cell damage.

Serotonin receptor antagonist: Naftidrofuryl is a serotonin-2-receptor antagonist that has been shown to inhibit serotonin-induced vascular smooth muscle contraction and platelet aggregation.

Piracetam: is nootropic agent. A systematic review was performed by Cochrane Dementia and Cognitive Improvement Group. The evidence of effects on cognition and other measures was inconclusive.

Cholinesterase inhibitors drugs: A number of studies suggest that patients with vascular changes have cholinergic deficits that may benefit from cholinergic replacement therapy. A recent study evaluated the activity of rivastigmine in patients with mild to moderately severe AD with or without concurrent vascular risk factors. Data indicates that rivastigmine was associated with improvements over placebo for a wide variety of efficacy measures cognition, activities of daily living, and disease severity. There is no evidence for an effective treatment for established VaD. This partly depends on the heterogeneity of study patients, enrolled using too broad and non-specific clinical definitions of VaD. Treatments should be tested in groups of patients who are clinically homogeneous.

The Rehabilitation of the Patient with Stroke

Quality of Life and Functional Recovery after Stroke: Is there Any Causal Relationship?

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The negative influence of stroke on quality of life (QOL) of survivors is well recognised and widely demonstrated in observational studies [1–4]. A recent survey assessing well-being in stroke survivors reports a higher risk for these subjects to complain of a restriction in physical and cognitive function, to report worse mental health and to be living with a greater number of comorbid health conditions, as compared with community-dwelling seniors without a history of stroke [4]. Up to 50% of stroke survivors cannot perform household-related instrumental activities of daily living (IADLs), have restriction in traveling within and beyond the community and lack important and meaningful activities to fill the day. All these conditions allow both the development of depression and worsening of function and the impairment of health-related quality of life (HRQOL) and QOL [3]. Differentiating between HRQOL and QOL recognizes a theoretical rationale. The terms refer to two different dimensions of well-being, each influenced by specific clinical and personal variables. In particular, while basic ADL is a reliable predictor of HRQOL, it proves to be only weakly associated with overall QOL. On the other hand, QOL is directly affected by IADL performance and improves along with involvement in community activities, that is a measure of participation [2].

The choice of outcome measures is a keypoint in the *querelle* about the relationship between functional impairment and QOL after stroke. It has been already established as global disability measures lead to underestimate functional problems regarded as meaningful by the patients. In particular, they fail in capturing persisting difficulties in hand function, so that patients who still experience important limitations in their everyday performance and social participation may be labelled as functionally independent according to the Barthel index [3].

The use of the SF-36 as QOL index in stroke patients has been questioned by Hobart et al. who highlighted the floor/ceiling effects in 3 out of 8 SF-36 scales and rejected the assumptions for generating the 2 SF-36 summary measures [5].

Disease-specific rating scales have been developed within the last 5 years, in order to define the overall health impact of stroke. Among them, the Stroke Impact Scale (SIS) has been proposed as a comprehensive measure, addressing 8 domains (strength, hand function, ADL and IADL, mobility, communication, emotion, memory and thinking and participation/role function). It has already been shown to be valid, reliable and sensitive to change, compared to Barthel index and SF-36 in stroke patients [6] and has been recently applied to measure the impact of stroke 3 months after the event in order to define areas that require long-term disability rehabilitation and optimize QOL [3].

The research into QOL prognosis has so far supported different theories about the efficacy of interventions aimed at improving outcome after stroke. The findings from correlation analysis have shown the positive influence exerted by a large social support network on the sense of well-being in stroke survivors [7, 8]. Both satisfaction with social support and a greater number of years of education are independent predictors of higher scores in the dimensions of environmental mastery and sense of personal growth. Social resources are assumed to act as compensatory mechanisms, able to reduce the adverse effects of physical disability on QOL in stroke survivors coping in the community setting.

In this view, greater emphasis should be given to interventions aimed at enhancing social participation, empowering community support network, sharing with the family the responsibility for meeting stroke patients basic needs, including household tasks as well as traveling and entertainment provision.

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Stroke Patient Rehabilitation

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The re-education of patient affected with stroke pathology represents a practical method of facilitating the correct activation of recovery processes. The Author thinks that the correctness of activation depends on a series of knowledges, derived from the neurosciences field.

Particularly important are:

– *Neurophysiological knowledges*. For instance: in regard of the motor area often injured in case of stroke, it stands to reason that a rehabilitation based on conviction that this structure organization answers to "homuncular" pattern principles (only one representation for each segment, somatotopically organized), will be quite different from what the latest theories supposed. Again, always in regard of the motor area, the "homuncular paradigm" suggested that some body segments were represented in a more refined way than others; which could explain a treatment of shoulder and trunk less accurate than this of the hand. In fact, relatively recent studies have proved that also these segments, once considered endowed with postural motility – that is a coarse and scarcely selective motility- were, instead, represented in motor and sensitive area, in a most refined way, for shoulder as well as, with peculiar modality, for the trunk (see the researches on cortical representation of body mid-line). It is obvious, of course, that these knowledges change completely the rehabilitative intervention.
– *Neurobiological knowledges*. It is important considering, at least, the basic knowledges about fundamental processes of nervous system plasticity. For instance, recently, the neurologist has pointed out the importance of diaschisis in order to the recovery purpose. The knowledge of this inhibitory/protective phenomenon asks a rehabilitative behaviour aimed to get over it and suggests to avoid the strategies facilitating an emphasized inhibition.
– knowledges related to the functional meaning of the injured structures.

Certainly it is not at all correct, also in the light of the most simple notions of cerebral localizations, to re-educate a subject with a cerebral lesion on right hemisphere in the same way of one with the lesion on the left one, also if both seem affected by the same hemiplegia. As well as, it is not at all correct re-educating in the same way fronto-parietal or parieto-occipital lesions, also if both present troubles which can be called hemiplegia. An other example about the necessity of this kind of knowledges comes from the cerebellar lesions treatment. Some researches carried out since last ten years, have shown that cerebellum, specially for the neocerebellar portion, cannot be considered an exclusively motor structure. His task, in elaborating cognitive processes and in solving problems as well as in the first learning period but always before automatization, asks the rehabilitator to elaborate quite different exercises from those inspired by Gordon Holmes (!) ideas.

The specific task consists in providing a rehabilitative interpretation of pathology, often in a different way from what it has been carried out by the neurologist. For instance, the presence of sensorial troubles in patients affected with ideomotor aprassia, is only interesting for the neurologist, but much more important for the organization of therapeutical treatment. Particularly interesting is, besides, also the elaboration – based always on knowledges derived from neurosciences – of instruments suitable for the exercise. In this light, recently, it has been very significant the utilization of motor imagery, supported by studies of several neurologists, neurophysiologists and psychologists.

Shared Care for Patients with Stroke: The Role of the General Practitioner

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More than 50% of the patients with stroke need an efficient health care for all the period of their survival, involving different and manifold medical competency (physician, physiotherapist, speech therapist, nursing staff).

The objectives of the long-term health care for a patient with stroke are:

- Comorbidity limitation;
- Prevention of new brain damage;
- Strengthened recover of own autonomy;
- Long-term maintenance of the performances after rehabilitation.

The treatment must be oriented not only towards the patient, but it's necessary to give care of the whole family in the social environment with the final aim to readmit the disabled to the common live.

To obtain the global care it's necessary to have not only the most accurate clinical diagnosis of the brain damage and of the level of disability, but also an exact definition of a multimode prognosis evaluated on the family, the social environment and, of course, the personal expectative of the patient; it is mandatory to preview the needs and the resources needed in every step, the multimode approach. The individual program for rehabilitation must be periodically updated and changed, if necessary, looking at 1) the patient status, 2) the short, medium and long term evolution, 3) the socio sanitary framework, 4) the aims of the social and sanitary interventions, 5) the needed human and material resources, 6) the professional liability of each operator, 7) the evaluation of each step. The most effective transfer from the hospital to the territorial care is warranted by the programmed demission, conditio sine qua non for an effective management of the patient in the outside environment. It's necessary to individuate a case manager, with the responsibility and the co-ordination of the rehabilitation project.

The general practitioner is the health actor that can assure the correct attendance to the patient in the usual social environment, because he usually has a good knowledge not only of the patient but also of the relatives, before and after the acute hill; furthermore the general practitioner is able to co-ordinate all the medical team involved in this project.

Depression and Stroke

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Post-stroke depression (PSD) is a frequent neuropsychiatric syndrome occurring in 50% of acute patients and in 30% of chronically impaired patients (Robinson et al., 1983), with a range of incidence from 25 to 65%, according to different population samples, timing of psychiatric evaluation and different subtype of depression (major depressive disorder, dysthimia, adjustment disorder with depressed mood). In the acute phase of stroke, DSM-IV criteria of adjustment disorder with depressed mood were fulfilled by 27% of the patients, while severe depressive symptoms occurred in less than 5% of the patients with acute stroke, with a significant correlation between the severity of stroke and that of the depressive symptoms (Kellermann et al., 1999). Depression and the PSD-related cognitive impairment reduce the patient's compliance to rehabilitation treatment and slows down the recovery of social functioning (van de Weg et al., 1999). Moreover, the functional impairment may continue and become irreversible even after depression recovery: in fact, two years after stroke, patients with PSD present much more functional impairment than those non-initially depressed (Parikh et al., 1990).

The depressive comorbidity may also cause an increased death rate, with a mortality rate of 90% at ten years in depressed and socially isolated patients (Morris et al., 1993).

Depression seems to be more common with lesions affecting the frontal lobes and caudate nucleus. Also clinical features may be related to lesion localisation, i.e. dysthimia is more connected with parieto-occipital lesions and major depressive disorder is more related to the proximity of the stroke lesion to the frontal pole and with basal ganglia damage (Starkstein and Robinson, 1989).

Major depression seems not to be related with the degree of disability, whereas minor depression is more closely related to the patient's neurological deficits. The importance of biological and functional pathogenesis of PSD may also be different in post-stroke phases: among biological factors, although lesion location plays a relevant role, particularly in the first period after stroke, atrophy is more important after the second year; besides psychosocial factors are more important in the medium period (from six months to two years after stroke) (Astrom et al., 1993).

Another relevant problem is represented by the poor clinical attention given to the "subthreshold depression", i.e. those depressive symptoms failing shortly the major depressive threshold. These patients demonstrate high risk of morbidity and impairment, generally more pronounced than those of patients with the same medical condition without depression (Akiskal, 1997). This fact can dramatically contribute to an underdiagnosis and undertreatment of depression. The "observed depression" may be a valid criterium only to diagnose major depression, while minor depression and/or dysthimia can escape to be diagnosed, particularly in those patients that denied depression or demonstrate neurological interferences, such as aprosodia, anosodiaphoria, aphasias, etc. An association between post-stroke depression and cognitive impairment has been demonstrated (Kauhanen et al., 1999).

Even if the treatment of depression should be a must in depressed post stroke patients, there are only few reports concerning the benefit of antidepressant drug therapy on post stroke depression.

Until the late 1980s tricyclic antidepressants (TCAs) represented the major pharmacological treatment for depression. The range of their side effects is related to interactions on muscarinic, alfa-adrenergic and histaminergic receptors with the risk of, respectively, both peripheral and central antimuscarinic actions, orthostatic hypotension, sedation interfering with the cognitive functions. Another problem is represented by the TCAs cardiovascular effects on blood pressure, heart rate, cardiac rhythm and heart conduction.

The second-generation antidepressants, such as the atypical trazodone, bupropion and nefazodone, with less effects than TCAs on cardiac conduction and less anticholinergic activity, provide an alternative means of treating PSD.

The class of selective serotonin reuptake inhibitors (SSRIs) represented an important progress in pharmacotherapy for their efficacy and a safer profile than TCAs and atypical antidepressants. SSRIs present a safe cardiovascular profile: fluoxetine, that is the more studied SSRI, demonstrates clinically non significant decrease in heart rate, does not change PR and QRS intervals, neither acts on blood pressure or ventricular function.

However the increase of serotoninergic tone can temporary induce individually differentiated vascular responses, due to the complex vascular regulation exerted by the different subtypes of serotoninergic receptors: caution must be observed in the first phase of SSRIs therapy, in acute cardiovascular patients, until an adaptation of vascular response is obtained (Torta et al., 1998; Torta and Monaco, 2001). In the first phase of the treatment the temporary association with the substituted benzamides (such as amisulpride or levosulpiride) or with CNS transmetylants (such as the S-adenosil-L-methyonine) can be useful (Torta et al., 1998).

Some controlled trials demonstrate that SSRIs offer an advantageous treatment, both safe and effective, of PSD (Andersen et al., 1994; Stamenkovic et al., 1996).

In conclusion, cerebrovascular diseases are associated with a high incidence of depressive disorders, but, despite this high level of comorbidity, depression appears to go largely unrecognized and untreated. Depression may have serious consequences because worse the prognosis both *quoad vitam and quoad valetudinem*, increases medical costs and delays the return to work and to the normal social functioning. New antidepressants (SSRIs, NaSSA, NARI, etc.) may offer therapeutic advantages for their little or no effects on cardiac conduction, on orthostatic hypotension and on cognitive performances.

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