20th Anniversary of the International Course
«Summer Stroke School –
Healthy Life Style and Prevention of Stroke»
Inter – University Center, Dubrovnik

# Images and memories from the first 20 years

Edited by Vida Demarin & Marina Roje Bedeković

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# FOREWORD I

This booklet is an outgrowth of a teaching course „Summer Stroke School - Healthy Life Style and Prevention of Stroke" which has been taught in Dubrovnik for the past 20 years.

For many years, much of the medical community has had a rather pessimistic attitude toward stroke, believing that little or nothing could be done for the patient, aside from observation. However, many of us have always maintained that the specific cause of a stroke should be diagnosed and specific treatment started immediately if there is to be any hope of an increase in survival and improvement in the quality of life for the survivors.

As knowledge and awareness becomes wider, and as technology grows more sophisticated, the need for solutions to more complex problems becomes greater. Fortunately, in the last two decades, the development of technology has provided new means for solving many of these problems. This course was intended to elucidate the methods and techniques in epidemiology, pathophysiology, diagnostics and therapy pertinent to stroke, so that neurologists may apply them in order to solve practical problems in their everyday work with patients. The purpose of this booklet is not to be a compilation of medical and scientific achievements in the field of cerebrovascular disease. Rather, through these texts, the reader may become aware of some of the understandings developed during the past twenty years, in a condensed way, and use them and implement them in their work.

Unless we continue substantial progress in stroke prevention, we will see increasing numbers of people with cerebrovascular risk factors, increasing numbers of first and recurrent stroke victims, and increasing numbers of deaths from cerebrovascular diseases. Further, costs will increase because of the larger numbers of people needing stroke treatment and the higher cost for each cerebrovascular disease event, if the trend of increasing costs for health services continues as expected. In contrast, success in meeting this goal can reverse the unfavorable trends of the past decades.

Our heartfelt appreciation goes to all of you who have joined us and encouraged us in meeting this goal during the past two decades.

Our warmest acknowledgments go to the Inter-University Center of Dubrovnik and Mrs. Berta Dragičević, General Secretery of IUC, and her colleagues, Mr. Srećko Kržić and Ms. Nada Bruer, for their continuous support and hospitality, in good times and bad.

Many thanks to all the authors for their contributions to creating this booklet. Special thanks to Professor Roman Haberl for his devotion and encouragement from the very beginning, to Professor Kurt Niederkorn for his support and to Professor Zlatko Trkanjec for not sparing pains in this course. We would also like to thank to Mrs. Uta Schneider from Aloka Holding Europe AG for her generous support in making our whishes come true.

Our deepest gratitude goes to all of you who have been with us through all these years, sharing your knowledge and experiences with us, making our lives rich and fruitful. We hope that turning the pages of this book will bring back enjoyable memories.

We must build on the promise of knowledge and experience that awaits widespread translation into public health practice. So, celebrating the 20th anniversary of „Summer Stroke School - Healthy Life Style and Prevention of Stroke" we would like to thank you for being with us for the past two decades and also to welcome you and invite you to stay with us in the coming decades.

Vida Demarin
Founder of the course

Marina Roje Bedeković
Program Coordinator

# FOREWORD II

IUC Inter University Centre Dubrovnik

## 20TH ANNIVERSARY OF THE SUMMER STROKE SCHOOL AT IUC

The Inter-University Centre (IUC) Dubrovnik, as the host institution, congratulates the organizers and directors of the Summer Stroke School for their successful, longstanding operation in Dubrovnik, in the framework of the IUC academic programme. Over the last 20 years the Summer Stroke School has greatly enriched the IUC offerings and has contributed to the international reputation of the Centre. We are most grateful to the School directors for bringing this programme of utmost relevance to the IUC, to Dubrovnik.

The Inter-University Centre (IUC) Dubrovnik as an independent, international institution founded in 1971 promotes international cooperation among universities. Its programme includes a vast selection of topics, from humanities and social sciences to medicine and natural sciences, often organized in cycles which are continued from year to year. The IUC membership now includes almost 200 universities, mostly from Europe and North America, but also from other continents. In the year 2007 the IUC celebrated its 35th anniversary. Through those 35 years the IUC has offered more than 1500 courses and conferences with over 60.000 participants.

Twenty years ago, in 1990, the IUC welcomed the proposal of the organizers to include the Summer Stroke School in the IUC annual academic programme and throughout the following years the IUC was proud to list this School as its permanent event. The founder of the School, Professor Vida Demarin, in cooperation with her colleagues, set up School programmes which fully corresponded to the IUC basic goal, i.e. bringing together scholars and students from different backgrounds and cultures, thus promoting dialogue and understanding.

The IUC follows the best of traditions of Dubrovnik, a city which is part of the world cultural heritage under the protection of UNESCO. It provides a space for exchange of knowledge, ideas and experiences, and the possibility of work in an atmosphere of opennes, tolerance, mutual respect and friendship. The genius loci of Dubrovnik contributes to the successful operation of the Centre and to the fulfillment of its mission.

We at the Centre hope that the spirit of the IUC will continue to attract many new partners and old friends. We very much hope that the directors and participants in the Summer Stroke School will also continue their cooperation with the IUC for the many years to come.

I am personally happy that on behalf of the IUC I have the privilege and pleasure to offer thanks to Professor Vida Demarin and her colleagues for their most valuable work and input into the IUC programme through the past twenty years, to express gratitude for their continuous support to our institution and to present best wishes for the future successful work of the Summer Stroke School.

Berta Dragičević
General Secretary of IUC

# FOREWORD III

## 20TH ANNIVERSARY OF THE SUMMER STROKE SCHOOL IN DUBROVNIK

Celebrating the 20th anniversary of the „Summer Stroke School - Healthy Life Style and Prevention of Stroke" is a significant event not only for Croatian neurology, but also for the city of Dubrovnik, which has throughout history been open to all new scientific and social achievements. Dubrovnik, whose rich medical tradition includes centuries of quality medical and pharmacy services, is always happy to accept new medical knowledge. Today we are very pleased that we can host fellow neurologists from many countries and exchange knowledge and experience in the prevention and treatment of stroke.

We are especially grateful to Professor Demarin who recognized and chose our city for this meeting, and managed to maintain continuity and quality for all these years. In that way she has brought neurology to young doctors and motivated them for further learning and research.

Stroke risk factors in different countries are introduced to neurologists, radiologists and family practitioners, giving them a chance to discuss diagnostic and therapeutic procedures as well as new options in treatment of cerebrovascular disease. They have a chance to meet colleagues from different parts of the world and make new friendships.

Each year we look forward to teaching the „Summer Stroke School - Healthy Life Style and Prevention of Stroke" and look forward to its further continuation.

Welcome to Dubrovnik, and to the 20th anniversary of the Summer Stroke School Healthy Life Style and Prevention of Stroke.

Best regards,

Mira Ivanković
Head of Department of Neurology
Dubrovnik General Hospital

KLINIKA ZA NEUROLOGIJU

KB "SESTRE MILOSRDNICE"

# CHRONICLE OF INTERNATIONAL POSTGRADUATE COURSE «STROKE SUMMER SCHOOL - HEALTHY LIFE STYLE AND PREVENTION OF STROKE»

The International Postgraduate Course „Stroke Summer School – Healthy Life Style and Prevention of Stroke" was conceived by a few enthusiasts under the leadership of Professor Vida Demarin, head of the University Department of Neurology, Sestre milosrdnice University Hospital in Zagreb, to fill a need for educating neurologists and those who were about to become neurologists about a broad field of stroke. The course has been taught every year from 1990 with a total enrollment of over than 600 participants. The fact that the number of participants has grown within sight from year to year has given additional encouragement to the organizers to persevere with their original idea, spreading knowledge of stroke and reducing the number of stroke victims.

Since 1990 the Course is organized by the Croatian Stroke Society, the Croatian Society for Nurovascular Disorders of the Croatian Medical Association, and the Academy of Medical Sciences of Croatia. Since 2002, the School of Medicine of the University of Zagreb has also been an organizer. The course has been twice a Joint Meeting of the CEESS (Central and East European Stroke Society). The goal of the course is to produce highly capable neurologists and ultimately to assist those trainees in establishing their own comprehensive stroke centers, thus promoting better patient care. This goal is divided into four separate goals based on the different intervention approaches that would be needed to achieve them. These four goals are: prevention of risk factors, detection and treatment of risk factors, early identification and treatment of stroke and prevention of recurrent cerebrovascular events.

The course focuses not only on the facts but also on the process of learning about stroke. Since the most effective way to learn in general is by active engagement, the course organizers always give the opportunity to the youngest neurologist to share their experience and knowledge with more experienced ones.

It is not simple today, from a time distance of twenty rich and fruitful years to select the most important and relevant events and in the same time the dearest ones, to remember all those exceptional persons who participated in Course and gave their contribution to its creation and survival. With great enthusiasm Professor Demarin invited stroke professionals to Dubrovnik and the world responded to her invitation with great enthusiasm. The fact that participants came from all around the world (Austria, Bosnia and Herzegovina, Croatia, Czech Republic, Germany, Hungary, Israel, Latvia, Poland, Slovenia, Spain, Switzerland, Ukraine, United Kingdom and United States) gives this Course its personal identity: a course that brings together people from different backgrounds and cultures united in the same goal – healthy life style and prevention of stroke. And the course, like everything else in life, is made by people. Everyone gave his own contribution for which

we are all grateful. Directors of the course (Prof. dr. Vida Demarin, University of Zagreb, Croatia; Prof. dr. Roman Haberl, University of Munich, Germany; Prof. dr. Kurt Niederkorn, University of Graz, Austria; Prof. dr. Tanja Rundek, Columbia University, New York, USA and Prof. dr. Zlatko Trkanjec, University of Zagreb, Croatia) willing to share their knowledge and experience and prepare to direct the younger colleagues. And all the participants have added their own personal „touch", each in his own way, to keep this course on the right track and to stay on it.

It all started in 1990 as a result of another creative idea of Professor Vida Demarin who had a primary goal: to encourage cooperation and to promote exchange of knowledge about stroke among professionals from different countries. Since the idea was great, she had to find a great place to host the event. Dubrovnik was a logical choice: a City that has managed to survive as an independent city – state between various imperial ambitions during several centuries; a City that is a cradle of western culture and science, an everlasting inspiration for artists and scientists and almost a fatal attraction to everyone who has set foot on its streets; and a City from which a few of us even claim family roots (Figure 1.).

By choosing Dubrovnik as a host-city for the course, Professor Demarin has placed Dubrovnik on the world map of stroke science. And since the choice of city seemed logical, finding an institution that would support the idea was not hard – Inter – University Center Dubrovnik (IUC), established in 1970, an institution which has become a synonym for independent and autonomous thinking.

It all started in 1990 as an adventure: few enthusiasts lead by Prof. Demarin were willing to try and to work hard. The greatest challenge for the course was for sure the war years. In June 1991 the Course was still held in the IUC (Figure 2.), but just several months later, from September 1991 to mid - 1993 the city was under aggressive attack, including shelling from the sea and the mountains, snipers from the surrounding hills and the occupation of the surrounding villages and the siege of the city itself. In spite of the destruction of the IUC building in December 1991, the 3rd „Healthy Life Style and Prevention of Stroke" was held in Dubrovnik in September 1992 (Figure 3). And that was a dangerous period to be in Dubrovnik! However, fortunately the spirits of IUC and the course survived the physical destruction. In spring 1992 the Croatian Government started the reconstruction of the IUC building. The main part of the reconstruction was completed in the fall of 1993 and the IUC operation returned to its home. Because of the war situation in 1993, Course organizers decided to move to Zagreb. But the very next year, in 1994, course participants were among the first to come back to Dubrovnik lead by great wish for the continuity and for a return to the course's „home", IUC Dubrovnik (Figure 4 and Figure 5). By 1995 war has spread directly to Croatia's capital, Zagreb, which was also bombarded, and course found a shelter on the Brijuni islands (Figure 6). The years 1996 (Figure 7), 1997 (Figure 8) and 1998 (Figure 9, Figure 10) brought back peace to Croatia and course could have peacefully moved back to IUC, Dubrovnik. Unfortunately, because of war in the Republic of Kosovo in 1999, thanks to the efforts of the organizers, course took place in Medulin where it celebrated its 10th anniversary (Figure 11). From the year 2000 (Figure 12) on, until the 20th anniversary that we are celebrating in this very year, 2009, course has been held in IUC, Dubrovnik. Having such a strong basis, we can fortunately hope that it will remain this way for many years to come.

But, let's go back to the past ones again for a while. The idea of healthy life style and prevention of stroke originally brought people together, but what held them together for so many years, apart from spreading knowledge and preventing stroke, is certainly the mutual spirit and similar way of thinking: openness, friendship and cooperation. There was always time to discuss a healthy life style and to carry it out during the hours of repose (Figure 13). The atmosphere was always friendly and close (Figure 14, Figure 15) in front of IUC as well as in the class (Figure 16, Figure 17). The Course also gave us the opportunity to feel like home in Dubrovnik and to enjoy all its natural attractions (Figure 18, Figure 19). As the time passed, the number of participants has certainly grown (Figure 20) and so has the number of new friendships made (Figure 21, Figure 22) among participants from all around the world (Figure 23, Figure 24) during the working part of the course and during the evening hours (Figure 25, Figure 26). The organizers have succeeded in maintaining the same cheerful atmosphere during all those years of the course (Figure 27, Figure 28) and for support and contribution to the continuing development Professor Demarin earned a Certificate of Appreciation from the Inter-University Centre, Dubrovnik in 2006 (Figure 29). Great support from all around the world in 2007 (Figure 30) and the last year, 2008, was an ouverture to this years 20th anniversary. Again, great number of participants (Figure 31), scientific part of the Course (Figure 32, Figure 33, Figure 34, Figure 35) combined with joy and fun (Figure 36, Figure 37). Through the past 20 years the organizers always took care to provide rich „outside of the classroom" program to participants, including sight-seeing, concerts, visiting Dubrovnik's surroundings and islands (Figure 38, Figure 39, Figure 40, Figure 41). For the special 20th Anniversary of the Course a Celebration Concert is organized for all participants in Gallery Pulitika (Figure 42).

Let's just hope that rich and fruitful past 20 years will bring us as quality and productive time to come!

Marina Roje Bedeković

*Figure 1. Vida Demarin with her mother – in law, Gina Buterin.*

*Figure 2. June 1991, participants in IUC during a break.*

*Figure 3. September 1992, Nevenka Čop Blažić, Vida Demarin, Tanja Rundek in front of destructed IUC building.*

*Figure 4. 1994 - participants in front of IUC.*

*Figure 5. 1994 - participants in front of General Hospital in Dubrovnik.*

*Figure 6. 1995 - Course found its shelter in Brijuni islands.*

*Figure 7. 1996 – participants in front of IUC.*

*Figure 8. 1997 - participants in front of IUC.*

*Figure 9. 1998 - participants in front of IUC.*

*Figure 10. 1998 - during the evening hours (Vlasta Vuković, † Tomislav Šoša, Vida Demarin, Bojana Žvan, Silvije Vuletić).*

*Figure 11. 1999 - 10th Anniversary celebration in Medulin.*

*Figure 12. 2000 – participants in front of IUC.*

*Figure 13. 2000 - participants playing picigin on Lopud island.*

*Figure 14. 2001 – participants in front of IUC.*

*Figure 15. 2001 - Marina Roje Bedeković, Vida Demarin, Vesna Vargek Solter in front of IUC.*

*Figure 17. 2001 – Johannes Schenkel and Vida Demarin.*

*Figure 16. 2001 – in the classroom.*

*Figure 18. 2001 – Roman Haberl and his son on the boat for Lopud.*


*Figure 19. 2001 – participants during a coffe - break in Sesame caffe near IUC.*

*Figure 20. 2002 – participants in front of IUC.*

*Figure 21. 2002 – evening in Trubadur.*

*Figure 23. 2003 – participants in front of IUC.*

*Figure 22. 2002 – in Dubrovačka kuća, Uta Schneider and Vida Demarin.*

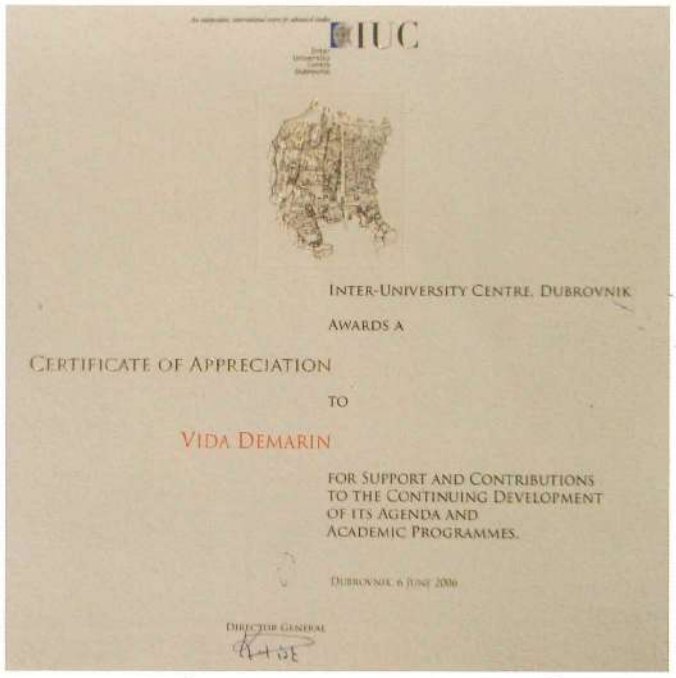
*Figure 24. 2004 – participants in front of IUC.*

*Figure 25. 2004 – in restaurant; Zlatko Trkanjec, Kurt Niederkorn, Vida Demarin, Carlos Molina, Marina Roje Bedeković, Vlasta Vuković, Tomislav Breitenfeld.*

*Figure 26. 2004 – evening hours; Nikola Barić, Sandra Morović, Zlatko Trkanjec, Vida Demarin, Roman Haberl.*

*Figure 27. 2005 – participants in front of IUC.*

*Figure 28. 2006 – participants in front of IUC.*


IUC

INTER-UNIVERSITY CENTRE, DUBROVNIK

AWARDS A

CERTIFICATE OF APPRECIATION

TO

VIDA DEMARIN

FOR SUPPORT AND CONTRIBUTIONS
TO THE CONTINUING DEVELOPMENT
OF ITS AGENDA AND
ACADEMIC PROGRAMMES.

DUBROVNIK, 6 JUNE 2006

DIRECTOR GENERAL

*Figure 29. 2006 – Inter – University Centre, Dubrovnik - Certificate of Appreciation to Vida Demarin.*

*Figure 30. 2007 – participants in front of IUC.*

*Figure 31. 2008 – participants in front of IUC.*

*Figure 32. 2008 – in the classroom.*

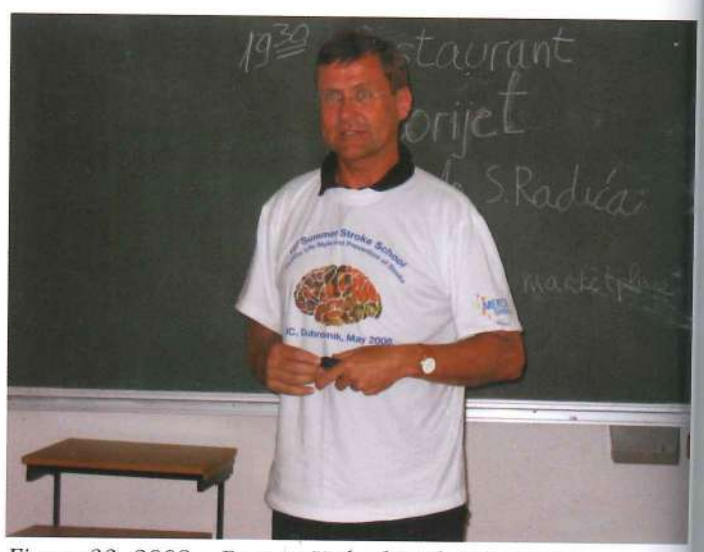



*Figure 33. 2008 – Roman Haberl in the classroom.*

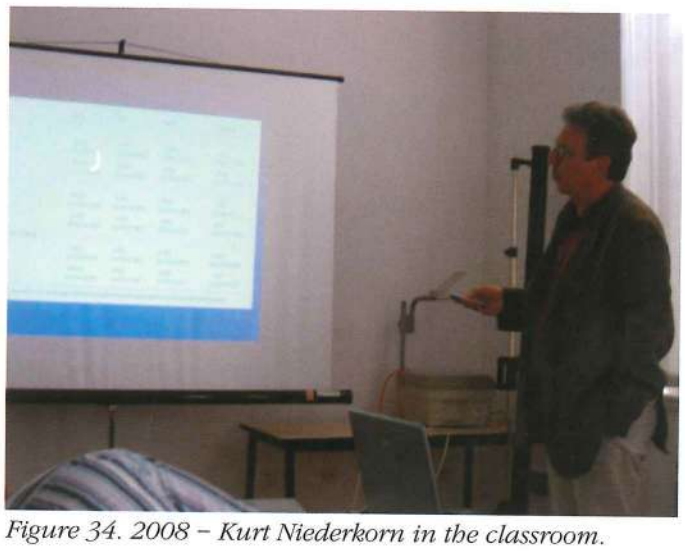


*Figure 34. 2008 – Kurt Niederkorn in the classroom.*

*Figure 35. 2008 – Vida Demarin in the classroom.*

*Figure 36. 2008 – Johannes Schenkel.*

*Figure 37. 2008. – evening hours.*

*Figure 38. 1995 – participants on Brijuni islands.*

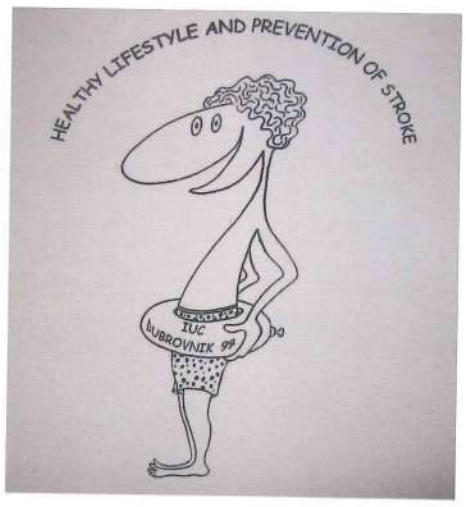

*Figure 39. 2001 - Martin Wimer and Johannes Schenkel on the boat to Lopud.*

*Figure 40. 1997. – visiting Korčula.*

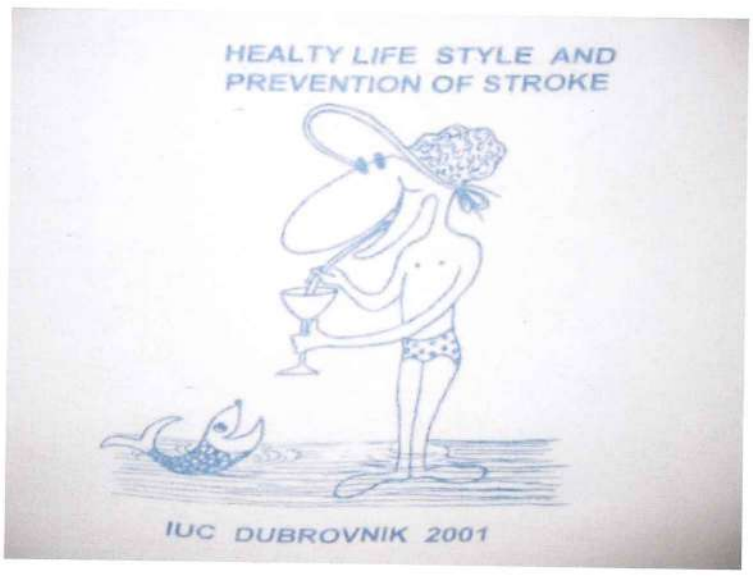
*Figure 41. – evening hours. Uta Schneider, Krunoslav Rastovčan, Filip Dražančić, Vida Demarin, Ivan Šarić, Hans Van Elst, Bojan Žvan.*

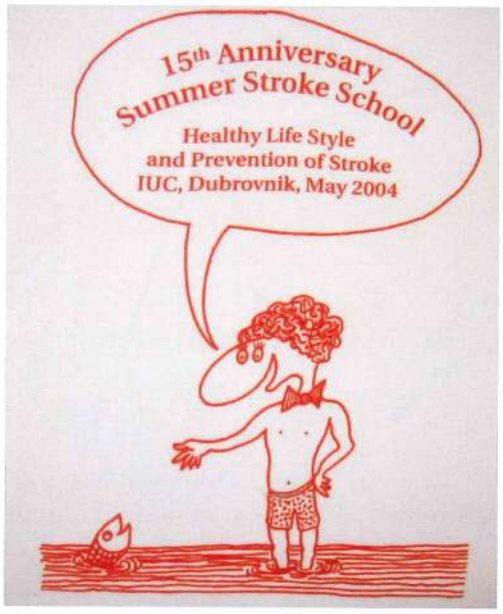

*Figure 42. 2009 – 20th Anniversary Celebration Concert for Professor Vida Demarin in Gallery Pulitika, Dubrovnik.*

Traditional „Stroke Summer School – Healthy Life Style and Prevention of Stroke" T- shirts as a gift from the organizers to each participant. Caricatures by Ivan Šarić.

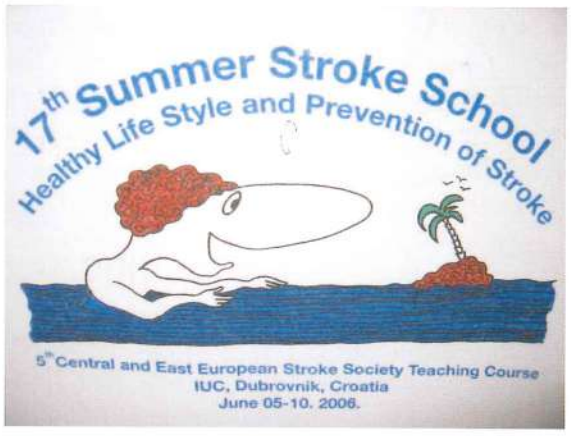



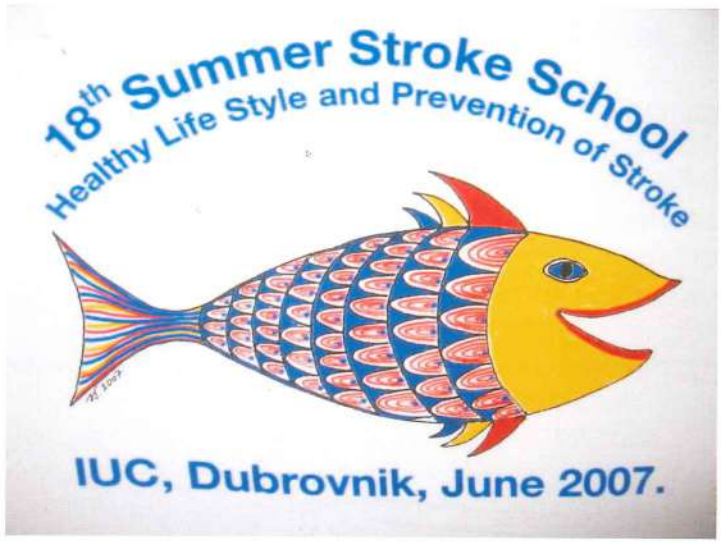


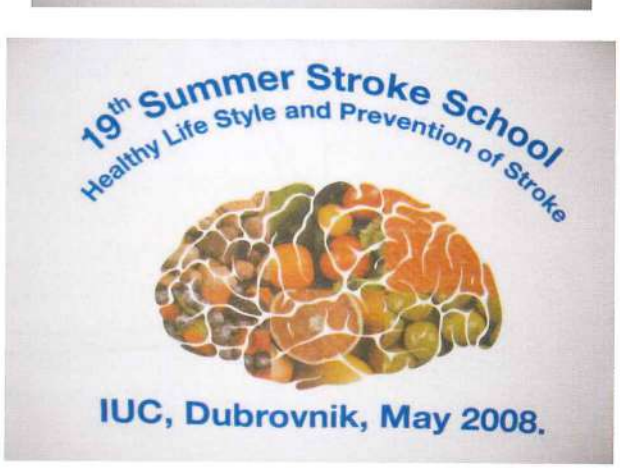




15th Anniversary
Summer Stroke School
Healthy Life Style
and Prevention of Stroke
IUC, Dubrovnik, May 2004


16th Sumer Stroke School
Healty Life Style and Prevention of Stroke
Inter - University Centre Dubrovnik
May 2005.


17th Summer Stroke School
Healthy Life Style and Prevention of Stroke
5th Central and East European Stroke Society Teaching Course
IUC, Dubrovnik, Croatia
June 05-10. 2006.


18th Summer Stroke School
Healthy Life Style and Prevention of Stroke
IUC, Dubrovnik, June 2007.


19th Summer Stroke School
Healthy Life Style and Prevention of Stroke
IUC, Dubrovnik, May 2008.


20th Summer Stroke School
Healthy Life Style and Prevention of Stroke
20
serono
biotech & beyond
MERCK
SERONO
IUC, Dubrovnik, June 2009.

# 1. CHRONICLE OF DUBROVNIK MEDICINE

**Marina Roje Bedeković**

**University Department of Neurology**
**Sestre milosrdnice University Hospital**
**Zagreb, Croatia**

*To all my dear ancestors from Dubrovnik.*

As a start, I will pose a simple question to the potential reader as well as to myself: why write about the history of Dubrovnik medicine?

The answer I give myself and my reader is simple: as a small token of my gratitude to all those who contributed in one way or another to the history of Dubrovnik medicine and the history of Dubrovnik in general, as well as to all those who have written about it before me. My story is not a long one considering how much they left us. I will leave it to you to imagine the whole magnitude that is hidden behind this story. So, let's begin.

Dubrovnik's successful economic development was based on maritime and trade activities, enabled by its strategic geographic location. After entering the Adriatic Sea, Dubrovnik is the first port protected by islands on the route to the west, and the nearby Neretva valley provides direct access to the interior hinterland regions (1). Archeological excavations indicate that a settlement existed on the site of today's city in the 6$^{th}$ century or even earlier. The original settlement was enlarged by the arrival of Croats fleeing the destruction of nearby Epidaurus (modern day Cavtat) by an earthquake in the 7$^{th}$ century (2).

Intensified contact between East and West during and after the Crusades of the 12$^{th}$ and 13$^{th}$ centuries heralded the prosperity of maritime and merchant centers in the Mediterranean and Adriatic, including Dubrovnik. Liberation from Venetian influence, which Dubrovnik achieved in 1358, was crucial for its later successful development (3). During the 14$^{th}$ and 15$^{th}$ centuries, Dubrovnik, along with Venice and Ancona, became the most significant seafaring and merchant centre of the Adriatic (1).

In the 16$^{th}$ century, the legal status of the Dubrovnik Republic was fully established, calling for the independent election of the rector and councilors, its own currency and flag featuring its patron St. Blaise, an independent legislature and the right to establish consulates abroad (1,2).

In accordance with the aristocratic social order of the time, permanent supreme power was vested in the Great Council, which consisted of members of aristocratic families. The Great Council elected members of the Senate and of the Small Council which served as the executive body of the Great Council. The Rector was elected for a period of only one month as a nominal symbol of power (1,2).

Under pressure from the aggressive expansion of the Turkish Empire into the Balkans, the Dubrovnik Republic accepted Turkish patronage and agreed to pay an annual tribute in 1525. In return, the Republic obtained a license for free trade throughout the entire Turkish Empire with payment of only 2% customs tax. The small state, deprived of an army, successfully conducted its defense through skilful diplomacy and wide-ranging consular activities. Neutrality in international conflicts and the supportive patronage of great states, particularly of Spain and the Vatican, enabled the Republic to uphold its sovereignty. The only permanent rival and enemy of the State was the Venetian Republic (1,2).

Dubrovnik Republic enjoyed its golden age in the 16th century as the splendor and power of the Venetian Republic declined. The basis of prosperity was seaborne trade. Material prosperity and a feeling of security and freedom formed the basis for a humanistic culture and stimulated a creative spirit. Dubrovnik reached a magnificent stage in its urban and architectural development which has been sustained to the present time. Famous names in literature, poetry and science, art and culture created its history (1,2).

A general crisis in maritime affairs in the Mediterranean in the 17th century struck the Dubrovnik mercantile as well. A disastrous earthquake in 1667 forced the Dubrovnik Republic to fight for its very existence and the protection of its political sovereignty. In the 18th century, Dubrovnik found an opportunity for economic revival in seaborne trade under a neutral flag until the arrival of Napoleon and the fall of the Dubrovnik Republic in 1808 (4).

At the Congress of Vienna in 1815, the Dubrovnik region became a part of Dalmatia and Croatia and has shared their political destiny ever since (2).

Among all Croatian cities, Dubrovnik has made the greatest contribution to the development of medicine. The Republic achieved great success in organizing public health services and improving medical practices.

Dubrovnik adopted the tradition of ancient Epidaurus in the worship of Esculap, the Greek god of medicine and the patron of Epidaurus. A legend about a fight between St. Hilarion and a great snake indicates that Christianity replaced pagan practices in the Dubrovnik area too. The saint patron of the city became St. Blaise (2) (Picture 1), who was invoked in the healing of various diseases, especially ailments of the throat. Esculap, however, was not forgotten, and his image was carved on one of the capitals of the porch of the Rector's palace (Picture 2). The

*Picture 1. Saint Blaise - saint patron of Dubrovnik. A statue of St. Blaise holding a model of Dubrovnik high atop the façade.*

accompanying Latin inscription claims that Esculap was born in Dubrovnik.

In addition to teurgical and plebeian medicine, scientific medicine also developed early in the history of Dubrovnik. The city had political and economic connections with Salerno, just when Salerno's medical school began to flourish. The Benedictines brought medical manuscripts from Southern Italy. A fragment of a treatise about poisonous animals and their bites, from the 10th or 11th century, is preserved on the cover of one incunabula, found in Dubrovnik's scientific library. It is the oldest extant medical manuscript in Croatia (5).

*Picture 2. Rector's palace; Aesculapiu's Capital.*

Educated physicians in Dubrovnik are mentioned for the first time in documents from the 13th century (6). They are not clergy, but rather members of the laity, students from Italian medical schools. The earliest record of an educated physician with a Croatian name was mentioned Prvoslav of Dubrovnik in 1280 (7). Ever since then, the Dubrovnik Republic always had at least two doctors-physicians and two doctors-surgeons in the civil service. In addition, private doctors and medics who treated wounds practiced medicine as well. Public doctors received stable salaries, and their obligations were to care for public health, publish certificates, to control epidemics, provide expert medical advice in court, and cure aristocrats and certain citizens without additional pay. Since the Dubrovnik Republic paid its foreign officers fairly well, many well educated doctors from Italy, Spain and Greece enlisted in its service (7).

Because of the very tolerant and positive attitude of the Dubrovnik Republic towards Jews, a large number of persecuted Jewish doctors settled safely in Dubrovnik. Particularly important for the history of Dubrovnik medicine was a Jewish doctor named Amatus Lusitanus (1511-1568), who spent two years in Dubrovnik, between 1556 and 1558. In his writings, *Curationum medicinalium libri septem*, he described about a hundred cases from his medical practice in Dubrovnik (8,9). In the history of medicine he is credited as making a discovery in the circulation of the blood. He is also said to have discovered the function of the valves in the circulation of the blood (10).

Other distinguished doctors from abroad included Jacobo Mazia of Salerno, who was the first to ligate vena saphena in the case of the crural ulcers. The Pope's personal doctors, Elia di Sabbato and Giorgio Hispano, wrote a treatise about curing patients in Dubrovnik's favorable climate (6) .

The first document about a medical doctor in Dubrovnik dates from 1280, and it is difficult today, eight centuries later, to have a precise view of the whole range of activities and the scope of medical expertise in those distant years. Nevertheless, we can still explore and understand some of the activities of the medieval medicus, noted in the archives of the Dubrovnik offices, in records written during the meetings of the three Councils and in other documents that the government of the Republic preserved until today (6).

In the 14th century there were two different profiles of medical doctors in Dubrovnik: doctors-physic *medicus physicus* and doctors-surgeons, *„medicus plagarum", „cirologus".*

Curares, herbalists, barbers, healers and other people with special talents, instructed either by their ow experiences or by the experiences of older experts, excelled in repositioning bone fractures or distorted joint in preparing various medicinal poultices and liniments, in healing wounds, lubricating swollen and painfu parts of the body, treating insect bites, nursing invalids, extracting teeth, and curing constipation and flatulenc (6,11).

The medical duties and obligations of the *medicus plagarum* were somewhere in-between a duties o barbers-surgeons and barbers-curarers and the duties and responsibilities of the *medicus physicus*, educated i medical sciences and praxis.

*Medicus physics* were members of the medical society, educated for four or more years in one of th famous medical schools. The most famous medical school at the end of the 13th and at the beginning of the 14 century was the one in Salerno, Italy, founded in the 9th century. In those schools, the works of Hippocrate Galen, Razes and Avicena were expounded. Students studied about the pulse and urine, about fever medicines and medication, herbs and the anatomy of the human body, but without practical work on cadaver All knowledge was based on ancient theories of medicine, in knowing the difference between sickness an health. They argued about the influence of nature, magical forces and astronomy on the course of disease an medication applied.

Ignorance of the rules of nature as well as very weak knowledge about the structure and function of th human body, diminished the value of educated physics, no matter how respected a medical school the attended. Nevertheless, the authority of a *medicus* who came from, for example, Padova, Florence, Bologna o Salerno, was untouchable; his learning was never criticized; his skills were respected and he was very well paid The *medicus physics*, himself, besides very profound speculation by a patient's bed or in his own home, ver well paid by the Government, did not do any „physical" jobs. He left those to the surgeons, members of a lowe class, who always handled the problem according to the instructions and orders of a respected physic, *medicus* who was on a higher level on the scale of medical classes and society in general. The surgeon could b insulted, disparaged, judged and condemned; it was permissible to interfere in his work. The physic was spare all of that. The difference in payment was more than double in benefit of the physic; respect from the public wa much more obvious again in benefit of physic.

At the end, all of those things do not mean that surgeons had hard and poor lives in the Republic. On th contrary, in numerous documents regarding the status, work, esteem and appreciation for doctors in the middl ages in the Republic, support from all the Councils, respect and concern for the living standards an undisturbed work of all *medicus*, physics and surgeons in the civil service, was obvious (12). Both the thoughts and deeds were highly respected. Their work was very authoritative and of great help to th Government. They were often asked for help in matters of state, or sent to foreign countries as ambassador

They were often members of various delegations representing the political, economic and other interests of the Government (6,11).

The government of the Dubrovnik Republic always strived to have excellent, valuable and diligent physicians in the area (13,14). One of the oldest contracts between a doctor and a patient concerns medication. A surgeon named Marko undertook to heal a boy from the island of Korčula. It was signed in Dubrovnik on 3rd of June 1306. The oldest contract is from the 21st of January 1306, connected with a *magistrus* named Ostesanus, also a surgeon. Older contracts probably existed, but unfortunately have not been preserved (6).

From a document from 2nd of November 1302, according to which a *physicus* from Salerno, named Rikard, was taken into civil service in Dubrovnik, we learn that he was obligated to cure any citizen without regard to payment, but was allowed to ask for compensation from foreigners in an agreed upon amount (6).

Contracts signed between a doctor, on one side, and a patient or his delegate on the other, in the presence of a notary public, tell us a great deal about medicine in the middle ages. Those contracts specified in detail all the obligations of a doctor in the therapeutic procedure, the responsibilities of a doctor in case of malpractice, the duration of a course of medication, the total amount of expenses that should be refunded etc. They were burdened with all the usual pitfalls of official paperwork: they were clumsy, full of repetition, long, boring, with plenty of legal terms, in an attempt to anticipate all the possible difficulties during the process of medication, especially possible longer duration.

These documents were written for solid legal validity, obligating both sides to stick to all the arranged terms. The security and validity of a contract were guaranteed by signatures of witnesses and delegates chosen among the most respected citizens.

In order to be admitted into the civil service, doctors had to sign contracts with the state. As far as we know, those contracts were renewed every year in most cases, rarely once in two years. The contents of those contracts allow us to glimpse the work, duties and obligations of doctors.

Once they entered public service, they received free lodging (*domus conveniens*) and a fixed salary (*salariatus communis*). In return, they had to cure any citizen without any charge. The contract strictly prohibited receiving any money as payment for medication or medicines from the citizens. The medicus had to treat all citizens, no matter rich or poor, the Rector and Bishop, all the State employees and their families. It was forbidden to become partners with any pharmacist in the matter of medicines or in any other way, under the punishment of exclusion from the holy sacraments. To prevent any doctor-pharmacist relation, trading and speculation between them was avoided. Doctors were allowed to sign a contract with foreigners working or traveling through the Republic who unfortunately became ill. Numerous documents exist stating that the Government constantly tried to help eastern countries preserve the health of their population and cure disease. The officers, doctors, architects, traders, craftsmen, barbers, pharmacists and other educated and skilled citizens were sent to the East in the service for a certain period. The Dubrovnik archives hold notes which indicate that Dubrovnik doctors traveled very often to interior regions of the Balkan Peninsula to cure Serbian and later Turkish aristocrats. Dubrovnik played a very important role as a mediator in supplying medicines and medical books to Serbia and Turkey. Famous Dubrovnik public doctors also treated the governors of eastern

countries and other citizens and their families with the permission of and payment from their own Governmen Not a single extant document describes the reverse situation (6,11).

One document from the 14th century, of great value to Croatian and European historical, cultural an medical heritage, describes two doctors who came to Dubrovnik from Parma, Italy. As far as we know toda they were the first doctors in Croatia to conduct a private medical practice. They did not receive a *salariatu communis* like all of the other public doctors, but were paid directly by the citizens. Contracts signed betwee them and their patients tell of compensation in money as well as in valuable goods, as a pledge, confirmatio and guarantee that the doctor would be adequately rewarded for his work, which, of course, should b completed with success. Otherwise the pledge would be given back. *„Conti chiari-amici chiari"* (11).

Doesn't it sound nice to hear that all the citizens of the Republic enjoyed the privilege of free medical car and were insured against mercantile connection between doctors and pharmacists as far back as the beginnin of the 14th century? It seems it was nice living in Dubrovnik, at least in terms of health insurance, and the right t free medical treatment by respected doctors!

Before signing a contract with a professional doctor, most patients tried to treat their own diseases i many, very strange ways. Signing a contract was the last decision after exhausting all the other possibilities fo cure, mostly using magic and ritual medication. Documented „causes" of disease were also very interestin „numbers of bats in the cave", „power of last year's storm", „number of thunder claps„ or „stories of on neighbor" etc (6).

A contract signed on the 4th of July 1414 with one of the best specialists for cataracts actually led to recovery. A certain man from the island of Šipan made an agreement with a doctor Samuel to cure his blindnes (16). Specialists of that kind were in high demand in that period so they were invited to different regions, citie and courts. They were called „traveling doctors for eye diseases". They could sell their skills for very goo money. And at the end, as their nickname suggests, they didn't need to pay much attention to what would happen after their mostly successful intervention. And how did a surgical operation for removal of a catarac look like in the 14th and 15th centuries? A turbid old lens was pushed from the front to the posterior chamber wit a sharp instrument. Success was immediate and evident, in the absence of infection. The procedure wa painless and a blind patient was able to see again. At a distance of 1-1,5 m he was able to see nicely the object surrounding him but without a possibility of a lens to accommodate. But pushed once into a posterior chambe the lens sooner or later, caused glaucoma, along with great pain and blindness. That usually happened one o two years later. By that time, our „traveling doctor" was already far away from that place and the patient. And h couldn't have cared less about his failure. And in case that he even came to know about the outcome of hi treatment, he could always find about a thousand reasons to blame either the patient or fate (6,11).

That is how we can view the situation from a distance of a few centuries. But one thing is sure. Traveling ophthalmologists did a fair and reasonable job, since the medical knowledge of the 14th and 15th centuries was not advanced enough to see the connection between the operation on a cataract, the immediate success after the procedure, the blindness after a year or two and the need to remove the eye because of the tremendous pain caused by the glaucoma (6,11).

16th century and Dubrovnik gave as another exceptional person, *Marin Getaldić*. Born in Dubrovnik in 1568, raised in a noble family, he started his elementary education in grammar and literacy in the Franciscan Monastery and in Latin and mathematics at the Dubrovnik *Gymansium*, where he graduated in 1588 (17). As an adult aristocrat he became a member of the Great Council in1588. He worked as a state officer and in the meantime did research on mathematics and astronomy. In 1590 he was appointed captain of Janjina, Pelješac as a penalty for the „carless attitude towards his duties". In 1597 he took a trip to Europe with his friend Marin Gučetić: *„We traveled all over North and South Germany, we stayed in England for two years, there was not a single part of France that we did not get acquainted with, we visited all of Italy ...".* In Rome he participated in lectures by Christophor Clavius, mathematician and astronomer in the *Collegium Romanum*, and became a friend and associate of the *Collegium* professors. In 1598 he went to England where he stayed for two years. In 1599 he went to Belgium where he was offered the position of professor of mathematics in Louvain, one of the most prestigious university centers in Europe, and there he earned his scientific reputation. In 1600 he visited Paris and became a good friend of the French mathematician Froncois Vieté. Getaldić studied his unpublished work and prepared it for publishing (18).

In Padua, Italy, Getaldić met Galileo Galilei and became a friend of Pope Urban VII who supported the publication of his work. In 1603 he left Rome without saying goodbye to his friends. It is presumed that the reason for his escape was that he committed some kind of crime for which he could have been prosecuted. Anyhow, he went back to Dubrovnik and enjoyed high esteem and fame all over Europe for his scientific work (19).

However, the government of the Dubrovnik Republic preferred practical to theoretical discoveries. So, in Dubrovnik he was engaged in politics. In 1604 he was assigned to the fortification and restoration of the Podzvizd Fort in Ston. He did not enjoy his work at all and got malaria. So, he was sent as an envoy of the Dubrovnik Republic to Constantinople in 1606 and became a reputable councilor of the Great and Small Council, the political bodies of the Republic. He also worked on State affairs as an officer of the Wine Department, an officer of the Department of wool manufacturing, consul of the civil law-cases, judge of the Appeal Court and a customs-house officer (20).

While he was staying in his hometown, he was nominated as a member of the Academy *Lincei* in Rome, but could not be elected because no one there knew where he was. He was busy performing experiments with parabolic mirrors in the cave of St. James in Dubrovnik, the so called „Betina's cave". His mirrors destroyed metals, lead and sliver alike at a distance and because of it Getaldić endangered sailing ships and certainly

frightened his fellow-citizens. Getaldić had the best scientific results in physics, especially optics, an mathematics. He became renowned for the application of algebra in geometry and his research in the field geometrical optics on which he wrote seven works. His contribution to geometry was cited by Dutch physici Christian Huygens and Edmond Halley in England. His work is described in Herigone's work from 1634, *Curs mathematicus*. Today, he is known as the creator of the parabolic mirror (2/3 m or 66 cm in diameter), ke today at the National Maritime Museum in London. Thanks to him, the Dubrovnik Republic had a telescop before Newton's discovery (constructed by Getaldić?). Marin Getaldić wrote several scientific books: *Promot Archimedus*, published in Rome in 1603 – an accurate table of specific weights of solids and liquids, *D resolutione et compositione mathematica*, published in Rome in 1630. He has also published a pamphlet wi the solutions of 42 geometrical problems, *Variorum problematum colletio*, in 1607, an early application of geometry to algebra (21).

Marin Getaldić and his wife, Marija Sorkočević Getaldić, had three daughters. After the third childbirth, his wife died. Marin Getaldić died on April 7, 1626. Above the entrance of their home there is still today a sign written in Latin: *„Stay away, jealousy, quarrelling, vanity and worry! Let peace and tranquility adorn caves, gardens and cliffs!"* (Picture 3). The best description of Marin Getaldić was given by Paolo Scarpi, a Venetian scientist: *„Marin Getaldić (1568 – 1626) - A devil in mathematics, an angel in his heart"* (22).

*Picture 3. Inscription written above the entra of Marin Getaldic' house: „Stay away jealousy quarreling, vanity and worry! Let peace and tranquility adorn caves, gardens and cliffs!"*

In the 17th century, the reputation and opulence of the Republic declined, and foreign doctors with great skills stopped joining its service. But, in the meantime, the number of Dubrovnik's own native doctors started to increase, taking advantage of the opportunity to earn recognition at home. Specialists appeared very early among Dubrovnik doctors, and they limited their medical activities to particular surgical operations o particular group of diseases. For instance, an ophthalmologist was practicing in Dubrovnik by the year 141 and by 1475, specialists for fractures and sexual diseases were recorded (6,11,23). However, it was not un 1784 that Dubrovnik had a dentist (6).

Some of Dubrovnik's doctors became very famous abroad. For instance, Dominco of Dubrovn became a professor in Bologna and Siena. Dominco is the first medical writer of Croatian background who manuscripts have been preserved to the present day. He became Rector of the University of Padua and credited with reviving the long-neglected practice of clinical education at the patient's bedside (6,11).

In the 19th century, Du doctors started to write expert treatises in Croatian, and conduct research on th national level. But even before that period, the black friar Ignatus Aquilinie (1642-1715) wrote the first no

conceptualisation of disease and concrete approach to the patient. He applied the principles of Galileo's „ne mechanics" to life phenomena, created a modern concept of disease as a clinical syndrome and a nov definition of nosologic entities and their systematic classification (27).

In his letter of June 8, 1700 to Roman cardinal Aldobrandini, Turkey's Sultan physician, Israel Conigliano, wrote: *„With the immortal masterpiece De praxi medica by Mr. Baglivi, the number of books in m library, so far consisting of a single volume, i.e. Hippocrates, has doubled and now it includes two book Hippocrates and Baglivi. Reading through Baglivi's monograph, I feel like a fly in St. Peter's Cathedral. Still, feel honoured to be there, although quite late, after so many years pregnant with experience and errors. I a deeply impressed indeed by the vast knowledge Mr. Baglivi has acquired young as he is"*(24).

Baglivi performed microscopic experiments and investigated the fine structure of tissue of youth, adul and embryos and compared them with the fine structure of tissue of chickens, dogs, rabbits, porcupine, turtle fish and a circus lion. In his book *De fibra motrice et morbosa* (1702) which was published in its third revise edition in 1703 in Lion, Basle, London and Utrecht, he presented his original theory of fibrillary patholog within the frame of his iatrophysical and solidistic medical approach. It was a significant event in the history biostructuralism, subsequently followed by Rudolf Virchow's cellular pathology in a logical sequence (28).

He presented his iatromechanical conception of the organism: the basic structural element of the huma body and animal organisms is fibre. Fibers as carriers of all vital functions and a seat of diseases, are mor important than the four bodily humours (in contrast to traditional/humoral medicine). He explained fibre as basic compound of atoms, passive mechanical features and *vis innata*, genuine characteristic of conductibili and active contraction. He divided bodily fibers into fleshy and membranous ones, differentiated smooth fro striated muscle and distinguished the autonomic (natural) and voluntary (animal) nervous system (29).

However, he misunderstood the authentic pulsation of dura mater; his basic mistake was about th function of the meninges – his wrong conclusions were based on the premise that membranous fiber wa formed from neural fluid and lymph and that it was a continuation of the meninges. He presumed that a membranous fibers were moved by dura mater of the brain. According to Baglivi, the two central starters of th organism, heart and dura mater, pulsate all the time, supporting and regulating activities of the whole organism Through the activities of dura mater, systolic movement is carried from the brain to the periphery an contrasystalic/reflexive movement vice versa (24,30).

In spite of his misapprehension of the authentic pulsation of dura mater, he recognized the superiority the brain to all neural events: *„... The supreme and overall power belongs exclusively to the brain, not so muc for some fluid secretion but for the continuous vibrations of its meninges, their effect then reaching individu parts"*(30).

He was among the first to recognize the vegetative nervous system function: *„The body is a machine, sort of a clock, horologium oscillatorium, that is continuously controlled by the soul. The soul is seated in th brain, near the meninges,..."* He was the first to locate the bodily clock within the brain and the first who did complete and consistent survey of the function and role of the vegetative nervous system as a carrier biorhythmic functions. As we know today, several centuries would have to pass until F.X. Buchat woul differentiate vegetative from the somatic nervous system until in 19th century (30).

By the 17th century Baglivi had written his first description of the vasomotor function and its independence from cardiac effects: *„...thus, all blood vessels that are tissues made from fleshy and membranous fibers, and a consistent mixture of two movements subject to two initial triggers, i.e. the heart and dura mater, obviously constitute a separate system independent of other parts ...; ...The more so, by performing tests and thinking properly, we will realize that they – due to their conical shape and harmonious merging of sensory and motor fibers – thus arise hidden movements and impulses in the liquid parts; these impulses have nothing in common with cardiac impulses"*(30).

Today, all the credit for the description of vasomotor nerves is given to Claude Bernard, who described it in 1854 (30).

Baglivi was also the predecessor of the concept of the hematoencephalic barrier: *„It is widely known that the occipital (vertebral) arteries and main cervical (carotid) arteries, when reaching the brain cortex glands, are so thin, small and motionless due to almost unlimited ramifications (capillares) ...; .... the task of the very small brain cortex glands (neurons) is to separate neural fluid from the blood, an to transport it to other parts of the body via excretory vessels; all excretory vessels that belong to the brain cortex glands constitute an important part of the brain, while the brain – dividing into various branches, thus being distributed both within the head and outside the head in the spinal cord – produces nerves that serve as ducts for the previously filtered fluid"* (30).

He was the first to define the features of irritability and sensitivity. With his concept of the membranous fibrillary system being capable of sensations, Baglivi opened the way to the teaching of Albrecht von Haller (1707-1777) on sensitivity (*sensibilitas*) and irritability (*irritabilitas*) as the basic properties of living structures. In that way he clearly differentiated these two properties and even provided the first physiologic formulation of the term *stimulus* (30).

Baglivi was a pioneer of the concept of membranes as insulation material. Membranes had a central place in Baglivi's conceptual framework, both in the global organization and functioning of the nervous system. He considered membranes as a demarcation line between the rigid and liquid parts, whose continuity ensures functioning of the whole body. He explicitly distinguished sensory (afferent) from motor (efferent) parts of the nervous system and spoke about the reflex organization of the nervous system, locating the reflex center within the meninges (30).

Baglivi also described the concept of pathogenesis of periodic headache (migraine): on the basis of the postulated authentic pulsation of the meninges and their marked painfulness in his experiments and clinical pathology, he considered migraine to be caused by meningeal changes (24,30). He presumed the existence of parenchymal and meningeal trigeminovascular connections and neurogenic inflamation of the meninges as the main cause of the migraine. As we know today, a trigemino-vascular complex is in the center of the pathophysiological mechanism of the migraine (31).

As he wrote himself in one of his books: *„... such a novel and comprehensive work I would hopefully be able to complete only when, as an 80-year-old man, I collect, may God help me, an adequate amount of experience"*(24).

Unfortunately, Baglivi died very young, at the age of 39, in Rome, on 14th of June, 1707.

His whole scientific and medical work was based on *ratio, experimentum et experientia*; critical readin and interpretation of previous writings; authentic clinical observation of the patients; inventive experiments o live animals; and systematic post mortal findings (24).

He is today credited with several medical discoveries: the importance of the medulla oblongata as a sit of some vital functions; experimental demonstration and proof of the influence of vagal nerve on digestion, an the observation that brain injuries cause the palsy of the contralateral parts of the body (24).

Although his grandfather was Armenian, his other ancestors Croatian, he was born in Dubrovnik, an lived in Italy where he got fatherly love and protection, a name, a medical education, friends and followers from where his scientific glory spread throughout Europe, Gjuro Armeno Baglivi, an *Epidauro Pirgense* as the used to call him, actually belonged to all mankind. He wrote himself in Opera omnia medica: *„Medicine is not product that human genius creates all at once, in the moment, but a child of extensive time"*(24).

Pharmacies were organized in an exemplary way in Dubrovnik. Since ancient times, people ha collected and sold medicinal herbs for which the Dubrovnik area is well-known. Druggists are mentioned in th Dubrovnik statute of 1272, and in 1318 the Small Council decided to take a chemist into regular service (6). H was responsible for keeping the pharmacy well supplied with all sorts of medicines. The government o Dubrovnik provided chemists with regular annual salaries, interest-free loans interest and free lodging, in order to attract skilled professionals and provide citizens with high quality inexpensive medicines. The state physic continuously supervised the condition of the pharmacies. Official medicines were determined and very soon, official taxes and prices of medicines were established (6).

The pharmacy in the Franciscan monastery in Dubrovnik is one of the oldest pharmacies in this part of Europe and generally in the world. Since the Franciscan monastery (Picture 5) has a rich library, with one of the best preserved collections of manuscripts, everything there still seems to smell of ink. Since the oldest times, other, more aromatic smells have also been associated with the Franciscans – odors of sage, wormwood and mint and dozens of other medicinal herbs and preparations sold in the Franciscan pharmacy (Picture 6), an institution whose founding is traditionally dated to 1317 (32).

*Picture 5. Franciscan Monestary (53).*

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*Picture 5. Franciscan Monestary (53).*

*Picture 6. Franciscan Pharmacy (54).*


*Picture 7. Franciscan Pharmacy Museum.*

At first, the pharmacy only served the monastery. Soon, however, the needs of the town began to grow. Also, a growing number of citizens began to contribute money for the development of the pharmacy. The objects on display today in the small pharmacy museum (Picture 7) are only a few remaining relics of an institution which was at one time decorated with pictures of Hypocrites and Galenus and was by far the best stocked pharmacy in the entire area. The location of the pharmacy within the monastery complex was often changed, but it always remained an important influence on scientific medical practice in the city (33).

Medicines were also of course often referred to by writers. One of them was Sabo Bobaljević, a poet, who, in the middle of the 16th century was the object of the scholarly attention of a famous doctor on his visit to Dubrovnik. The doctor was Amatus, a Jew from Portugal, and he treated Bobaljević for syphilis. The patient had been ailing for quite some time, but did not take proper care of himself and continued an immoral life, so the illness spread to his brain and he began to lose his hearing. He described himself in a poem as *„deaf as a stump in the forest"*. There are descriptions of Amatus' treatment: he gave Bobaljević very strong antidotes which led to great perspiration and finally „black and white pus" started coming out of his ears. The poet was not Amatus' only patient. In 1560 this Portuguese doctor published a whole book in Venice, describing his Dubrovnik cases (8). Especially notable among them were the cases of sterility or excessive potency (9). For example, he treated the prioress of a monastery who allegedly had *furor uterinus* (and incessantly asked to be sexually satisfied). However, being a Jew, Amatus certainly could not have set foot in the Franciscan pharmacy. In spite of his medical skill, he was looked down upon by citizens, just as contemporary cultural historians today neglect the medical writings of the past. They forget, however, that medical writings often offer us a revealing view of contemporary mores (32).

Another very important Dubrovnik pharmacy was founded in 1420 at the Domus Christi (Picture 8). Located on the main street, it functioned as an public institution, owned by the state, from the day of its foundation until 1808, when it became the private property of the chemist Mato Šarić (32).

*Picture 8. Domus Christi Pharmacy.*

*Picture 9. City aquaeduct; water system above the city's western gate (Pile Gate).*

*Picture 10. Small Onofrio's Fountain.*

*Picture 11. Domus Christi Hospital, noursing home – Latin inscription above the main entrance: „Tolle crucem tuam et sequi me" („Take your croos and follow me").*

The Republic paid great attention to public sanitation and established numerous regulations about the cleanliness of houses and streets. Paving of the streets with bricks and stone plates began in the first half of the 14th century, and by 1415 regular street sweeping service was organized. Major drainage pipes were laid in the Middle Ages and in 1436 the Great Council published a regulation about the system of sewage (1,34). In the same year, the Italian architect Onofrio della Cava built a city aqueduct (Picture 9). To celebrate the completion of the Dubrovnik water-works, the small Onofrio fountain was built, a real jewel and masterpiece of sculpture (35) (Picture 10).

The leprousorium in front of the eastern city gates is mentioned in documents from 1306. The main Dubrovnik hospice, called Domus Christi (Picture 11), was founded in 1347, as a shelter for the poor. After that, a few smaller hospices were established, and in 1432, the first orphanage, was opened (Picture 12). By a decision of the Great Council in 1540 the construction of a major hospice was arranged and new housing regulations were established. In the Middle Ages, the hospice was converted into a public hospital, the first in this region. The Domus Christi hospital was the first with an organized medical service. A

*Picture 12. Orphanage – Latin inscription above the entrance: „Cochaluit cor meu itra me et ditatioe mea exeardescet igni" (The heart was burning inside me, on the very tought the flame would burst").*

surgical operation using ether narcosis was performed in that hospital as early as 1847. A new hospital was built in 1888 in Boninovo and thanks to the hard work of the doctors, new specialties developed (1,6).

Dubrovnik was struck several times by epidemic diseases, mostly of the plague, typhus, smallpox and influenza. Dubrovnik historians described the devastation of the each epidemic. From 901 to 1784 for instance, Dubrovnik was very vulnerable to the epidemics because of the very intensive, sea-borne traffic (1,6).

Dubrovnik's greatest contribution to medical history is the fact that it was the very first town to establish a quarantine.

In 1348 the epidemic called „the black death" ravaged the population of Dubrovnik. In the following years, several epidemics of pestilence followed, so the people of Dubrovnik decided to institute some protective measures. Other states, for instance, Venice, prohibited commerce with contaminated areas during epidemics. This caused great economic losses, and so was only a temporary measure. However, Dubrovnik introduced a new form of epidemiological protection, without cutting off trade. The first decision about quarantine was made by the Great Council on the 27th of July 1377. At first, the quarantine was established on the island of Mrkan or in the town of Cavtat, and it lasted for 30 days. In the 15th century the period of the time spent in the quarantine was prolonged to 40 days, and the isolation occurred on the island of Mljet, where an old monastery was converted into a quarantine facility. Later, a special facility was built near Dančе and finally in 1590, the government order a large new complex, known today as the Lazareti to be built near the Ploče Gate. The Lazareti was used as a quarantine, but also contained storage rooms. Before that time, Turkish and other Levantine merchants, who constituted the great majority of foreign traders, usually resided outside of town, while some of them found accommodation inside the walls of the city. The Government was anxious to keep these foreigners under control, both with regard to public health and with a view toward maintaining law and order in the city at night (1,6,35).

The Great Council established various measures for fighting epidemics. A special Health magistrate, consisted of five senators elected by the Great Council. In the service of the magistrate were the captains, officers of the lazareti and special sanitary officers which had great power during epidemic outbreaks. They had the power to physically punish anyone who broke the rules of the quarantine. The most severe punishment was cutting off an ear (36).

Cereals and new goods could be imported into the city immediately, but clothing and used goods had to stay in the quarantine with their owners. A sanitary cordon was arranged at the border with Turkish regions.

Special care was taken in dealing with ships entering the Dubrovnik harbour. Each ship had to have a sanitary passport from its harbour of origin and a certificate from the Dubrovnik consul. The state secretary verified the passports and delivered the health documents to ships leaving Dubrovnik (36,37).

*Picture 13. Quarantine – Lazareti; view from the sea.*

The original architectural features of the Lazareti have been preserved to the present day (Picture 13). An interesting literary description of the buildings was offered by a Turkish writer and traveler who stayed in Dubrovnik in 1664. He described the Lazareti as a fine building with several stores, and comfortable rooms, but he also wondered why the facility which he took to be an inn observed such strict regulation, forbidding their residents to go out at night and have a good time. If he came to Dubrovnik today he would be pleased to find out that his „inn" has been turned into an art and recreation centre (35).

The 18$^{the}$ century, the so-called modern age in that time, was the century of philosophers, artists, criticism and philology, the century when the first encyclopaedia was written. It brought science to everyday life, progress in technology and manufacturing, practical interests and hunger for profit and separated political interests and scientific ideas from religion. Dubrovnik, on the other hand, in 18$^{th}$ century, was still recovering from the great earthquake of 1667 and moving toward the decline of the Republic, which was formally abolished in 1806 (2).

The old and tired patient, which had lost one quarter of its citizens and a great fortune in the quake, had one main interest: to preserve the neutrality of the Dubrovnik Republic. In that time, it had three academies, the first printing-house, a state orchestra and a national literature and culture. It produced another great son, *Rudjer Bosković*, born in Dubrovnik in 1711 (Picture 14), the son of Nikola Bosković and Pavle Bettera. Rudjer Bošković, in his fifteenth year, after completing the usual


*Picture 14. Ruder Bošković's house in Dubrovnik.*

elementary studies, entered the Society of Jesus and joined the *Collegium Ragusinum* where he acquired his education (38).

His education in mathematics and physics continued in the *Collegium Romanum* where he was appointed a professor of mathematics in 1740. At first he became famous because of his elegant solution to the problem of finding the Sun's equator and determining the period of its rotation by observation of the spots on its surface (39).

Rudjer Bošković was a versatile genius: he studied astronomy, mathematics, physics, and geodesic design and wrote poetry. He was well-known for his elegant features, brilliant in public contacts, although he sometimes showed a prickly temper and had arguments and sorrows. His investigations covered all the fields of physical science and he published a very large number of dissertations. His great scientific discoveries are as follows: the transit of Mercury, the Aurora Borealis, the figure of the Earth, the observation of the fixed stars, the inequalities in terrestrial gravitation, the application of mathematics to the theory of the telescope, the limits of certainty in astronomical observations, the solid of greatest attraction, the cycloid, the logistic curve, the theory of comets, the tides, the law of continuity, the double refraction micrometer and various problems of spherical trigonometry (40).

In 1742 he was consulted, with other men of science, by Pope Benedict XIV, in securing the stability of the dome of St. Peter's in Rome, in which a crack had been discovered. His suggestion was adopted (38).

Bošković was also engaged in diplomacy: in 1757, as an agent of Lucca, Bošković was sent to Vienna to try to resolve a dispute between the grand duke of Tuscany and the republic of Lucca with respect to the drainage of a lake. His trip was successful and he managed to orchestrate a satisfactory conclusion to the matter. As a diplomat, he participated also in resolving a conflict between the British government and the Dubrovnik Republic: the British government had a suspicion that warships had been outfitted in the port of Dubrovnik for the service of France, violating the neutrality of Dubrovnik. In 1760, Bošković was selected to undertake an ambassadorship to London to vindicate the character of his native place and satisfy the government. His mission was completed successfully, bringing great credit to him and delight to his countrymen (38).

In 1764 Bošković was appointed chair of mathematics at the University of Pavia. In 1769 he led an expedition to California to observe the transit of Venus and in 1777 he accepted the directorship of the Brera observatory near Milan for six years. Because he had many enemies, he was driven to frequent change of residence. Deprived of past and intrigues of his associates, he was about to retire to Dubrovnik. In 1773, after the suppression of his order in Italy, Bošković accepted an invitation from the King of France. He went to Paris where he was appointed director of optics for the navy, a position created especially for him, receiving a salary of 8000 "livres". He became a naturalized citizen and stayed there for ten years, but the position became intolerable. In spite of everything, he continued to work in the pursuit of science and published many remarkable works (41).

Bošković designed a telescope filled with water in all its components, which was later created at the Greenwich observatory in 1871, 84 years after his death. He was the first to detail a procedure to compute a planet's orbit from 3 observations of its positions and the first to devise a procedure for determining the equator

of a planet from 3 observations of a surface feature (38). Prominent as a scholar, with a reputation for honesty, integrity and scholarship, Bošković managed to persuad Pope Benedict XIV to finally remove Copernicus from the Index of Forbidden Books, minimizing in that way the hostility of Catholic Church to the Copernican system. He also helped in popularising the theories of Newton. In recognition of these accomplishments, a large lunar crater was named in his honor (38).

His masterpiece, *Theoria philosophiae naturalis*, was published in Latin in 1758 in Vienna, and a second edition was published in 1763 in Venice, also in Latin. In 1922 a bilingual edition, in Latin and English, was published in London. In *Theoria philosophiae naturalis*, Bošković presented and elaborated his radical hypothesis: that matter is not infinitely extensible, that there is no real *continuum* and that matter is a *discretum* with atoms representing centers of repulsive and attracting forces determined by the distances between them (42).

*Theoria philosophiae naturalis* was the first coherent description of atomic theory: bodies could not be composed of continuous matter, but of countless *„point-like structures"*; the ultimate elements of matter are indivisible points, *„atoms"*, which are centers of forces and this force varies in proportion to distance. His work appeared well over a century before the birth of modern atomic theory (43).

A century later, Friedrich Nietzsche wrote in his works *„Jenseits von Gut und Boese (Beyond Good and Evil)"*: *„...Bošković and Copernicus, the greatest and most victorious opponents of illusion"* and *„Die Unschuld des Werdens (Innocence of Existence)"*: *„I consider Bošković one of the most significant turning-points, like Copernicus"* (44).

In the second half of the 20th century, Werner Heisenberg and Niels Bohr, Nobel Prize winners said: *„Bošković's theory of forces is a predecessor of quantum theory, i.e. Bohr's atom model"* and *„Bošković's philosophy of nature as a complete entity will become the philosophy of the century to come"* (45).

In his work *„Appendix ad metaphysicam pertinens de anima et Deo"*, Bošković gave a short commentary in the field of neurophysiology of vision, concerning the sense of colours, using an example of stroke patient to illustrate his classification of neural functions (45,46).

But, in that very book, Bošković's direct great contribution to the field of neurology was his explanation of the phenomenon of phantom pain: *„Some people's belief that the soul is spread all over the body is, among others, based on the strange phenomenon of occasional sensation of pain in fingers after amputation of the arm, as if still having the fingers. As the pain is felt although the soul is not present in the fingers, they consider it a basis to state that whenever feeling pain in the fingers, we feel it without the presence of soul in them. This, however, does not appear to actually prove anything, because it might well be that only the initial sensation inducing finger pain requires the presence of soul in the fingers, without which the very idea of pain could not be initiated: once formulated by its presence, the idea of pain might therafter be stimulated without it, by mere movements of the nerves previously associated with the finger fiber movements in the initial sensation of pain"* (47).

The terms of the soul, idea and fiber movements that he used in his interpretation using the medical terminology of the time stand for the modern account of the genesis of phantom pain within the concept of peripheral cause and central pathogenesis. Bošković anticipated the concept of denervation and deafferentation hypersensitivity, divining the very core of the specificity of the sensorineural functioning (45,47).

Bošković's explanation of phantom pain implies the presence of a specific sensory modality at the level of interpretation and a projection specificity of the neuron, as a basis and precondition for future experience.

Bošković's intention was to support, by a clinical example of the central pain, his concept of the constitution of the soul. In addition, he gave a solution to the problem which would have to wait for more than two centuries to be discursively elucidated by means of scientific experiments (45).

In 1746 Bošković became a member of the *Scientarium et Artium Institutum atque Academia* in Bologna, in 1748 of the *Academie des Sciences*, Paris, in 1760 of the Empire Academy of Science in St. Petersburg and in 1761 of the Royal Society in London, all the most prestigious scientific societies in the world. In June, 1747 he paid his last visit to his hometown, Dubrovnik (38). On August, 28th 1786, his sister, Anica Bošković, a poetess, wrote her last letter to her brother, saying: *„You could have spent your life much more usefully, if only you didn't care so much about your own comfort"* (49). Those words also partially reveal the sensibility and the mentality of Dubrovnik citizens!

After a visit of several months to the convent of Vallombrosa, he went to Brera in 1786 and resumed his literary labours. At that time his health was failing, his reputation was on the wane, his works did not sell, and he gradually fell prey to illness and disappointment. He suffered from depression together with paranoid ideas. Was it the comprehension of a genetic disorder or presentiment of a terrible end? We don't know (50).

He died in Milan on *February 13, 1787* and was buried in the church of St. Maria Podone. On the same day, the Senate of the Dubrovnik Republic arranged a ceremony in the Dubrovnik Cathedral with the performance of a requiem composed by Julije Bajamonti (1744-1800), a Croatian medical writer, composer and historian, from Split (38).

*„Were it not for gravity one man might hurl another by a puff of his breath into the depths of space, beyond recall for all eternity".* (Ruđer Josip Bošković: *„Theoria Philosophiae Naturalis"*) (51).

In order not to hurl ourselves recklessly into the future, let us not forget our past!

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KLINIKA ZA NEUROLOGIJU


KB "SESTRE MILOSRDNICE"

# 2. NEUROLOGY OF ART

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The creativity and art for many centuries were the point of interest for scientist trying to reach the secret of artistic talent. The much easier task was to explain motoric and sensoric functions of human brain. In spite of extreme technological development it is not possible for neuroscience to oversimplify the art as a pure sensorimotor function of brain areas, though to observe it as a complex product of creative mind. During the past decades, investigations in the field of neuroscience resulted with number of new facts about cognition and consciousness. In the field of art it was discovered that during listening of music, playing of an instrument or dancing, as well as watching colors or specific types of paintings, specific changes in brain functioning occur.

Till 1950 only five scientific papers in the field of neuroscience of the cognition and consciousness were published and till year 2000 this number multiplied up to more than 1800 papers. The reason for such a great difference lies certainly in rapid and large development of medical technology that is able to show not only the morphology of the brain, but also a function of certain brain areas, sometimes even in the real time (1).

Introduction of modern diagnostic procedures for visualization and measurement of brain morphology and function, as positron emission tomography (PET), magnetic resonance imaging (MRI), functional transcranial Doppler and some biochemical methods enable conducting number of neuroscientific studies.

At first, investigators started their search in great brain areas, defining the functions of cerebral hemispheres. It was found that in every person actions directed from one hemisphere is predominant; it was named the hemisphere dominancy. In majority of people the dominant hemisphere is the left one (90%), were centre for speech is located, and is responsible for logical thinking, mathematic skills, writing and organization skills, while right hemisphere is considered to be creative side of the brain, "visual" hemisphere, were centers for artistic expression, creative thinking, imagination and intuition are located. Right hemisphere is associated with musical skills and good three-dimensional orientation. Also it is associated with good coordination and athletic skills (2,3,4). Since the centers for visual conception in the right hemisphere are located, it was found that patients with right-sided brain lesion have difficulties when they are asked to imagine a picture of a named object. Results of the studies showed that uncreative people have marked hemispheric dominance, while creative people have less hemispheric dominance. The dilemma exists – whether is in the artists the right brain hemisphere dominant or in these persons hemisphere dominance doesn't even exists? Many examples are showing that left hemisphere suppresses creative states and processes. Some patients with left-sided brain

lesions (Alzheimer's dementia, stroke...) developed afterwards artistic skills for playing a musical instrument, painting or dancing (5,6,7,8). Astonishing example is Katherine Sherwood, professor of art, who suffered a severe dominant hemisphere stroke, but she continued to paint with her left hand. She achieved rather more acclaim and financial success after her stroke. She herself describes her recent work as unburdened, uninhibited by consciousness (9).

Numerous studies of the neural concept of the art, of the visual impressions, released very interesting results. One of these studies, in the field of painting, succeeded to show the activation of different areas of visual cortex during watching different kind of compositions: landscapes, portraits or abstract compositions. Different areas of the brain undertake different tasks, it is functional localization of the cerebral cortex. Different areas are responsible for different tasks, V4 area for colours, V5 area for motion, there are separate areas for object, face and recognition of position in space (11,12,13). Specific patterns of activation in visual areas of the brain is noticed during tests using different combinations of colors, which could explained why famous artists often have used same combinations of colors. Why we like some colors could be explained by results of the studies that discover the neural pathways between visual cortex and limbic system responsible for emotions (14). The results of further studies could help to understand artistic skills of painters and sculptors. In one of these studies persons were tested by visual, tactile and kinesthetic stimuli, and they were asked to classify the stimuli as new one or already experienced. Results showed that only one type of stimuli is enough to get familiar with the some object. In the test, the cube that first was presented as tactile stimuli was classified as familiar one after it was presented only as visual stimuli. It could be possible explanation how person can his visual impression or scene transfer by motor functions of his hands on canvas, producing a painting or on material producing a sculpture (15).

The studies of neural concept of the music answered to some questions from the past, when the influence of the music on human mind was first recognized.

For the music perception the interplay of activity on both sides of the brain is necessary. In the right side the centers for perceiving pitch, certain aspects of melody, harmony, timbre and rhythm are placed and in the left side the processes of rapid changes in frequency and intensity, both in music and words are taking place. For complete perception of rhythm both left and right side are necessary. Significant role in rhythm and melody perception has frontal cortex (16,17).

In the field of music, neuroscience is much helped by fMRI. This method is able to show the cerebral activity pattern associated with musical perception. This pattern is different in musicians and non-musicians (18,19). In musician's activation of the left dominant secondary auditory areas in the temporal cortex and the left posterior dorsolateral prefrontal cortex during a passive music listening task occurs, while in non-musicians the activation in the right dominant secondary auditory areas during the same task occurs. Also, the functional transcranial Doppler study showed a different brain hemisphere activation pattern in musicians and non-musicians during listening to music (20, 21). Special interest in influence of the music occurred after the studies showing that changes, adaptation of the brain, brain plasticity after listening or performing music can arise. The brain plasticity is occurring in the different periods of the human life. First one is during development of the child brain: outside stimuli influence on fetal, newborn and child's developing brain. In children, strict cerebral

hemisphere dominance for music and rhythm doesn't exist, than these centers are developing with age and it can be influenced by outside sound stimuli. So, in every child it is possible to discover and develop musical talent. Beside plasticity during brain development, the brain of the adult person can also be "plastic". It was found that in persons who play an instrument for number of years, reorganization of cortical centers occurs; the centers for perception of music as well as motor cortex. The part of motor cortex responsible for finger movements is for that reason much larger in professional pianist than in other people. Brain plasticity is also present in injured brain; the use of proper stimuli makes recovery of lost function possible by activation of other healthy parts of the brain cortex. One of the often used stimuli is music; listening of the rhythmic melodies and learning to play a musical instrument. The studies have discovered that during listening of the music some areas of motor cortex are activated, although the person is completely still. The similar situation occurs while person imagine some tune or rhythm. It is considered that music has a complex influence on human brain, motor and sensory areas, that could be explanation why music is a drive for dancing, singing or expressing of emotions by mimic and gesticulation (22,23).

The music as a therapy is used for centuries, since its influence on human mind, emotions and body was already then recognized. In the 19$^{th}$ and in the beginning of the 20$^{th}$ century first organized musical therapies was introduced in psychiatric hospitals, during dental operations and at pediatric departments. The significant effect of the music was obvious on reducing pain, depression and anxiety.

Great interest arose during the 1990's after publishing the results of studies investigating the effect of listening to music on cognitive and bodily functions; it was called the Mozart Effect (24). It means that enhancement of performance or a change in neurophysiological activity occurs while person listens to Mozart music. The basis of Mozart effect lies on the superorganization of the cerebral cortex that may resonate with the superior architecture of Mozart's music. First effect was observed at University of California during testing a spatial IQ. Students improved performance on test results of 8-9 points and increased scores on spatial-temporal reasoning after ten minutes of listening Mozart Sonata for two pianos in D-Major. Neurophysiologic explanation is that listening of Mozart music helps in organization of triggering of cortical neurons, especially enhancing creative processes in the right hemisphere associated visual-spatial reasoning. It was concluded that listening to the music has an effect of training, i.e. that music can enhance concentration and improve the intuition. The further studies showed that Mozart music has a positive effect on increasing of EEG coherence, increasing correlations of neurophysiolological activity on the temporal and left frontal areas, increased spatial-temporal reasoning after piano lessons in preschool children and in changes in amplitude of alpha and increased interhemispheric coherence (25,26). The Mozart Effect was showed also in patient with epilepsy. During and after listening Mozart's Piano Sonata in D Major (K.448) in 23 of 29 patients significant decreased epileptiform activity after very short period of time (immediately or after 40-300s). Also the amplitudes of discharges decreased (27,28).

In his book the „Mozart Effect", Don Campbell explained effect of music on mind and body. Not only the Mozart's music, than also listening to other kind of sounds, music and vibrations, starting as a fetus inside the womb, can have influence on health, learning and behavior. Music also can be used in the therapy of: pain, Alzheimer's disease, back pain, chronic fatigue syndrome, depression, diabetes mellitus, epilepsy, headache,

hypertension, Parkinson disease, stroke and as a help during rehabilitation. Patients after stroke who have listened to the music during physical therapy had better results than the group without musical background during rehabilitation. Also, they suffered of depression in a less degree and they were emotionally more stable and more communicative than control subjects.

Neuroscience does not only give us answers about the mechanisms of visual and hearing processes triggered by art. It also raises the questions and sometimes gives answers on dilemmas about how neurological conditions influenced art. In literature the great examples are books form authors Jean-Dominique Bauby who describes in his book *The Diving Bell and the Butterfly* his illness, the locked-in syndrome and Oliver Sacks, neurologist who describes in popular but still scientific manner the neurologic conditions and influence of music on humans (29). Several painters in their artistic work expresses their neurological illnesses. Francisco de Goya after developing auto-immune disorder affecting inner ear and the uveal tract changed the way of painting. Instead of established portraits he started to paint pictures with motives as a shipwreck, prison, lunatic asylum or a fire at night (30). Also the characteristics of Van Gogh's works coincide with the temporal progression of his illness, it is assumed that number of the motives in his pictures describes epileptic aura (31). For neurologist it is difficult not to see in the paintings of Giorgio de Chirico number of neurological symptoms: blurred vision, scintillating scotomas, visual field loss. Some scientists are assuming that this is predominantly the result of his migraine and others stand more for temporal epilepsy theory (32).

The connection between neurology and art is strong and bidirectional (33). Art helps neuroscience in exploring brain functions and different area connections. Art has been used in treatment and rehabilitation in neurological and other diseases. Neurology can explain different ways of artistic expressions. Neurology of art has large undiscovered potential and it will be very interesting to follow further developments in this field and more than this, the implementation of art in everyday clinical practice.

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KLINIKA ZA NEUROLOGIJU
KB "SESTRE MILOSRDNICE"

# 3. EPIDEMIOLOGY OF STROKE IN CROATIA

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## INTRODUCTION

Epidemiological indicators and results of neuroepidemiological research of stroke and other cerebrovascular diseases have great significance in estimating the scope of the problem of this disease in population. Such research states distribution of the illness and factors, which influence the distribution, follow short-term and long-term consequences, as well as socio-economic burden of the illness for the whole community. Epidemiological trials usually include hospital material, but population trials provide the most accurate epidemiological data. Regarding the fact that people with sroke are usually referred to neurological check-up and hospital treatment, it can be presumed that hospital registers include 85-90% of patients. Whereas population trials are important for stating morbidity (incidence and prevalence), mortality and long-term outcome and life quality after stroke, clinical epidemiological trials enable estimation of lethality and short-term outcome of this disease. Neuroepidemiological research encounters many methodological problems. Population research depends on specific knowledge and willingness of participants in the research. Although the most reliable data include deceased who died in hospitals, not even they are completely accurate, unless they are confirmed by an autopsy. Test results of a coroner are even less accurate. Some cases of stroke do not have to manifest themselves in classic signs of motor paralysis, speech problems and other, what causes difficulties in diagnosis. It is hard to make diagnosis on people, who died suddenly outside the hospital, due to more difficult differentiation of cardiovascular, cerebrovascular and other causes of death. Apoplectic syndrome can be caused by other factors, such as decompensated brain tumors or other central nerve acute disorders. Modern research of neurological diseases in Croatia started at the end of 60's and early 70's. Pursuant to the instructions of World Health Organization (WHO), group of experts performed systematic epidemiological research in the Centre for Cerebrovascular Diseases "Trnje" in Zagreb. The first symposium on cerebrovascular diseases was held in Zagreb in 1971. Already on the second symposium, which was held in 1974, with participation of experts from WHO, one of the main topics was epidemiology of cerebrovascular diseases (CVD). Methodologies of many specific subjects, important for diagnostics and therapy of these diseases, had epidemiological characteristics. In that way modern concept of treating CVD started to form: prevention, early diagnosis and urgent treatment, as well as directed neuroepidemiological research of problems in this area (1).

## DEFINITION AND CLASSIFICATION

World Health Organization (WHO) defines stroke as "rapid development of clinical signs of focal (or global) brain function disorders, with symptoms which last 24 hours or longer or lead to death, without other clear cause, except signs of blood vessel damage" (2). This disease is classified into two main types: brain ischemia due to thrombosis, embolism or systemic hypoperfusion and brain hemorrhage due to intracerebral or subarachnoidal hemorrhage. 80 % of strokes are caused by ischemia and the rest by hemorrhage. Two main categories of this disease are diametrically opposite: hemorrhage is characterized by an excessive amount of blood inside the closed intracranial cavity, whereas ischemia is characterized by lack of blood and inadequate amount of oxygen and nutrients in a specific part of brain. Each of these categories can be divided into subtypes, which have different causes, clinical manifestations, clinical course, outcome and therapeutic strategies.

There are different approaches to classification of acute stroke. International classification of diseases and problems made by the WHO regarding health (tenth audit-ICD 10) includes diseases and signs, symptoms, abnormal test results, complaints, social circumstances and external causes of injuries and illnesses. This classification classifies stroke under codes I 60-I 69 into following subgroups: subarachnoidal hemorrhage, intracerebral hemorrhage, other non-traumatic hemorrhages, cerebral infarct caused by extracerebral or intracerebral occlusion, as well as non-specific stroke (3).

Classification of Oxford Community Stroke project is primarily based on initial symptoms; episodes of stroke are classified based on development of symptoms such as: primary intracerebral hemorrhage, total anterior circulation syndrome, partial anterior circulation syndrome, lacunar circulation syndrome and posterior circulation syndrome. These five entities anticipate development of stroke, part of brain which was attacked, main cause which lies in the basis and disease prognosis (4,5). TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification of ischemic stroke is very practical and is based on clinical symptoms, as well as on results of further research; based on that, stroke is classified as a consequence of: thrombosis or embolism due to atherosclerosis of big blood vessels; embolism, which started in heart; occlusion of small blood vessels; other stated causes; undetermined causes (two possible causes, one unidentified cause or incomplete research) (6).

Classical definition of transitory ischemic attack (TIA) is a sudden start of focal neurological symptom and/or sign, which lasts less than 24 hours and probably is caused by temporary reduced bloodstream, which leads to brain ischemia in the area, which produces symptoms. Recovery period of blood stream is enough to make ischemia temporary and to avoid infarction. Nevertheless, arbitrary nature of 24-hour time limit and lack of specific pathophysiological significance reduces clinical and research usefulness of the TIA term. Recognition of these terms leads to evolution in a definition and that process was supported by improvements in neuroimaging, especially by imaging measured by diffusion, what enables very early identification of ischemic brain damage. Infarction is usually developed when focal temporary neurological symptoms last more than one hour. So the benign connotation, which is described by term „TIA" is changed with cognition that even small ischemia can cause permanent brain damage. Based on stated facts in the past years, redefining of criteria

is suggested, according to which TIA would include neurological symptoms, which last less than an hour without image evidence on ischemia of brain tissue, and ischemic stroke includes neurological symptoms, which last more than an hour and/or where there are image evidence on brain tissue damage (7).

**NEUROEPIDEMIOLOGICAL DATA**

*Incidence:* well performed trials on stroke incidence include usage of standard definition, which was provided by WHO, prospective stating the cases in big, well defined and representative sample, as well as comprehensive and understandable methodology of detecting the ill and identifying non-fatal cases, treated outside the hospital or those who died soon after the illness started. Stroke incidence, strictly speaking, would refer to incidents, which appear for the first time in life of a person (first-ever stroke), but some trials include also recurrent strokes. It is estimated that annually approximately 4 million people fall ill from stroke. Out of that number Europe includes approximately 570.000, and United States of America approximately 500.000 ill people. Age-standardised incidence rates are usually used in stroke incidence reviews. International epidemiological trials show that rates grow exponential with age, and go between 0,3‰ in the third and fourth decade of life, all the way to 30‰ in the eighth and ninth decade of life, what makes an average amount of 1-2‰. In our country population trials on stroke incidence were made quarter of century ago. By following stroke incidence on a population of 100.000 inhabitants in Zagreb, in 1972, rate amounted to 2,02‰, 1974 2,20‰, 1982 2,34‰, and in 1983 2,49‰ (8,9). Stroke incidence of 2,4‰ was noted in Bjelovar but it was exclusively hospital material and methodologically unreliable data (10). Four years ago a multicentric trial of incidence of stroke and transitory ischemic attacks was implemented in Croatia, with the aim of determining real incidence rates of acute CVD: stroke and transitory ischemic attacks in the area of the Republic of Croatia (RC). The paper used internationally accepted methodology and research was performed during one year period from 1 January, 2005 until 31 December, 2005. All cases of stroke and TIA were carefully recorded in cooperation with primary care physicians. Multicentric trial included population of 89 501 people of all age in four macroregional centres of RC (Osijek-Slavonski Brod, Split, Rijeka and Zagreb). Stroke incidence rate for the entire area of RC amounted to 251/100 000. In individual regional centres the following stroke incidence rates were noted: Osijek- Slavonski Brod 302/100 000, Zagreb 290/100 000, Rijeka 220/100 000, Split 196/100 000. TIA incidence rate for the entire area of RC amounted to 101/100 000. In individual regional centres the following TIA incidence rates were noted: Osijek-Slavonski Brod 157/100 000, Zagreb 87/100 000, Rijeka 90/100 000, Split 22/100 000. In continental part of the RC (Osijek-Slavonski Brod, Zagreb) Stroke incidence rate amounted to 298/100 000, and TIA incidence rate amounted to 130/100 000. In coastal part of the RC (Split, Rijeka) stroke incidence rate amounted to 205/100 000, and TIA incidence rate amounted to 49/100 000. Stroke incidence is 1,45 times bigger, and TIA incidence is 2,64 times bigger in continental part than in coastal part of the RC. The trial revealed relatively high incidence rates of acute CVD (stroke and TIA) in the RC, what confirmed that CVDs are a big public health problem. Significantly higher incidence rates in continental part of the country than in coastal area show that way of life and environment influence development of stroke and other cerebrovascular disorders (11).

*Prevalence:* data on stroke prevalence are the best indicators of how spread a disease is in a population and they also enable creating right strategies of health actions and total health care in a specific area. Stroke prevalence rates in the world vary between 5‰ and several percentages. The latest data on stroke prevalence in our country were published in 1984. Research implemented on a small sample of 1000 inhabitants showed stroke prevalence of 2,5%, i.e., 3,1% for population older than 25 (12). Several years ago the population epidemiological trial was implemented in our country with the aim of determining prevalence of acute CVD: TIA and stroke in the Osijek-Baranya County. The paper used internationally acknowledged work methodology for the population epidemiological trials, which was recommended by the WHO. So-called door-to-door epidemiological research was implemented with a help of questionnaire, which was designed by experienced neurological experts in stroke problems, and afterwards additional data control was performed in medical charts of people included in the trial, in cooperation with doctors of primary health care. The trial included population of 1423 people of all age. Prevalence of acute CVD was 3,30%, out of which 2,04% was stroke prevalence and 1,26% was TIA prevalence. In men CVD prevalence amounted to 3,04%, out of which 1,88% was stroke and 1,16% was TIA. In women was recorded CVD prevalence of 3,56%, out of which 2,19% was stroke and 1,37% was TIA. Prevalence of acute CVD is progressively increasing as the population gets older and in the age group 55-64 it amounted to 9,44% (stroke 6,67% and TIA 2,78%), in the age group 65-74 it amounted to 10,60% (stroke 6,82% and TIA 3,79%), and the highest was in the age group 75-84 and amounted to 14,86% (stroke 10,81% and TIA 4,05%). The trial has shown high prevalence rate of acute CVD in the Osijek-Baranya area and has confirmed that these diseases are one of the leading public health problems in the area of East Croatia (13).

*Mortality:* mortality rates for stroke in Europe vary significantly. The highest rates of 249/100 000 are noted in Bulgaria, and the lowest of 27/100 000 in Switzerland. East European countries have higher total mortality, whereas the lowest rates were noted in Scandinavian countries, Switzerland and the Netherlands. Mortality rates were dramatically reduced in the past few decades in Japan and West European countries. In comparison, in East European countries there has been a constant increase in mortality rate caused by stroke in that period, what has continued in transition period of these countries. Trials which show secular changes in mortality caused by some diseases, throughout a long period of years or decades, have a special significance. To analyse secondary trend of dying age, periodical and generation impacts should be taken into consideration. Secular trend of dying from stroke in the USA in the period 1900-1995 is shown by the next mortality rates on 100.000 inhabitants. In 1900 106,3, in 1950 104, after which there was a decrease, in 1980 the rate was 74,6, and in 1990 57,9. After that trend of decreasing, mortality rate was stopped, and in 1995 rate of 60,2 was noted. We have a significant trial on secular trends of dying from stroke in the RC, in the period of 30 years, from 1958 to1997, which shows a constant trend of mortality increase from this decease during that period. Whereas total number of inhabitants increased by 14% during the observation period, number of deceased from stroke increased by 64%. Proportional mortality rate from CVD, for population 35-74 years of age, increased from 9% in 1958 to 14,9% in 1987, and standardized mortality rate from stroke for population 35-74 years of age increased from 118/100 000 to 191/100.000 inhabitants. Data analysis for the next ten years showed that secular trend of

growth of total number of deceased and growth of proportional mortality rate from CVD has continued in a population 35-74 years of age. Mortality rates are especially high in continental area, in cities Osijek and Varaždin, and their amounts are somewhere 2-3 times higher than in coastal area (14). If we compare age standardized mortality rates in Croatia and in Europe from data base for the program "Health for Everybody" of the WHO, rate for cerebrovascular diseases for all ages in total amounted in 2004 127,8 for Croatia, for the EU members before 2004 57,1 (2003 was the last available year), and for the EU members since 2004 107,0/100.000. For age group 0-64 rate for Croatia was 20,9, slightly lower than rate for "new" EU members (21,1), but almost 3 times higher than mortality rate for "old" EU members 7,6/100.000. (15). The latest data show that from all deceased in Croatia, 15,7 percent die annually due to stroke and its consequences, that is 8154 people (16).

*Lethality* is a proportion of patients, who suffer from stroke, and who died after a specific period after the illness occurred. It is usually expressed as a percentage of deceased in the period of one month and one year. Predicators that influence early mortality are: localisation and size of infarct and hemorrhage, degree of loss of consciousness, degree of neurological deficit, increasing age, male gender, diabetes, arterial hypertension, cardiac diseases, temperature, dysphagia, sphincter incontinence, etc. Fatal outcome of stroke is caused by central and peripheral complications. The most frequent central complications are: cerebral edema, transtentorial herniation, hemorrhagic transformation of ischemia, epileptic seizures, depression. More frequent death of patient with stroke is caused by peripheral (systemic) complications: deep venous thrombosis and pulmonary embolism, bronchopneumonia, urinary infection, septicemia, aspiration, cardiac arrhythmia, myocytolysis, uncontrolled hypotension, sudden death. It is estimated that approximately one third of people who suffered from stroke die, one third has severe and one third milder residual neurological deficit, or is without deficit. Factors, which point out to bad outcome of stroke are: older age, male gender, presence of diabetes, arterial hypertension and cardiac disease in those who are ill, temperature, dysphagia, incontinence, loss of consciousness, severe neurological deficit, cognitive disorders, localisation and infarct size, edema and moving of central structures, biochemical and hematological disorders, etc. Our research of short-term and long-term outcome of ischemic stroke show that on average approximately one quarter of patients die in the first month and approximately half in the next six months. Mortality in five-year period after ischemic stroke, goes up to 60%. Among patients approximately 75% of cases are the first, and 25% of cases are recurrent strokes. Risk of recurrent stroke is the highest in the first year and goes around 10 %, and every second year around 5 %( 17). The most important indicators for recurrent stroke are: type of stroke, earlier TIAs, arterial hypertension, heart valve disease, arterial fibrillation, congestive heart weakness, high level of glucose in blood, male gender and alcohol abuse.

## CONCLUSION

Although data on stroke epidemiology in Croatia are incomplete and lack comprehensive population epidemiological trials, they give in a way a certain picture of current state and point out to unfavourable trends in getting the disease and dying from it. Croatian Association for Neurovascular Disorders of Croatian Medical Association and Croatian Association for Stroke Prevention created guidelines for modern approach to

treatment and stroke prevention (18). Also implementation of National Project of Taking Care of Patients with Stroke, which was created by the Ministry of Health of the Republic of Croatia is in the process. Final result of these activities should be reduced morbidity, mortality and lethality caused by this illness, prevented invalidity and incapability, improved life quality and reduced total social and economic burden of this decease for the whole community.

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# 4. STRESS AND CEREBROVASCULAR DISEASE

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Extremely fast contemporary lifestyle causes constant stress in majority of people living in developed countries. Today, stress is definitely implicated as a risk factor for cerebrovascular disease (1,2). Correct definitions of stress are still controversial, as well as the methods for measuring stress intensity.

Canadian physician Hans Selye was the first to define stress as the sum of total organism depletion during its lifetime (3). Eventually, he corrected his definition and defined stress as the "body's nonspecific psychical or physical response to a demand placed on it" (4). Stressors in general are divided into positive, negative, and neutral stressors, whereas duration of stress differentiates acute (short-term) form chronic (long-term) stress. Chronic stress is generally implicated as a risk factor for stroke (1,2,5,6).

Many neurobiological alterations are stress-related. Stress activates neurohumoral hypothalamic pituitary control mechanism and consequently increases levels of stress-hormone cortisol (7, 8). There are 2 types of receptors for cortisol in human brain: type I mineralocorticoid receptors found principally in hippocampus and type II classic glucocorticoid receptors that are widespread in the brain and regulate attention, alertness, and focus on potential danger (7, 9). During a stressful situation cortisol affects sympatic response by stimulating production of adrenalin and noradrenalin that directly increases cardiovascular tonus, blood pressure, heart rate, respiration rate and activates immunologic response, gluconeogenesis and lipolysis. Adrenalin, the most prevalent hormone of adrenal core, is also present in the adrenergic neurons in the brain stem whose axons are projected upstream into hypothalamus, dorsal nucleus vagus, nucleus tractus solitarii, and locus coeruleus (14). Over half of noradrenergic neurons are located in the locus coeruleus with dorsal projections into cerebellum, thalamus, hypothalamus, hippocampus, olfactory region, and neocortex. The most important role of adrenergic and noradrenergic neurons is vascular regulation, or blood pressure regulation (14). Very fast activation (even in several seconds) of adrenal neurons during stress causes fast vasoconstriction and increases blood pressure, thus rising the risk for acute myocardial infarction or stroke in patients with cardiovascular or cerebrovascular disease (7,8,11,12). In addition, stress promotes activation of renin-angiotensin system, leading to increased levels of angiotensin II. Finally, increased sympatic and cardiovascular tonus combined with high levels of angiotensin II induce atherosclerosis (7,10-13).

Shear-stress aggregation of platelets is related to arterial thrombosis and other different ischemic diseases, including cerebrovascular disease. It is also known that chronic stress causes immunosupression by lowering the number of granulocytes, T and B lymphocytes that contributes to increased general morbidity and mortality (16-20). Chronic stress induces development of arterial hypertension that is proven to be the most powerful inductor of atherogenesis than any other standard risk factor for cerebrovascular disease (21,23). Psychological and physical stressors are also related with increased levels of hemoglobin and hematocrite that are also linked with ischemic heart and brain disease (23,24). In addition to all above mentioned alterations, stress is related to development of other known risk factors: hyperlipidaemia, obesity, diabetes, nicotine and alcohol abuse (25-31).

Patients with chronic posttraumatic stress disorder (PTSD) have extended production of cortisol, adrenalin and noradrenalin, chiefly because of impaired hypothalamic pituitary control mechanism. Some studies showed that 62% of patients with PTSD had vasospasm of the Willis' circle (32,33). Since patients with PTSD have generally higher incidence of other standard risk factors, these data implicate PTSD as a solitary risk factor for cerebrovascular disease. This should also be tested in future prospective studies on large number of patients with PTSD.

There is a series of papers that indirectly show the role of stress in acute cerebrovascular disease. War is unquestionably one of the strongest negative stressors. There were significantly more patients with intracerebral and subarachnoidal hemorrhage during war time in Osijek area compared to peace time (34,35). Also, during war years in Sarajevo the incidence of stroke increased, chiefly due to increased numbers of hemorrhagic stroke (36).

Studies on the influence of chronic stress in development of cerebrovascular disease showed that war casualties and refugees had higher prevalence of arterial hypertension, hyperlipidaemia, obesity, and cerebrovascular disease in general than controls. It indicates that stress induces development of other risk factors, apart from being an independent risk factor itself (37,38).

Stress is mostly related to hemorrhagic stroke. However, there are studies that show significant correlation of stress and ischemic stroke (40,41). There are also some studies that show increased incidence of stress related stroke, regardless of ischemic or hemorrhagic etiology (42,43).

A study by a group of Japanese authors showed that work-related stress doubled the incidence of stroke, particularly in men (44).

Sleep disorders cause changes in the concentrations of stress-neurotransmitters and stress-hormones, and some studies showed increased risk for stroke in states of sleep deprivation, but also in extended sleep (45).

Significant increase in stroke incidence of 70% was observed in menopausal women who had more than 9 hours of every day sleep (46).

In conclusion, today's literature clearly shows that prolonged stress is unquestionably a risk factor for stroke. That correlation is mostly evident for hemorrhagic stroke. Chronic stress also promotes development of other standard risk factors for cerebrovascular disease.

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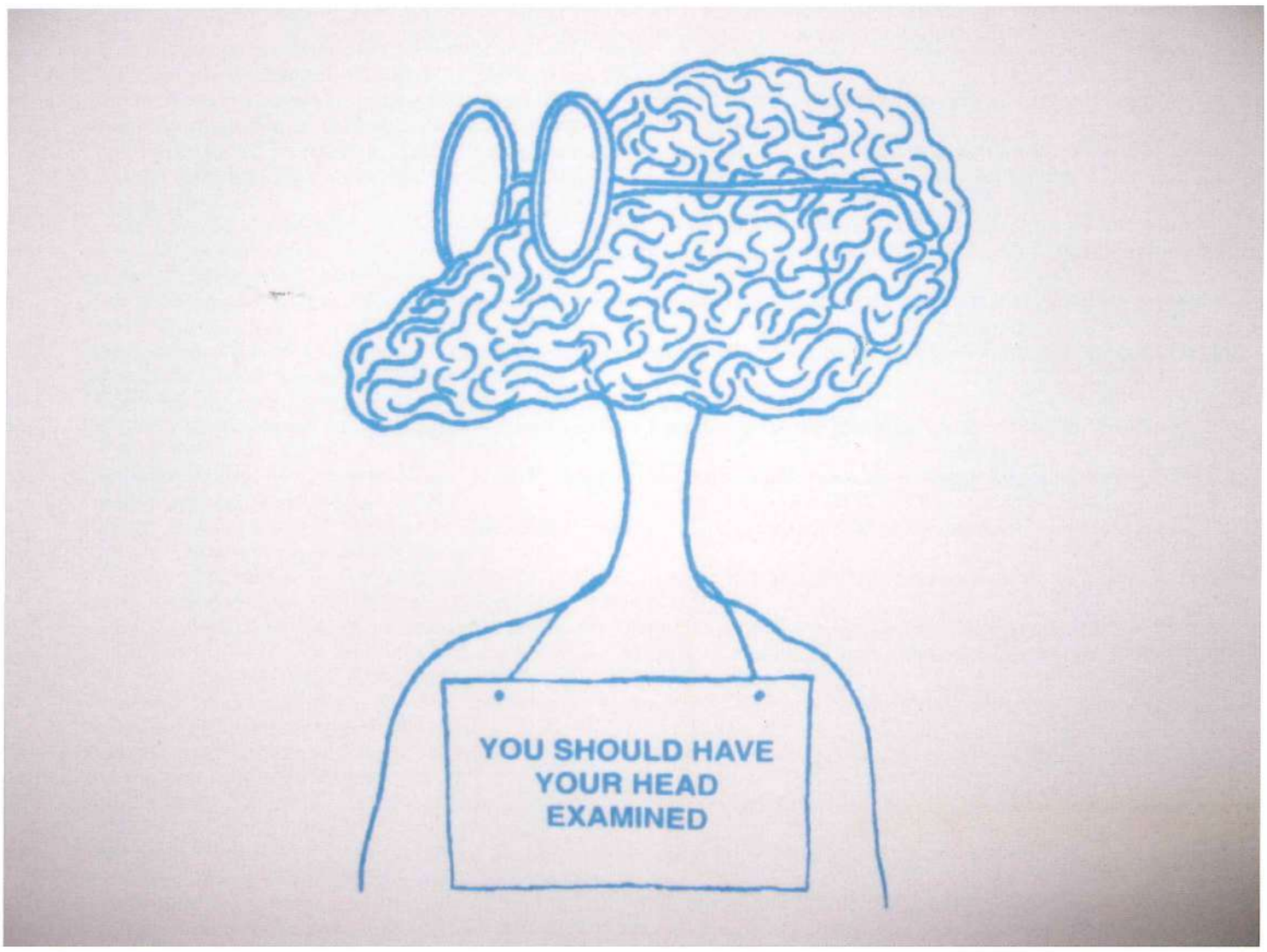
YOU SHOULD HAVE
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# 5. RISK FACTOR MANAGEMENT IN PRIMARY STROKE PREVENTION

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Despite substantial advances for treatment of patients with acute stroke, effective primary stroke prevention remains the best means for reducing the stroke burden (1). More than 70% of all strokes occurring each year are first strokes and therefore primary prevention of stroke is of immense public-health importance (2). High-risk or stroke-prone individuals can be identified and targeted for specific managements and interventions. The ultimate public health benefit, however, will depend on not only identification of stroke risk but also on assessing global vascular risk and the management and modification of these risks (3). Many preventive strategies are available to manage a number of factors that increase the risk of a first stroke. Such successful implementation in preventive medicine remains a great challenge worldwide.

The evidence based guidelines for the management of risk factors to prevent first stroke have been published (4). This overview provides current update on the management of traditional and novel risk factors in primary stroke prevention, the gaps in successful management and future directions for the research and management of stroke risk factors. The management of modifiable and potentially modifiable risk factors or risk markers for a first stroke is reviewed. Non-modifiable factors such as age, sex, race-ethnicity, and various genetic factors are mentioned in the context of risk stratification for a first stoke. The major focus is given to the management of modifiable stroke risk factors including hypertension, diabetes, dyslipidemia, atrial fibrillation and other cardiac conditions, carotid artery stenosis, smoking, poor diet, physical inactivity, and obesity. A brief discussion on the management of potentially modifiable risk factors such as alcohol and drug abuse, sleep apnea, and hyperhomocysteinemia, is included, as is the use of antiplatelet therapy in primary stroke prevention. The less well documented risk factors for first stroke such as inflammation, infection and hypercoaugable disorders are beyond the scope of this chapter. Finally, prognostic scores to assess an individual risk for a first stroke are reviewed.

## Management of Well-Documented Modifiable Risk Factors to Prevent First Stroke

Evidence based guidelines exist for the management of several modifiable risk factors of a first stroke. The modification of these risk factors clearly shows a reduction of risk of first stroke. Select, well-documented modifiable risk factors are discussed below.

## Hypertension

Hypertension is one of the most important modifiable risk factors for prevention of a first stroke. The control of high blood pressure contributes to the prevention of a first stroke but also to the prevention or reduction of other end-organ damage such as renal or heart failure (5). A comprehensive evidence-based approach to treatment of hypertension is provided in the document published by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (6).

*Table 1. Classification and Treatment of Blood Pressure according to the JNC 7*

| Classification | Blood Pressure mm Hg | No Convincing Antihypertensive Indication* | With Convincing Antihypertensive Indication* |
|---|---|---|---|
| Normal | <120/80 | No drug | No drug |
| Prehypertension | <139/90 | No drug | Drugs for the compelling indication |
| Stage 1 hypertension | <159/99 | Thiazide-type diuretics. May consider ACEIs, ARBs, β-blockers, calcium channel blockers, or combination. | Drugs for the compelling indication. Other drugs (diuretics, ACEIs, ARBs, β-blockers, calcium channel blockers) as needed. |
| Stage 2 hypertension | ⩾160/100 | Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or β-blocker or calcium channel blocker). | Drugs for the compelling indication and other drugs as needed |

* Lifestyle modifications are encouraged for all and include (1) weight reduction if overweight, (2) limitation of ethyl alcohol intake, (3) increased aerobic physical activity (30–45 minutes daily), (4) reduction of sodium intake (<2.34 g), (5) maintenance of adequate dietary potassium (>120 mmol/d), (6) smoking cessation, and (7) DASH diet (rich in fruit, vegetables, and low-fat dairy products and reduced in saturated and total fat). Compelling indications include (1) congestive heart failure, (2) MI, (3) diabetes, (4) chronic renal failure, and (5) prior stroke

† Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

The JNC 7 guidelines (Table 1) recommend lowering blood pressure to <140/90 mm Hg (or <130/80 mm Hg in individuals with diabetes). The optimal BP target levels are still being explored in ongoing trials (6). Overall, antihypertensive therapy is associated with a 35% to 44% reduction in the incidence of stroke (7). Several categories of antihypertensive medications such as thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-adrenergic receptor blockers, and calcium channel blockers reduce the risk of stroke, in patients with hypertension (8, 9, 10, 11).

Thiazide-type diuretics were recommended as the preferred initial drugs for treatment of hypertension in most patients (6). Several other classes of BP lowering agents such as ACEI and ARBs are recommended as next in priority. Beta-blockers seem to have a lesser role in the management of uncomplicated hypertension (6, 12).

The Systolic Hypertension in the Elderly Program (SHEP) trial found a 36% reduction in the incidence of stroke with treatment with a thiazide diuretic with or without a β-blocker in patients with isolated systolic hypertension over age of 60 (13). The results from ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), a randomized, double-blind, active, controlled clinical trial of 24,316 participants, showed the superiority of diuretic-based over alpha-blocker-based antihypertensive treatment for the prevention of stroke and CVD. A meta-analysis of 18 long-term randomized trials found that both diuretics and β-blockers were effective in preventing stroke (14).

The Captopril Prevention Project (CAPPP) among 10,985 patients did not show a difference in efficacy in preventing cardiovascular morbidity and mortality between an ACE inhibitor-based therapeutic regimen captopril in comparison to the conventional therapy group (diuretics, β-blockers) in hypertension (15). Interestingly, fatal and non-fatal stroke was more common with captopril.

The Systolic Hypertension in Europe (Syst-Eur) Trial showed a 42% stroke risk reduction in patients treated with a calcium channel blocker (nitrendipine) compared to placebo in patients with isolated systolic hypertension (16). Data from the CONVINCE (Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints) trial however, did not demonstrate benefit in cardiovascular risk reduction of a calcium channel blocker (verapamil) compared with a diuretic or beta-blocker treatment (17).

In the ASCOT-BPLA trial with a primary cardiovascular outcome, a combination of atenolol (β-blocker) with a thiazide prevented more major cardiovascular events and induced less diabetes than amlodipine (a calcium channel blocker) with perindopril (ACEI) (18).

The Heart Outcomes Prevention Evaluation (HOPE) study conclusively demonstrated that ramipril (ACEI), reduces the risk of cardiovascular events in patients at risk for cardiovascular events but without heart failure (19, 20). The cardiovascular risk for patients treated with ACE inhibitor ramipril was reduced by approximately 20 percent compared with placebo.

The angiotensin II type 1 receptor antagonist (ARB) losartan has been shown in the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) study to decrease stroke risk in hypertensive patients to a substantially greater extent than conventional therapy with atenolol (β-blocker) for a similar reduction in blood pressure (10).

Achieving maximum benefit may require treatment with both an ACEI and ARB. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared the benefits of ACE inhibitor treatment, ARB treatment, and treatment with an ACE inhibitor and ARB together and the parallel study Telmisartan Randomized Assessment Study in ACEI Intolerant Patients with Cardiovascular Disease (TRANSCEND) randomized patients unable to tolerate an ACE inhibitor to receive telmisartan or placebo (21). The results of these landmark trials have demonstrated that telmisartan, a second-generation ARB, is equally effective as the current standard, ramipril (ACEI), in reducing the risk of stroke, myocardial infarction, cardiovascular death, and hospitalization for congestive heart failure in a broad cross-section of high-risk cardiovascular patients with normal blood pressure or controlled high blood pressure, and resulted in fewer (21). Telmisartan is now the only ARB to have demonstrated cardio and vascular risk reduction benefits beyond lowering blood pressure in this high-risk population. However, a combination of an ACEI ramapril and an ARB telmisartan did not show that dual renin-angiotensin system (RAS) blockade provided additional risk reduction benefit compared to single blockade. In addition, a higher discontinuation rate was observed if telmisartan and ramipril were combined (21).

The treatment of patients with hypertension is beneficial in younger but also in older patients. In the Hypertension in the Very Elderly Trial (HYVET) among 3,845 individuals 80 years of age or older with a sustained systolic blood pressure of 160 mm Hg or more, a 30% reduction in the rate of fatal or nonfatal stroke and a 39% reduction in the rate of death from stroke was achieved on active treatment (the diuretic indapamide with addition of ACEI perindopril if needed to achieve the target blood pressure of 150/80 mm Hg) in comparison to placebo (22). In addition, fewer serious adverse events were reported in the active-treatment group. In the recent metaanalysis of 31 trials, with 190 606 participants, reduction of blood pressure produced benefits in younger (<65 years) and older ($\geqslant$65 years) adults, with no strong evidence that protection against stroke and other vascular events varies substantially with age (23).

The Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial was the first trial designed to compare the effects on major fatal and non-fatal cardiovascular events of two forms of antihypertensive combination therapy: benazepril plus hydrochlorothiazide and amlodipine plus benazepril in 11,454 hypertensive patients at high cardiovascular risk (24). The study was stopped early because combination ACEI plus the calcium channel blocker amlodipine was more effective than combination treatment with benazepril plus the thiazide diuretic hydrochlorothiazide.

Direct comparisons among the various types of antihypertensive agents however are still limited. Several studies comparing angiotensin-converting-enzyme inhibitors and calcium-antagonists, with β-blockers, diuretic drugs, or both, primary outcome did not differ between treatment groups (7, 25, 26). The optimal BP lowering for primary stroke prevention and BP targets are yet to be determined.

For secondary stroke prevention, the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) trial has confirmed that a perindopril (ACEI)-based regimen reduces the incidence of secondary stroke and primary myocardial infarction (27). In addition, combination therapy with perindopril and indapamide (non-thiazide sulphonamide diuretic) produced larger blood pressure reductions and larger stroke reductions

than monotherapy with perindopril alone. Treatment with these two agents should be considered routinely for all patients with a history of previous stroke or TIA, whether hypertensive or normotensive.

## Conclusion

It is well established that blood pressure lowering is effective for the primary prevention of stroke and other cardiovascular disorders. It has taken longer to prove that blood pressure lowering is equally effective for the prevention of recurrent stroke. Antihypertensive therapy has had a major impact on public health. Blood pressure control can be achieved in most patients, although majority of patients require combination therapy often with more than 2 antihypertensive medictions (28). Despite this knowledge, blood pressure levels are controlled in less than 25% of the hypertensive population worldwide (29). There is a real need to identify hypertensive subjects and treat them with blood pressure lowering drugs for primary prevention. Lack of diagnosis and inadequate treatment are particularly evident in minority populations and in the elderly (6, 30). The real challenge now is to implement effective strategies for the control of blood pressure. Strategies should include lifestyle measures, such as stopping smoking, exercise and weight reduction (31). Choice of a specific regimen must be individualized, but reduction in blood pressure is generally more important than the specific agent used to achieve this goal. However, it remains unclear whether specific classes of antihypertensive drugs offer special protection against stroke in addition to the BP lowering effects.

## Diabetes

Individuals with type 2 diabetes are considered at high risk for vascular events and diabetes is a CHD risk-equivalent with >20% likelihood of a major coronary event or stroke in 10 years according to the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (32). Individuals with type 2 diabetes also have an increased vulnerability to atherosclerosis and an increased prevalence of hypertension, obesity, and abnormal blood lipids. Since 1990, the prevalence of those diagnosed with diabetes rose 61%, with an increase of 8.2% from 2000 to 2001 (1).

Cardiovascular disease develops earlier in the presence of diabetes and to reduce this increased risk, a multifactorial approach to the management of type 2 diabetes has been advocated (33). The American Diabetes Association recommends not only good glycemic control but also identification and aggressive treatment of associated cardiovascular risk factors, with more stringent target levels for lipids and blood pressure than those recommended for the general population (34). Yet, data have been lacking on the effects of such a multifactorial approach to reduce risk of stroke among individuals with type 2 diabetes. In a small trial of multifactorial intensive interventions with 160 patients with type 2 diabetes and microalbuminuria randomized to receive conventional care or intensive treatment, the risk of cardiovascular events was reduced almost by 50% in those on intensive treatment (30). Recommended lifestyle interventions included reduced intake of dietary fat, regular participation in light or moderate exercise, and cessation of smoking and all participants in the intensive-therapy group were advised to take aspirin and a dietary supplement including vitamins E and C, folic acid, and chrome

picolinate. In addition, individuals in the intensive-therapy group were given an ACE inhibitor (or, if contraindicated, an ARB), regardless of the level of blood pressure. The evidence that a multifactorial approach substantially reduces stroke and cardiovascular risk in type 2 diabetes is also supported by subgroup analyses of diabetic participants in large clinical trials. A reduction in major cardiovascular events including stroke was about 50% with blood-pressure reduction, 25% with statin therapy, and 15% with aspirin therapy (35).

Certainly, there is good justification for aggressive treatment of elevated blood pressure and lipid levels in diabetic patients with these risk factors. Several trials have compared the effect on stroke and other cardiovascular outcomes of tight control of blood glucose and blood pressure in type 2 diabetic patients versus less stringent management. In the UK Prospective Diabetes Study Group, tight blood pressure control (mean BP achieved 144/82 mm Hg) resulted in a 44% reduction of fatal and nonfatal stroke as compared with more liberal control (mean BP achieved 154/87 mm Hg) (36). Also, over 20% risk reduction was achieved with antihypertensive treatment in diabetic subjects in the Systolic Hypertension in the Elderly Program (37). In a substudy of HOPE among diabetic patients, a 25% reduction of the primary combined outcome of MI, stroke, and cardiovascular and a 33% risk reduction of stroke was achieved by the addition of ACEI to the current medical regimen of high-risk patients (38). Whether these benefits were a specific effect of the ACEI or were an effect of blood pressure lowering is still the subject of debate. In a substudy of the LIFE in diabetic patients, a 24% reduction in major vascular events and a nonsignificant 21% reduction in stroke was achieved among those treated with the ARB as compared to a β- blocker (1).

The evidence for lipid reduction in diabetes mellitus in relation to vascular disease has, until recently, come predominantly from subgroup analyses of clinical trials which included people with diabetes. For people with established vascular disease several trials of statins, and one trial of the fibrate drug gemfibrozil, have all shown significant reductions in coronary and cardiovascular events in people with diabetes comparable to that seen in those without diabetes (39, 40, 41, 42). The Medical Research Council/British Heart Foundation Heart Protection Study (HPS) found that the addition of a statin to existing treatments in high-risk patients resulted in a 24% reduction in the rate of major vascular events and a 24% reduction in strokes (43). This treatment effect was independent of baseline cholesterol. In a subgroup analysis of the ASCOT-LLA trial among diabetic individuals, there was a non-significant 16% reduction in the primary end point of vascular events, and was likely a result of reduced statistical power in a trial which was stopped early and therefore had a lower number of primary end points (44). The Collaborative Atorvastatin Diabetes Study (CARDS) is the only trial to date to evaluate statin therapy exclusively in diabetes in the primary prevention of vascular events. A total of 2838 people with type 2 diabetes and one risk factor (retinopathy, albuminuria, current smoking, or hypertension) were randomized to a statin or placebo (45). Like the ASCOT-LLA trial, the CARDS trial was also stopped prematurely because the pre-specified stopping rule for efficacy was met. In people with diabetes treated with a statin the primary combined end point of acute coronary events, coronary revascularization, or stroke was reduced by 37%. In particular, stroke was significantly reduced by 48%. These trials provide convincing evidence that statin treatment is quite effective for prevention of stroke in individuals with diabetes mellitus.

Glycemic control is important for individuals with diabetes and ideally the glucose target is normoglycemia with the avoidance of hypoglycemia. Glycemic control is also effective way to reduce stroke

risk. The UK Prospective Diabetes Study (UKPDS) study has shown that good glycemic control reduces the risk of stroke (46). In type 1 diabetes glucose control requires appropriate insulin therapy and concomitant professional dietary and lifestyle therapy. In type 2 diabetes professional dietary advice, reduction of weight, and increased physical activity should be the first approach to achieve good glucose control. If these measures do not lead to a sufficient reduction of hyperglycemia, oral hypoglycemic drugs (biguanide, sulfonylurea, thiazolidinediones, or a combination) or insulin has to be added to the treatment regimen. In overweight and obese people metformin is the drug of first choice (31). Metformin in obese people with diabetes had a better cardiovascular outcome in an analysis of the UKPDS trial than those on treatment with insulin or a sulfonylurea (47). There is also evidence of cardiovascular benefit with metformin as compared to conventionally treated obese people. Second line agents could include sulfonylureas, postprandial glucose regulators, and thiazolidinediones. A randomized controlled trial of a thiazolidinedione in 5238 people with type 2 diabetes showed a 16% reduction in all cause mortality, non-fatal myocardial infarction and stroke. So there is now prospective trial evidence for another oral anti-diabetic drug (in addition to metformin) in relation to cardiovascular events (48). Insulin treatment should be considered as soon as treatment with oral agents fails to achieve the HbA1c target of ≤7.5%.

## Conclusion

A comprehensive program that includes tight control of hypertension with ACEI or ARB treatment reduces the risk of stroke in individuals with diabetes. Treatment of adults with diabetes, especially those with additional risk factors, with a statin to lower the risk of a first stroke is recommended (29). The role of tight glycemic control in reducing the risk of stroke is still uncertain (49). Glycemic control reduces microvascular complications, but evidence showing a reduction in stroke risk with tight glycemic control is lacking. Surely the most effective way to reduce cardiovascular risk associated with diabetes would be to prevent diabetes itself. But for patients who already have diabetes or in whom it will develop, the advantages of a multifactorial approach to the reduction of cardiovascular risk are clear. The challenge is to ensure that this approach is widely adopted.

## Dyslipidemia

Most epidemiologic studies find no consistent relationship between cholesterol levels and overall stroke risk. Some studies, however, have found a positive relationship between total and LDL cholesterol levels and the risk of ischemic stroke (4, 50, 51, 52, 53). Increased HDL cholesterol levels are associated with reduced risk of ischemic stroke, in men and women, in the elderly, and among different racial or ethnic groups (54, 55, 56, 57). These data add to the evidence relating lipids to stroke and support HDL cholesterol as an important modifiable stroke risk factor. Triglyceride levels vary considerably, making elevated levels difficult to evaluate as a risk factor for stroke. Trends toward higher triglyceride levels in patients who subsequently experience ischemic stroke have been reported (4, 58). Elevated levels of triglycerides are one of the important

components of the metabolic syndrome, a modifiable risk factor for stroke. The etiologic fraction estimates suggest that elimination of the metabolic syndrome would result in a 19% reduction in overall stroke, a 30% reduction of stroke in women and a 35% reduction of stroke among Hispanics (59).

A compelling body of evidence documents that lipid lowering agents reduce major cardiovascular events in both secondary and primary prevention of stroke and cardiovascular disease. Current evidence suggests that high-dose lipid lowering agents can halt and, in some cases, reverse atherosclerotic progression. Furthermore, lipid lowering agents are in general safe and well tolerated.

Statins (HMG-CoA reductase inhibitors) are FDA approved agents for the prevention of ischemic stroke in patients with coronary artery disease (CAD). The rates were reduced 27% to 32% among subjects assigned to the statin as compared with placebo in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA), which enrolled high-risk hypertensive subjects, and the Heart Protection Study (HPS), which enrolled high-risk subjects mostly with previous coronary events (41, 60). In a meta-analysis of 9 trials including 70,070 patients, statin treatment provided 21% relative risk reductions of stroke and 0.9% absolute risk reduction (61). It was estimated that statins prevent 9 strokes per 1000 coronary heart disease or high-risk patients treated for 5 years. Although statins prevent recurrent stroke in patients with prior stroke or TIA (the SPARCL trial) (62), they have not shown a definite benefit in the risk reduction of first stroke in the typical general population without known CHD.

In the population at high CHD risk, although without documented CHD, statins however were beneficial for first stroke risk reduction (63). Two (ASCOT-LLA and CARDS) out of five primary CVD prevention statin trials showed a considerable reduction in stroke rates among individuals on 10 mg atorvastatin as compared to placebo (41, 42). In ASCOT-LLA, a relative risk reduction of stroke was 23%, and in CARDS (primary diabetic population) was 48%. In two (MIRACL and PROVE-IT) out of five acute coronary syndrome trials, the prevention of first stroke was significant among individuals receiving a high-dose atorvastatin (80 mg) versus placebo (MIRACL) or versus pravastatin (PROVE-IT) (64). Most secondary CHD prevention trials (4S, CARE, LIPID, HPS, GREACE and TNT) involving a total of >50,000 patients with CHD showed a beneficial effect of statins in stroke prevention with the relative risk reduction of fatal or nonfatal stroke by 19-50% (4). In the Treating to New Targets (TNT) trial which randomized 10,001 individuals with stable coronary heart disease (65), those in the high-dose statin group had significantly fewer major vascular events and fewer strokes than those in the lower-dose group. In addition to the significant stroke risk reduction by 25% on high-dose atorvastatin in the TNT trial, stroke was reduced by 47% relative to 'usual' care in the GREACE study (66).

In a recent review and meta-analysis of 42 randomized trials evaluating statin therapy for stroke prevention (n=121,285), a pooled relative risk reduction of all strokes on statin therapy was 16% (67). Eleven trials reported hemorrhagic stroke incidence and 21 trials reported on fatal strokes, some due to hemorrgahe. This indicates the need to consider prolonged statin treatment in patients at high risk of stroke and major vascular events, but caution remains for patients at risk of bleeds.

Nonstatin lipid-modifying therapies also may offer stroke protection, although the supporting data are less certain. Other lipid-modifying strategies include niacin, ezetimibe, bile acid sequestrants, CETP inhibitors and omega-3 fatty acids. Particularly, ezetimibe/statin combinations provide superior lipid-modifying benefits

compared with statin monotherapy in patients with atherogenic dyslipidemia (68). Atherogenic dyslipidemia is associated with increased levels of chylomicrons and their remnants containing 3 main components: apolipoprotein B-48, triglycerides and cholesterol ester of intestinal origin. Reduction in accessibility for one of them (specifically cholesteryl ester lessening due to ezetimibe administration) could lead to a decrease of the entire production of chylomicrons and result in a decrease of the hepatic body triglyceride pool as confirmed in number of clinical studies. However, the ENHANCE study showed no difference in the progression of carotid atherosclerosis between ezetimibe and simvastatin vs. simvastatin alone over a 2-year period (69). Conclusions regarding ezetimibe and statins combinations, however, should not be made until the large clinical outcome trials are completed (70).

Niacin (nicotinic acid or vitamin $B^3$) treatment was associated with a 24% reduction in known or suspected stroke and TIA (71). In the Veterans Administration HDL Intervention Trial (VA-HIT), a trend toward a reduction of stroke in the gemfibrozil (fibrate) treated group (6.0% versus 4.6) of men with coronary heart disease and low levels of HDL cholesterol was reported (72). In addition, HDL cholesterol can be increased by 25% to 40% when multiple modalities are used, in particularly when niacin is added (73, 74). Because fibrates, niacin, ezetimibe, omega-3 fatty acids and statins each regulate serum lipids by different mechanisms, combination therapy - selected on the basis of their safety and effectiveness, could be more helpful in achieving comprehensive lipid control as compared with statins monotherapy.

In primary stroke prevention by lipid-lowering agents, surrogate markers of atherosclerosis such as carotid intima-media thickness (IMT) and small non-stenotic carotid plaque measured by B-mode ultrasound may be useful markers to monitor the effect of lipid lowering therapies. Carotid IMT and plaque are preclinical surrogate markers of stroke and other atherosclerotic vascular diseases (75). Lipoprotein levels and metabolic syndrome have been correlated with carotid IMT and plaque (76, 77, 78, 79). In clinical trials, colestipol-niacin combination therapy, statin monotherapy, and statin-niacin combination therapy each retarded the progression of carotid IMT (80, 81, 82, 83, 84). In the recent clinical trials which evaluated the effect of LDL reduction and HDL elevation, however, a beneficial effect resulting in halting carotid IMT progression or IMT regression was not observed. Paradoxically some individuals experienced the growth of atherosclerotic plaque and increased carotid IMT on a combination of a statin and CETP inhibitor. More importantly, increased cardiovascular morbidity and mortality, despite achieving an aggressive reduction in LDL cholesterol and increased HDL cholesterol, was reported (65, 85, 86). This evidence confirms the complex nature of an association between dyslipidemia, atherosclerosis, stroke and cardiovascular diseases.

## Conclusion

Lipid-modifying medications can substantially reduce the risk of stroke in patients with coronary heart disease. Treatment with statins is associated with the reduction in the risk of a first stroke in various populations of patients at increased risk of cardiovascular events. National Cholesterol Education Program III guidelines for the management of patients who have not had a stroke and who have elevated total cholesterol or elevated non–HDL cholesterol in the presence of hypertriglyceridemia are endorsed (Table 2) (29, 87). It is

recommended that in patients with known CAD and high-risk hypertensive patients even with normal LDL cholesterol, therapy is initiated with lifestyle measures and a statin. Suggested treatments for patients with known CAD and low HDL cholesterol include weight loss, increased physical activity, smoking cessation, and possibly niacin or gemfibrozil administration.

Whether lipid-lowering is effective in the primary prevention of stroke in general population without CHD is still not clear. Whether the benefit of statins in reducing the risk of stroke is due to their potent lipid-lowering effects, pleiotropic effects, or a combination of the two cannot be determined based on current clinical trial data. Although from a benefit-risk perspective, the benefits of statin therapy outweigh the low risk of serious side effects, there are still populations for which more data on safety of lipid-lowering therapies are needed to clarify the risk associated with the effect of treatment, especially in older persons (>70 years of age) and women (88).

*Table 2. Management Recommendations for Dyslipidemia According to NCEP ATP III*

| **Factor** | **LDL-Cholesterol Goal** | **Recommendations** |
|---|---|---|
| 0–1 CHD risk factor* | <160 mg/dL | Diet, weight loss, physical activity; Drug therapy if LDL-C remains ⩾190 mg/dL. If LDL-C 160–189 mg/dL drug therapy optional |
| ⩾CHD risk factors and 10-y CHD risk <20% | <130 mg/dL | Diet, weight loss, physical activity; Drug therapy if LDL-C ⩾160 mg/dL |
| ⩾2 CHD risk factors and 10-y CHD risk 10% to 20% | <130 mg/dL, or <100 mg/dL | Diet, weight loss, physical activit; Drug therapy if LDL-C remains ⩾130 mg/dL (or ⩾100 mg/dL) |
| CHD or CHD risk equivalent† (10-y risk >20%) | <100 mg/dL, or <70 mg/dL | Diet, weight loss, physical activity; Drug therapy if LDL-C is ⩾130 mg/dL and optional for LDL-C 70–129 mg/dL |
| CHD or CHD risk equivalent† (10-y risk >20%) | <100 mg/dL, or <70 mg/dL | Diet, weight loss, physical activity; Drug therapy if LDL-C is ⩾130 mg/dL and optional for LDL-C 70–129 mg/dL |

| | | |
|---|---|---|
| Non-HDL-C in persons with triglycerides ⩾200 mg/dL | Goals 30 mg/dL higher than LDL-C | Same as LDL-C with goal 30 mg/dL higher |
| Low HDL-C | No consensus goal | Weight loss, physical activity. Consider niacin or a fibrate in high-risk individuals with HDL-C <40 mg/dL |

* To screen for dyslipidemia, a fasting lipoprotein profile (cholesterol, triglycerides, HDL-C, and LDL-C) should be obtained every 5 y in adults. It should be obtained more often if ⩾2 CHD risk factors are present (risk factors include cigarette smoking, hypertension, HDL-C <40 mg/dL, CHD in a male first-degree relative <55 y of age or in a female first-degree relative <65 y of age, or age ⩾45 y for men or ⩾65 y for women) or if LDL-C levels are borderline or high.
† CHD risk equivalents include diabetes or other forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease).

**Atrial Fibrillation**

Atrial fibrillation (AF) is an important well-documented risk factor for stroke. AF is associated with a 3- to 4-fold increased risk of stroke (89). Among those without prior stroke or TIA, risk of first stroke is 2% to 4% per year (90). Incidence of AF increases with age; approximately 6% to 10% of people aged >75 years have AF (91). About one quarter of strokes in the very elderly (over 80 years) are due to atrial fibrillation (85).

Anticoagulation and antithrombotic therapies remain the main agents for stroke prevention in patients with AF. Several randomized controlled studies have shown that adjusted-dose warfarin reduces the overall risk of stroke by 68% with a 1% increase in the risk of major bleeds (92, 93). Risk of stroke is reduced by 20% with aspirin (94). Warfarin reduces stroke by 45% as compared to aspirin (95). However, reanalysis of pooled data suggests that the margin between expected benefit and harm may be less than originally believed. The reduction in annual incidence of major stroke was <1% and the increase in major bleeding was nearly 2% (96). Although clinical trials have showed that an orally administered direct thrombin inhibitor ximelagatran is as effective as warfarin in atrial fibrillation, the FDA has not approved its use because of the safety concerns (hepatotoxicity, a possible increased rate of MI and coronary artery disease) (97, 98).

Anticoagulation is underused in patients with AF in the community, and there is little information on treatment with anticoagulation in patients at low risk of stroke (99). Several stroke risk–stratification schemes have been developed and validated (100, 101). The American College of Cardiology (ACC), American Heart Association, and European Society of Cardiology 2001 guideline recommends anticoagulation for patients with atrial fibrillation who are older than 60 years and have a history of hypertension, diabetes, coronary artery disease, impaired LV systolic function, heart failure, or prior thromboembolism, and for all those with atrial

fibrillation who are >75 years of age (102). However, this stratification model has not been validated. A new stratification model to assist clinicians in choosing patients for antithrombotic therapy, $CHADS_{2}$, has been recently proposed and validated (96, 103). $CHADS_2$ stands for Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, and prior Stroke or TIA. The $CHADS_2$ score was derived from independent predictors of stroke in patients with nonvalvular atrial fibrillation (99). The score gives 1 point each for of congestive heart failure, hypertension, age $\geqslant$ 75 years, and diabetes mellitus, and 2 points for prior stroke or TIA. Before prescribing anticoagulation, several factors should be considered: the absolute risk of stroke, the estimated risk of bleeding, patient preferences, and access to anticoagulation monitoring clinic. Risk stratification in these patients is the first step in the decision making process (Table 3).

*Table 3. Nonvalvular Atrial Fibrillation Risk Stratification by $CHADS_2$ Scheme (99) and Treatment Recommendations*

| **$CHADS_2$ Score** | **Risk Level** | **Stroke Rate per Year** | **Treatment Recommendations Based on Risk Stratification** |
|---|---|---|---|
| 0 | Low | 1.0% | Aspirin (75–325 mg/d) |
| 1 | Low–moderate | 1.5% | Warfarin INR 2–3 or aspirin (75–325 mg/d)** |
| 2* | Moderate | 2.5% | Warfarin INR 2–3** |
| 3 | High | 5.0% | Warfarin INR 2–3# |
| $\geqslant$4 | Very high | >7% | Warfarin INR 2–3# |

Congestive heart failure, Hypertension, Age >75 y, or Diabetes = 1 point. Stroke or TIA* = 2 points
*All nonvalvular AF patients with prior stroke or TIA should be considered high risk and treated with anticoagulants; the $CHADS_2$ scheme should be applied for primary prevention.
**Consider patient preferences, bleeding risk, and access to INR monitoring.
#If patient is >75 y of age, an INR target of 1.6–2.5 is recommended by some

Most patients with atrial fibrillation who are less than 75 years of age and have no history of prior stroke or TIA have a relatively low risk of stroke (1% to 2% per year) if given aspirin, and they do not benefit sufficiently from anticoagulation to warrant its use for primary stroke prevention (91, 104). It is generally agreed that atrial fibrillation patients whose estimated stroke risk exceeds 4% per year should be anticoagulated in the absence of contraindications (98).

However, warfarin therapy is underutilized in patients with AF. Only about half of patients with atrial fibrillation who are candidates for anticoagulation receive warfarin (105). Anticoagulation is particularly underused in elderly patients (106). In addition to age, poorly controlled hypertension and concomitant aspirin or nonsteroidal anti-inflammatory drug use confer higher bleeding risk during anticoagulation (4, 97).

The optimal target international normalized ratio (INR) for primary prevention of stroke in patients with nonvalvular atrial fibrillation is in the 2 to 3 range for most atrial fibrillation patients (4, 99, 102, 107). A lower target INR of 2 is recommended in very elderly by some (108). Control of hypertension in atrial fibrillation patients is also critically important, reducing both the risk of ischemic stroke and the risk of intracerebral hemorrhage (109).

All patients with mechanical heart valves, regardless of the presence of atrial fibrillation, require anticoagulation (110). The rate of thromboembolism in patients with mechanical heart valves is 4.4 per 100 patient-years without antithrombotic therapy, 2.2 per 100 patient-years with antiplatelet drugs, and 1 per 100 patient-years with warfarin (111)

### Conclusion

Atrial fibrillation is an important stroke risk factor, which can be treated successfully. Validated stroke risk-stratification models may help identify individuals with low risk of first stroke who can be treated with aspirin. Anticoagulation reduces risk of stroke in those at high risk and without contraindications to this treatment. The development of safer, easier-to-use oral anticoagulants might improve the risk-benefit ratio.

### Other Cardiac Conditions

Other types of cardiac disease that can contribute to the risk of thromboembolic stroke include MI, dilated cardiomyopathy, valvular heart disease (eg, mitral valve prolapse, endocarditis, prosthetic cardiac valves), and intracardiac congenital defects (eg, patent foramen ovale, atrial septal defect and aneurysm) (112). Incidence of stroke is also increased in patients with reduced cardiac ejection fraction (113). The use of warfarin for cardioembolic prophylaxis in patients with reduced LV ejection fraction in the setting of idiopathic cardiomyopathy remains controversial, and clinical trials are in progress comparing warfarin with antiplatelet treatment (114). Patients undergoing cardiac surgical procedures have a perioperative stroke risk of 1 to 7% (115). Presence of aortic arch atheroma is also associated with increased risk of ischemic stroke (116).

## Conclusion

Various guidelines recommend strategies to reduce the risk of stroke in patients with cardiac conditions. These include the management of patients with acute MI (117), unstable and stable angina (118, 119), and valvular heart disease (107). Studies proving the benefits of specific prophylactic procedures for patients with a variety of cardiac conditions are lacking.

## Asymptomatic Carotid Stenosis

Carotid stenosis of 50% or greater can be detected in about 5-10% of men and women older than 65 years of age, and stenosis >80% in 1% of the population (120, 121, 122, 123). An annual stroke risk between 1% and 3% occurs among individuals with asymptomatic carotid artery stenosis of 50-99% in the natural history studies (124) and is higher in those with carotid stenosis >75%, progression of carotid stenosis, heart disease, and in men (125). However, about 45% of ipsilateral strokes in patients with carotid stenosis could be attributable to lacunes or cardioembolism, emphasizing the need to fully evaluate patients with asymptomatic carotid stenosis for other treatable causes of stroke (119). In summary, data from observational studies and clinical trials indicate an annual rate of stroke ipsilateral to a significant extracranial carotid artery stenosis of about 1-2%.

There have been 2 large published randomized controlled trials designed to assess the benefit of CEA in patients with asymptomatic carotid artery stenosis. In t*he Asymptomatic Carotid Atherosclerosis Study (ACAS)* designed to test the efficacy of CEA in subjects with asymptomatic CAS >60 to 99%,1662 subjects were randomized to CEA and best medical therapy or to medical therapy alone (126). The overall risk of perioperative stroke or death was 2.7%. The study was stopped prematurely after a median follow-up of 2.7 years because there was a significant benefit of surgery over medical treatment alone. The aggregate rate of ipsilateral stroke, any perioperative stroke, or death was estimated at 5% over 5 years in surgically treated patients, and at 11% in medically treated patients (53% risk reduction). The benefit began to accrue after 1 to 2 years. The study was not statistically powered to detect differences among patient subgroups. No surgical benefit was observed in relationship to the degree of carotid artery stenosis, but women appeared to benefit less than men (17% nonsignificant risk reduction in women vs. a 66% risk reduction in men), This difference was in part contributed to by a higher rate of perioperative complications in women (3.6% vs. 1.7% in men).

In *the Medical Research Council Asymptomatic Surgery Trial (ACST)*, the largest randomized trial comparing a strategy of immediate versus deferred CEA, 3120 asymptomatic patients with CAS > 60% on carotid ultrasound were enrolled. There was a 3.1% risk of stroke or death within 30 days of surgery (127). Although the overall periprocedural complication rate was similar to that in ACAS, the surgical complication rate of the ACST was actually twice that of ACAS in which the complication rate of 1.5% was due to surgery only. The overall 5-year risk of any stroke or perioperative death was 11.8% with deferred surgery vs. 6.4% with immediate endarterectomy. The benefit began to accrue after about 2 years. Although subgroup analyses need to be interpreted with caution as in ACAS, there did not appear to be any difference in benefit based on the degree of carotid stenosis. Women also appeared to benefit less than men after CEA and had a somewhat higher but non

significant rate, of perioperative complications (3.8% vs 2.7% in men). In the pooled analyses from ACAS and ACST, surgical benefit is greater in men than in women (128).

The benefit of endarterectomy in asymptomatic CAS is very much dependent on surgical risk, with the benefit observed only if the periprocedural complication rates are less than 2.7% as observed in ACAS or less than 3.1% as in ACST. Community-wide scrutiny of CEA in asymptomatic CAS in 10 US states shows an overall risk for stroke or death of 3.8% (129). Most physicians, however, are not aware of the CEA complication rates in their respective hospitals.

Since ACAS, „standard" medical therapy has been enhanced with widespread use of antiplatelet agents and blood pressure and lipid lowering drugs, and therefore the risk of stroke in asymptomatic CAS may be further reduced without CEA. Although screening of general populations for CAS may not be cost-effective (130), screening for „high-risk" individuals with asymptomatic CAS such as screening for those with impaired cerebral vasoreactivity (131) or presence of microemboli on TCD (132) may help select those who may benefit from CEA.

Carotid angioplasty with stenting has been available for over 10 years, but data from clinical studies proving its equivalence or superiority to CEA in asymptomatic CAS is still limited. The *Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) Trial* showed that stenting was not inferior to CEA among CAS subjects at high risk for the surgery (133). About 70% of the enrolled subjects had asymptomatic CAS, with 5.4% rates of stroke, MI, or death with stenting versus 10.2% in CEA group at 30 days ($P$=0.20), and 9.9% versus 21.5% at 1 year, respectively ($P$=0.02). Because, the outcome in SAPPHIRE included MI, the results are not directly comparable to ACAS or ACST. But even in the stenting arm of SAPPHIRE with lower rates of combined major cardiovascular outcomes of 9.9% at 1 year, it is considerably higher than the stroke risk associated with asymptomatic CAS (1% to 2% per year) in ACAS or ACST. The study did not include medically treated controls, so a comparison to the best medical treatment could not be performed.

Although pivotal stenting trials including SAPPHIRE were initially limited by a lack of equipment dedicated to carotid artery stenting including embolic protection filters, their results have compared favorably to both direct and historical surgical controls (134). While this has led to Food and Drug Administration approval of several carotid stent systems in the US, recent European randomized carotid stenting trials (SPACE and EVA-3S) had mixed results as they failed to prove noninferiority of stenting compared to CEA and confused the perception of the place of this technology in the care of asymptomatic CAS patients (135). The carotid stent registries with a wide range of operator experience, and patient enrollment based on surgical risk criteria (CAPTURE II, EXACT, CABERNET) were able to meet the guidelines of 3% procedural events in the asymptomatic CAS (136). Ongoing carotid stenting trials in the US and Europe will further contribute our understanding of the benefit of stent therapy in CAS patients.

## Conclusion

In individuals with asymptomatic CAS who are at low risk for surgery, CEA in a combination with 'usual medical care' is superior to 'usual medical care' alone for reduction of ischemic stroke if the perioperative

complication rate is lower than 3% (Table 4) (137). The total 5-year risk of stroke or procedural morbidity after CEA is 11.5% for deferred endarterectomy versus 6.0% for immediate endarterectomy (18 subjects are needed to treat to prevent 1 event over 5 years) (123). Perioperative risk is not balanced by benefit for 2 years. Patient selection, comorbidities, life expectancy, and patient preferences should be discussed, and the risks and benefits of the procedure should be carefully considered. The benefit of CEA in patients with asymptomatic CAS seems to be more pronounced in men, and it still remains uncertain whether there is benefit of CEA in women. One must keep in mind that women have been underrepresented in CEA trials, and some observational data have suggested benefit of CEA for women. Carotid angioplasty with stenting may be a reasonable alternative to CEA in asymptomatic CAS at high risk for the surgical procedure.

*Table 4. Guideline Management Recommendations*

| **Factor** | **Goal** | **Recommendation** |
|---|---|---|
| Asymptomatic carotid stenosis | No carotid stenosis | Endarterectomy may be considered in selected patients with ⩾60% stenosis without occlusion, performed by a surgeon with surgical morbidity and mortality <3%. Careful patient selection should be guided by individual factors including comorbid conditions, life expectancy and patient preference |
| Cigarette smoking | Cessation | Counseling, nicotine replacement, varenicline, and formal programs are recommended. |
| Diet/nutrition | Well-balanced diet | A diet containing ⩾5 servings of fruits and vegetables per day may reduce the risk of stroke. |
| Physical activity | ⩾30 minutes of moderate activity/day | Moderate exercise (eg, brisk walking, jogging, cycling, or other aerobic activity). |
| Alcohol | Moderation | No more than 2 drinks/day for men, and no more than 1 drink/day for women. |
| Drug abuse | Cessation | A history of substance abuse should be part of health evaluation. |

| | | |
|---|---|---|
| Sleep apnea | Treatment for obstructive sleep apnea (OSA) | Overnight sleep study in patients with snoring, excessive daytime sleepiness, body mass index over 30 and drug-resistant hypertension. CPAP treatment. |

**Cigarette Smoke**

Cigarette smoking is a well-recognized and modifiable risk factor for ischemic and hemorrhagic stroke (85, 138, 139, 140). A meta-analysis of 32 studies estimated a 2-fold increased risk of ischemic stroke for smokers vs. nonsmokers and a 3-fold increased risk for subarachnoid hemorrhage (141). Passive cigarette smoke is a risk factor for stroke (142). The stroke risk for passive smoking is close to the risk for active smoking suggesting that tobacco exposure may have "threshold" rather than a dose-response relationship (143).

The most effective preventive measure is to never smoke as well as to minimize exposure to environmental smoke. The risk of stroke is also reduced with smoking cessation. Smoking cessation is associated with a rapid reduction in the risk of stroke to a level that approaches, although never reaches, the risk of those who never smoked within 2-5 years of cessation (144). Sustained smoking cessation is difficult to achieve. A combination of nicotine replacement therapy, social support, and behavioral treatments offers an effective management for smoking cessation (Table 4) (145). Varenicline, Chantix(R), is a novel smoking-cessation agent that acts at a number of nicotinic acetylcholine receptors, and recently has been shown to be superior to the current standard patch in achieving abstinence and in reducing withdrawal phenomena such as urges to smoke and withdrawal symptoms (146). Varenicline may be addtional treatment option and may likely become very popular with patients and clinicians.

**Conclusion**

Cigarette smoking is clearly associated with the risk of stroke. Comprehensive smoking cessation programs are effective. Data, however, on the effects of these programs on reduction of the risk of stroke are lacking.

**Diet and Nutrition**

Diet is associated with the risk of stroke. Increased fruit and vegetable consumption is associated with a reduced risk of stroke in a dose-response manner (147). For each 1-serving/day increment in fruit and vegetable intake, the risk of stroke was reduced by 6% in the Nurses' Health Study and the Health Professionals' Follow-Up Study (148). A higher level of sodium and lower level of potassium intake is associated with an increased risk of stroke, possibly mediated through mechanisms dependent on blood pressure (149). Diets rich in fruits and vegetables lower blood pressure and therefore may decrease risk of stroke (150). Other dietary factors may

affect the risk of stroke, but specific evidence is lacking. The Dietary Approaches to Stop Hypertension (DASH) diet includes high consumption of fruits, vegetables, low-fat dairy products, and reduced intake of total and saturated fat (Table 4) (145).

### Conclusion

Diets rich in fruits and vegetables, reduced sodium, increased potassium, and reduced fat may reduce the risk of stroke. Dietary trials specifically focused to reducing the risk of stroke are lacking.

### Physical Inactivity

Physical inactivity is well-established and modifiable risk factor for strokem (151). The protective effects of physical activity have been reported for different ages, sexes and race-ethnicities in large studies including the National Health and Nutrition Examination Survey (NHANES) Study and the Northern Manhattan Stroke Study (152, 153). In the Northern Manhattan Stroke Study, a dose-response relationship was reported as more intensive physical activity provided additional benefits compared to light to moderate physical activity. The protective effect of physical activity may be mediated through blood pressure and body weight reduction and control of diabetes (154).

The benefits of physical activity are outlined in the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health guidelines (Table 4) (155, 156) which recommend moderate exercise for at least 30 minutes per day. The benefits for stroke are evident for light to moderate activities such as walking.

### Conclusion

Although clinical trials on the benefit of physical activity on risk of stroke do not exist, it is clear that a sedentary lifestyle increases the risk of stroke. Physical activity is beneficial in reduction of risk factors, and therefore is recommended to reduce risk of first stroke.

## Management of Less Well-Documented Modifiable Risk Factors to Prevent First Stroke

### Obesity and Metabolic Syndrome

Obesity is a risk factor for stroke and is associated with increased risk of hypertension, dyslipidemia, hyperinsulinemia, and glucose intolerance (157). In addition, higher weight during young adulthood and weight gain after young adulthood are associated with an increased risk of stroke (158). Recent studies have also reported the association between measures of the distribution of body fat, such as the waist-to-hip ratio as a measure of abdominal obesity (159) and increased risk of stroke. About one in three adults in the United States is overweight, and the prevalence of obesity has been steadily increasing (160).

Obesity is an important component of the metabolic syndrome, a potentially modifiable risk factor for stroke (29). Insulin resistance is an important marker of the metabolic syndrome and may be a prevalent risk factor for stroke (161). The prevalence of metabolic syndrome in general populations worldwide is high (24-50%) (162). Drugs which can reduce insulin resistance reduce the metoblic syndrome, incidence of type 2 diabetes and may also be effective in prevention of stroke (163).

Weight reduction is beneficial in risk factor reduction, reduction of metabolic syndrome and therefore in possibly reducing the risk of stroke. Clinical trials aimed to test the effects of weight reduction on reducing the risk of stroke do not exist. Numerous studies however, report the beneficial effects of weight reduction on blood pressure. In a meta-analysis of 25 clinical trials, blood pressure was reduced by 3.6-4.4 mmHg with an average weight loss of 5.1 kg (164).

**Conslusion**

Obesity and metabolic syndrome are associated with an increased risk of stroke. Individual components of the metabolic syndrome have been associated with an increased risk of ischemic stroke, and therefore should be treated by lifestyle measures and pharmacotherapy as recommended by JNC 7 and ATP III guidelines (6, 29). Despite a lack of clinical trials on the effects of weight reduction and stroke risk, weight reduction is important for lowering blood pressure and metabolic syndrome risk which may lead to reduction of stroke risk. In addition exercise and diet, and glycemic and lipid control are important factors in reducing the risk of first stroke.

**Alcohol and Drug Abuse**

The J-shaped relation of alcohol consumption to the risk of stroke has been reported (165). The relative risk of ischemic stroke associated with moderate alcohol consumption (one to two drinks a day), as compared with nondrinking, is between 0.3 and 0.5 in some populations and increases to 2 for persons consuming three or more drinks per day. For hemorrhagic stroke, the relative risk varies from 2 to 4, with some increased risk at all levels of intake (166). Alcoholism is a major public health problem. In the US, over 10 million adults have alcoholism and alcohol-related diseases such as hypertension and cirrhosis (167). Despite the potential benefit of moderate alcohol consumption, alcohol should not be considered as a preventive agent for stroke, given the health risks associated with excessive intake.

Light-to-moderate alcohol consumption (for women $\leq$ 1 drink/day and for men $\leq$ 2 drinks/day) can increase HDL cholesterol, reduce platelet aggregation, and lower plasma fibrinogen concentration (168). Heavy alcohol consumption can lead to hypertension, hypercoagulability, reduced cerebral blood flow, and a greater likelihood of atrial fibrillation (169). In a meta-analysis of 35 observational studies, consumption of <1 drink per day (1 drink defined as 12 g of alcohol), but not abstention, was associated with a significant 20% reduced risk of stroke and consumption of 1 to 2 drinks per day with 28% reduced risk (170). As compared with abstainers, those who consumed >5 drinks per day had a 69% increased stroke risk.

Abuse of drugs such as heroin, cocaine, and amphetamines are associated with an increased risk of ischemic and hemorrhagic stroke (171, 172). These drugs may cause metabolic and hematologic changes including increased platelet aggregation, changes in blood pressure, and lead to vasculopathy or cerebral embolization form various sources (173).

**Conslusion**

Light to moderate alcohol consumption is associated with a reduced risk of stroke and heavier consumption with an increased risk of stroke. Alcoholism is a major public health problem as alcohol consumption can induce dependence. Reduction of alcohol consumption in heavy drinkers is recommended (174). A suggested consumption of alcohol in those who consume alcohol is ⩽ 2 drinks per day for men and ⩽ 1 drink per day for nonpregnant women (Table 4).

Identification and management of drug abuse is challenging. Long-term treatment strategies based on medication, psychological support, and outreach programs play an important part in treatment of drug dependency (Table 4).When a patient is identified as having a drug addiction problem, referral for appropriate counseling is recommended.

**Sleep Apnea**

Sleep-related breathing disorders are highly prevalent in patients with established cardiovascular disease. Obstructive sleep apnea (OSA) is being increasingly recognized as an important risk factor for stroke. It is a less well-documented but modifiable risk factor. The evidence of the association of OSA with first ischemic stroke is primarily derived from the association with heart disease. OSA affects an estimated 15 million adult Americans and is present in a large proportion of patients with hypertension, obesity, and CVD (175). Prevalence of OSA in the populations ranges between 3% and 7%. Factors that increase vulnerability for OSA include age, male sex, obesity, family history, menopause, craniofacial abnormalities, and certain health behaviors such as cigarette smoking and alcohol use.

OSA is characterized by repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway or central nervous system dysfunction. The overnight polysomnogram is the standard diagnostic test for OSA. A diagnosis of OSA syndrome is made when a person has an apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) >5 and symptoms of excessive daytime sleepiness (176). A recent analysis from more than 6000 adults participating in the Sleep Heart Health Study showed that hypopneas accompanied by oxyhemoglobin desaturation of >4% were associated with prevalent cardiovascular disease and stroke independent of confounders (177).

Habitual snoring and daytime sleepiness are risk factors for ischemic stroke (178). Snoring may be a marker for sleep-apnea, which can secondarily increase the risk of stroke by worsening hypertension and heart disease, reducing cerebral blood flow and autoregulation, impairing endothelial function, accelerating

atherosclerosis, hypercoagulability, and inflammation, and causing paradoxical embolism in patients with PFO (171).

Treatment of OSA is individualized and includes noninvasive continuous positive airway pressure (CPAP) ventilation, bi-level positive airway pressure, and automatic control of airway pressure delivery with CPAP devices. A variety of surgical interventions and prosthetic oral devices are available.

**Conclusion**

Obstructive sleep apnea is associated with vascular risk factors and an increased risk of CVD. Individuals with abdominal obesity and hypertension, snoring and daytime sleepiness are more likely to have OSA and should be referred to a sleep specialist for further evaluation (Table 4). Prospective randomized studies regarding the effect of treatment of sleep apnea on stroke risk reduction do not exist. However, successful treatment of OSA can lead to a reduction in blood pressure which may lead to a reduced risk of first stroke.

**Hyperhomocysteinemia**

Elevated plasma levels of homocysteine (hyperhomocysteinemia) are increasingly recognized as a potential risk for atherothrombotic vascular diseases including stroke (179, 180). In NOMAS, those with homocysteine level greater than 15 micromol/L had a 2-fold increased risk of ischemic stroke compared to those with levels <10 (175).

A key event in the vascular pathobiology of hyperhomocysteinemia seems to involve the induction of endothelial dysfunction due to a reduction of the endogenous antiatherothrombotic molecular nitric oxide (181). Elevated homocysteine levels can be efficiently and safely reduced in most of hyperhomocysteinemic patients by supplementation of folic acid and cobalamin. This reduction is associated with an improvement in endothelial function and other surrogate markers of atherothrombosis, such as carotid plaque area (182). Whether or not this translates into clinical benefits, is still under investigation. On the basis of the results of several recent clinical trials (e.g., VISP, or from ongoing VITATOPS which did not show a reduction of inflammatory markers by reducing homocysteine) many researchers doubt that vitamin therapy designed to lower total homocysteine concentrations is effective in reducing the risk of stroke and cardiovascular events (183, 184). However, these trials are designed for secondary and not primary stroke prevention when the influence of other factors may have been more important.

In a detailed assessment of the results of the recent HOPE-2 trial and a reanalysis of the VISP trial restricted to patients capable of responding to vitamin therapy, it has been suggested that higher doses of vitamin B12 and perhaps new approaches to lowering total homocysteine besides routine vitamin therapy with folate, vitamin B6, and vitamin B12 could reduce the risk of stroke (185). Thus, therapy to lower homocysteine could still help to prevent stroke. Unfortunately, many major trials of homocysteine lowering in the general cardiovascular literature have not shown benefit of vitamin therapy for reduction of major vascular endpoints.

A single-nucleotide polymorphism (SNP) in the methylenetetrahydrofolate reductase gene reduces activity of the enzyme that metabolizes homocysteine, producing an increase in serum homocysteine (186). This SNP can be found in 10% to 12% of the population and is associated with a 25% higher homocysteine level than in those with a wild-type genotype. In a recent meta-analysis of 72 studies, a 5-µmol/L increase in homocysteine was associated with a 1.6-fold increase risk of stroke (181). In addition, a 3-µmol/L decrement of homocysteine level was associated with a 24% risk reduction of stroke (187).

The current AHA guidelines recommend daily intake of folate (400 µg/d), $B_6$ (1.7 mg/d), and $B_{12}$ (2.4 µg/d) by consumption of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals. This diet may be useful in reducing the risk of stroke.

## Conclusion

No randomized trials have shown that lowering elevated homocysteine levels reduces the risk of a first stroke. Until the results of more clinical trials are available, the question whether homocysteine is a risk predictor or a modifiable risk factor for stroke remains unanswered. However, there is consistent evidence regarding overall relationship between homocysteine levels and vascular risk, and a benefit of treatment of elevated homocysteine levels cannot be excluded. There are insufficient data to recommend specific treatments to reduce the risk of first stroke in patients with elevated homocysteine. Use of folic acid and B vitamins in persons with known elevated homocysteine levels is safe and may be useful in primary stroke prevention.

## Aspirin for Primary Stroke Prevention

Despite conclusive evidence of the benefits of aspirin in the secondary prevention of stroke, only a few clinical trials addressed aspirin use in primary prevention. In the US, the Physicians' Health Study (188) showed nonsignificant reduction of ischemic stroke risk among men using 325 mg of aspirin every other day for an average of 60.2 months vs. placebo. The risk of hemorrhagic stroke however doubled among those on aspitrin. In the British Doctors' Trial with a daily dose of 500 mg of aspirin for six years, no significant difference in the incidence of stroke between the treatment and control groups was found, but a higher incidence of disabling stroke among those taking aspirin was reported (189). In a recent meta-analysis of 6 randomized trials (the Physicians' Health Study, the British Doctors' Trial, the Thrombosis Prevention Trial, the Hypertension Optimal Treatment study, the Primary Prevention Project, and the Women's Health Study) that evaluated the benefits of aspirin for primary prevention in a combined sample of 47,293 subjects on aspirin and 45,580 on placebo (or non aspirin), superiority of aspirin was suggested for total cardiovascular events but there was no significant difference in the incidence of stroke (190). Many of the patients in these studies, however, were at relatively low risk, and a study of persons at moderate risk might show a benefit of aspirin therapy.

The effects, and the risk-benefit ratio of aspirin in primary prevention, may be different in women and men. In the Women's Health Study (191) among 39,876 asymptomatic women $\geqslant$ 45 years of age who were followed for 10 years for a first major vascular event, a significant 17% reduction in the risk of stroke was found

among those who received 100 mg of aspirin compared to placebo, but a nonsignificant 9% reduction in the risk of the combined primary end point. The risk of hemorrhagic stroke was nonsignificant. The overall average stroke rates were 0.11% per year in aspirin-treated patients and 0.13% per year in placebo-treated patients (absolute risk reduction=0.02% per year, and a number needed to treat of 5000). The average gastrointestinal hemorrhage rates were 0.06% per year for aspirin and 0.05% per year for placebo (absolute risk increase=0.01% per year, number needed to harm of 10 000). The most consistent benefit for aspirin was among women $\geqslant 65$ years of age, with a history of hypertension, hyperlipidemia, diabetes or a 10-year cardiovascular risk $\geqslant 10\%$.

**Conclusion**

Aspirin is not recommended for the prevention of a first stroke in men (4). The use of aspirin 75 mg/d is recommended for cardiovascular (including but not specific to stroke) prophylaxis among a person whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of greater than 6-10%) (192). There is no evidence that this class of drugs reduces the risk of stroke in the general population of persons at low risk (187). Aspirin can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment. The reasons for the differences between men and women remain uncertain.

**Assessing the Risk of a First Stroke**

Many therapeutic options exist for risk factor management to prevent a first stroke. The choice of an appropriate risk modification program will depend on individual stroke risk. Each individual should have an assessment of risk of first stroke. Many factors can contribute to stroke risk and many individuals have more than one risk factor, some of which are well and some less well documented. Several stroke risk assessment tools are available to use for primary stroke prevention screening programs (193). These stroke risk estimation tools are generally focused on several major vascular risk factors and do not include the full range of contributing factors, and especially do not consider different characteristics of various race-ethnic populations. The Framingham Stroke Profile (FSP) is gender specific and provides a gender-specific 1, 5 or 10-year cumulative stroke risk (194). Independent stroke predictors included in FSP are age, systolic blood pressure, hypertension, diabetes mellitus, current smoking, established cardiovascular disease (any one of MI, angina or coronary insufficiency, congestive heart failure, or intermittent claudication), atrial fibrillation, and left ventricular (LV) hypertrophy on EKG. It has been updated to include the use of antihypertensive therapy and the risk of stroke or death among individuals with AF (Table 5) (195). Although very useful in some populations, the FSP has not been sufficiently studied in different race-ethnic groups.

Table 5. Modified Framingham Stroke Risk Profile (190)

| **Risk factor; Points** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age** (years) | 54-56 | 57-59 | 60-62 | 63-65 | 66-68 | 69-71 | 72-74 | 75-77 | 78-80 | 81-83 | 84-86 |
| **SBP** (mmHg) | 95-105 | 106-116 | 117-126 | 127-137 | 138-148 | 149-159 | 160-170 | 171-181 | 182-191 | 192-202 | 203-213 |
| **SBP Rx** | No | | Yes | | | | | | | | |
| **DM** | No | | Yes | | | | | | | | |
| **CS** | No | | | Yes | | | | | | | |
| **CHD** | No | | | Yes | | | | | | | |
| **AF** | No | | | | Yes | | | | | | |
| **LVH** | No | | | | | | Yes | | | | |

SBP Rx, Treated Systolic Blood Pressure
CS, Cigarette Smoking
LVH, Left Ventricular Hypertrophy on EKG

Alternative prediction models using Framingham risk factors and adding continuous levels of risk factors have been developed in other cohorts but their validity has not been well tested (196, 197, 198).

**Conclusion**

A goal is to develop a generally applicable and simple stroke risk-assessment tool. Such a risk assessment tool that is widely accepted does not exist, and the current ones have limitations. New risk factors associated with the risk of stroke are emerging and they would need to be considered in newer stroke risk assessment tools. Validation of the current stroke risk assessment tools is needed in different age, gender, and race ethnic groups. The complexity of risk factors predicting a first stroke in an individual makes development of new stroke risk assessment tools a challenging task.

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For many decades the value of right nutritional habits in improvement of health and in management of diseases is well known. For cerebrovascular and cardiovascular diseases the risk factors associated with eating habits are clearly identified. Also, the influence of food on other neurological conditions came into focus during last decades (1,2).

In 1958 the large survey, The Seven Countries Study started in 18 areas of seven countries: Yugoslavia, Italy, Greece, Finland, Netherlands, USA and Japan. The main hypothesis of the study was that differences among populations in the frequency of heart attacks and stroke would be found related to lifestyle, particularly to diet. After 5-15 years of follow-up the results showed that the mortality rate from coronary heart disease in southern Europe was two to three folds lower than in northern Europe or USA. The mortality from coronary heart disease and other causes was the lowest in the cohort from Crete which was strongly correlated to dietary habits. Surprisingly, the serum cholesterol concentrations in the population of Crete was similar to other in Mediterranean cohorts what indicated that healthy diet is not based only on the lowering of blood cholesterol (3). The Lyon Diet Heart Study was randomized single blind secondary prevention trial with the goal to test the influence of a Mediterranean-type diet on the reduction of risk of recurrence in people who suffered first myocardial infarction. After 46 months of follow-up the risk of recurrent heart disease and total deaths reduced for 50-70% in the group consuming Cretan Mediterranean diet. Also the lower incidence of malignant disorders incidence was noticed. The findings from the Lyon Diet Heart Study illustrate the potential importance of a dietary pattern that emphasizes fruits, vegetables, breads and cereals, fish, as well as alpha-linolenic acid (4,5). Exactly these are the characteristics of the common Mediterranean dietary pattern which include high daily intake of fruits, vegetables, bread and other cereals, potatoes, beans, nuts and seeds; olive oil is a principal fat; dairy products, fish and poultry are consumed in low to moderate amounts and red meat is consumed rarely. This diet also implies the regular consumption of low to moderate amounts of wine. The benefit of this diet lies in several mechanisms, it increases blood concentration of omega-3 fatty acids, oleic acid and alpha-linolenic acid (<10% of energy intake is from saturated fats), it decreases blood concentration of linoleic acid, increases plasma concentrations of antioxidants, vitamin C and E and it is rich in folate and selenium. These substances are associated with the reduction of inflammatory processes in the organism, and it is well known that the inflammation is a crucial factor in pathogenesis of cardiovascular diseases. During oxidation of LDL molecules

free radicals are produced; it promotes inflammatory reaction and plaque formation. The cardioprotective effect lies in combination of high intake of natural antioxidants and low intake of saturated fatty acids, low intake of omega-6 acids and high intake of omega-3 acids, high intake of oleic acid and folates. Selenium showed the protective effect against cancers. Beside the influence of Mediterranean diet solely on atherogenesis, the positive effect have been proved also on metabolic syndrome (dyslipidaema, hypertension, glucose intolerance, abdominal obesity, pro-inflammatory state) reduction, the increased omega 3 fatty acids intake protects against central obesity (6).

Numerous studies have showed the biological effect of different food components from Mediterranean diet. The foods included in this diet are high in antioxidants, vitamin E, carotenoids, vitamin C, polyphenols, trace elements and minerals. Vitamin E can inhibit the free radical mediated oxidation of LDL. The main dietary sources of vitamin E are: nuts, wheat germs, vegetable oils, butter and eggs. Nature carotenoids, particular lycopene are highly correlated with lower incidence of coronary artery disease and lung cancer and they have lipid lowering effect. But the studies showed that the artificial ß-carotene supplementation excess can lead to harmful effects (increasing of lung cancer incidence). Dietary sources of carotenoids are tomato and its products (higher bioavailability of lycopene is from cooked food), other pigmented fruits, carrots, broccoli, red peppers and pumpkins. Vitamin C restores endothelial function with an effect on plaque stabilization and vasorelaxation. It is also potent scavenger with a protective role against cancer. Citrus fruits and leafy vegetables are rich in vitamin C if they are consumed raw. Selenium is a cofactor of an antioxidant enzyme and it acts synergistically with vitamin A and E. It can be found in grains and sea food and the supplementation is not advisable (7). Polyphenols are known for a long time, they have been used as antibiotics, antidiarrheal, antiulcer and anti-inflammatory agents. Their antioxidative activity is associated with a reduction of incidence of vascular diseases. Particularly abundant in polyphenolic compounds are olives and grapes so the regular and moderate consumption of olive oil (virgin and extra-virgin), red wine, fruits and vegetables is strongly advised.

Folates are important food compound, they lower plasma homocysteine levels. Hyperhomocysteinaemia is recognized as an independent risk factor for stroke and coronary heart disease. Decreased plasma levels of folates, vitamin B6 and B12 is linked to hyperhomocysteinaemia. A high intake of cereals (wheat flour), legumes, vegetables, fruits and nuts can provide sufficient amount of folates in organism (8,9).

Unsaturated fatty acids are important part of cell membrane. Depending on omega-6/omega-3 fatty acids ratio, the structure of cell membrane is changing. Satisfactory intake of docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) (omega-3 acid) leads to replacement of arachidonic acid (AA) (omega-6 acid) in membranes of all cells, which decreases production of molecules involved in prothrombotic and inflammatory processes. Optimal ratio of omega-6 and omega-3 fatty acids is 1:1 to 4:1, in the past this ratio for the human food was about 2:1, however, over the last 50 years in modern countries the ratio has changed to 10-20:1. This means that modern western diet includes mainly omega 6 fatty acids from corn oil, safflower oil, cottonseed oil, peanut oil, soybean oil and we have decreased our intake of omega-3 fatty acids from whole grains, beans and seafood (10,11). In Mediterranean diet the principal fat is olive oil, composed from fatty acids (palmitic, oleic and linoleic), triacylglycerols and secondarily free fatty acids and about to 1,5% nonglyceridic constituents.

The fatty acid composition depends on the zone of production, climate and the maturity of the fruit. Due to its composition, olive oil has rich biological effects. Squalene and carotenoids have antioxidant properties, sterols and phytosterols inhibit absorption of cholesterol during digestion. Tocopherols acts as a free radical trapping agent and single oxygen quencher and polyphenols are influencing stability and flavor of oil; they stimulate production of enzymes, neutralize toxic chemicals and have antioxidative properties. There are numerous types of olive oil, extra virgin olive oil is the least processed form and this is the oil of the best quality. Virgin olive oil is derived after pressing fruit for a second time; ordinary and refined olive oil passed through more intensive refining processes and they have little nutritional qualities. The best sorts of olive oil are made in Istria, they have exclusive aroma and high content of antioxidants (phenols 185 ppm, tocopherols 274 ppm). Olive oil has a positive impact on cognitive functions, the study performed in south Italy on 287 subjects of older age showed that regular intake of olive oil, 3 spoons a day, is associated with significant reduction of memory loss. Similarly as a fish oil, olive oil helps maintaining the structure and integrity of neuron cell membrane (12). Also olive oil increases serum level of HDL in diabetic patients, even during eating food with sugar. It can neutralize the effect of food with high glycemic index (13,14). For many years the beneficial effects of moderate wine consumption on human health have been debated. Mediterranean wine is rich in polyphenols; cis- and trans- resveratrol (isolated in wine in 1992) and flavonoids (flavonols, antocianins, catechin oligomers and polymers, quercetine). The biological effects of resveratrol are platelet aggregation inhibition, hypolipemic effect, inhibition of LDL oxidation. In red wine the content of resveratrol is 1-2mg/L but after intake of 500ml of wine only 1 mcg of resveratrol in blood is available. The amount of flavonoids in red wine is 1-3g/L and in white wine 0,2 g/L, the highest biological effect comes from a epicatechin and quercetine that are also present in fresh fruit and in green and black tea (15). Light intake of alcohol reduces risk of cardiovascular and cerebrovascular disease (French paradox) (16), recommended daily intake is 1dL a day for woman (and men>65y) and 2dL a day for men. Boston study after five years of follow-up have showed that light to moderate alcohol consumption is related to lower risk of myocardial infarction and the highest relative risk for cardiovascular diseases was present in the cohort with alcohol consumption of less than two drinks a day (17). On the other side, heavy alcohol consumption is associated with an increased risk of stroke (J-shaped and U-shaped curve) (18,19).


The principles of healthy diet can be summarized in the Mediterranean Diet Pyramid (Picture 1) (20). The primary source of fat is olive oil. In large amounts the food from plant sources should be consumed (fruits and vegetables more than 5 servings a day, breads, grains, beans, nuts, and seeds). Fish and poultry can be eaten weekly in low to moderate amounts. Cheese and yogurt can be consumed daily in low or moderate amounts. Wine is allowed in moderate amount, one to two glasses per day for men, one glass per day for women. The very important part of Mediterranean diet is daily physical

activity; it is the base of Mediterranean diet pyramid. Sedentary life style is a major risk factor for chronic diseases and regular physical activity stimulates the functional adaptation of all tissues and organs in the body making them less vulnerable to degenerative diseases. Physical activity lowers blood levels of triglycerides, total cholesterol, HDL and LDL, serum level of glucose, total body fat and waist circumference, C reactive protein, C3 and homocysteine (21). Next to physical activity is the social part of eating, it is recommended to eat meals in company of family members or friends.

The Mediterranean diet (Picture 22) and life style has not only the beneficial impact on reduction of atherogenesis and chronic disease incidence, but also the positive impact on mood and well-being. It is not only way of eating; it is the right way of living.

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MOŽDANI UDAR NIJE KRAJ
TROMBOLIZU ODMAH DAJ!

# 7. STROKE IN WOMEN

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Until recently it had been presumed, that cardiovascular diseases in adults, including stroke are associated with male predominance. In women more pressure is put on the problem of breast and reproductive system cancer and complications in the perinatal period. In the past cardiovascular disorders and stroke have not been so strongly stressed as a problem linked to female gender. Yet stroke constitutes a serious socioeconomic and health care in women since the nineties of the last century, because it is the principal cause of disability and a major cause of death in this population (1). The report of the American Heart Association has shown that every third women dies because ischemic heart disease and every sixth dies due to stroke, while only every ninth suffers from breast cancer and one in twenty five dies subsequently (2). The incidence of cerebral and myocardial infarction is lower in females than in males, but only before menopause. Later these differences diminish and disappear completely by the age of 65.

## Stroke risk factors

Hypertension is the most important hemorrhagic and ischemic stroke (IS) risk factor. It is diagnosed in 50-70% ischemic stroke patients (3-6). Elevated blood pressure is an established risk factor not only for stroke occurrence but also for stroke mortality (7-9). In the large International Stroke Trial (IST) of 17,370 patients with ischemic stroke females had significantly higher systolic blood pressures at baseline than males and had also a higher 14-day (11.0% vs. 8.7%, $p<0.001$) and 6-month ( 24.5% vs. 19.3%, $p<0.001$) case fatality (9). Elevated systolic as well as diastolic blood pressure increase the risk of stroke regardless of age. Hypertension has not been proved to be a more important stroke risk factor in women than men. Nevertheless in 12,396 stroke patients with IS from Polish Registry of Stroke hypertension was significantly more frequently found in women than in men aged over 55 – in the age group 66-80: 75.0% vs. 61.5% and over 80: 61.2% vs. 49.6% (5). In a large cohort study of 7,302 young women aged 18 to 39 years without previous coronary heart disease (CHD) during 31 years observation women with 2 or more risk factors high (including hypertension) had the highest death risk of CHD as well as cardiovascular diseases (CVD) including stroke. Mortality rate per 10,000 person-years for women with 2 or more risk factors high was 9.1, about 6 times that of women without any risk factors (1.5) (10). Antihypertensive treatment is associated with a 40% reduction of stroke risk in both females and males (11).

Atrial fibrillation (AF) is the most frequent cause cardioembolic strokes and accounts for ca. half of all cardiogenic strokes. The occurrence of AF increases with age. 10% of people aged over 70 have AF. Much analysis demonstrated that women are more often diagnosed with AF than men (5, 9). In a large cohort of 17,370 ischemic stroke patients AF occurred in 21% of females and 14% of males (9). A prospective study of 1,678 patients with first ever ischemic stroke demonstrated that the impact of AF is different in both genders and appears to be a specific ischemic stroke predictor of in-hospital mortality in women (12). The higher risk of early death in females in comparison with males in acute ischemic stroke patients with AF was also noted in the Copenhagen study (13), where the mortality rate was 2.5-fold greater in women than in men. These findings suggest that AF is a much more pronounced risk factor for stroke outcome and cardiovascular death in women than in men. Oral anticoagulants reduce the risk of stroke by 60% despite gender, but previous observations show that women take these drugs less frequently than men (14).

Diabetes mellitus is an independent risk factor of all vascular disease, including stroke. It is present in 10-15% of all stroke patients (15). In the Polish Registry of Stroke in 12,396 ischemic stroke patients diabetes was overall similarly distributed in both genders (16.7% men and 19.2% women), but in the older group (66-80 years) it was significantly more often in females in comparison with males (25.0% vs. 19.7%) (5). Another study showed that women with diabetes have a higher risk of suffering of stroke than men (RR 1.7 vs. 1.4) (15). Diabetes therapy reduces the risk of stroke similarly in both genders.

Elevated total and LDL (low density lipoprotein) cholesterol levels are an important risk factor of stroke and ischemic heart disease, but a direct correlation between lipid level in serum and risk of stroke has not been established. Many studies have revealed that administration of statins after myocardial infarction reduce the incidence of coronary disease and stroke. The Heart Protection Study (HPS) with simvastatin conducted on a group of 20,536 patients (aged 40-80 years) with high vascular risk (previous myocardial infarction, peripheral artery disease, stroke, diabetes, smoking, and hypertension) showed that administration of simvastatin 40 mg daily for 5 years reduced the risk of stroke by 40%. In this group 25% of patients were female and 25% were aged over 65. This has been the first time that statins were proved to be effective in stroke prevention in elderly women at high vascular risk (16). The later SPARCL study with atorvastatin in patients with a recent stroke or transient ischemic attack (TIA) showed that given 80 mg daily it reduced the risk of stroke and other cardiovascular events similarly in both genders (17).

Smoking is one of the most important modifiable risk factors due to its distribution. Undoubtedly lower smoking rate significantly reduces the risk of vascular disease. Women are more susceptible to the negative effects of smoking. The risk of stroke in smoking females increases twice, while only 1.5 times in smoking men [(5, 18). Smoking is associated with atheromatic destruction and stenosis in the internal carotid arteries (ICA). This can be treated by carotid endarterectomy (CEA) in primary and secondary prevention. Carotid artery stenting (CAS) until now has not been proved to be safer and more effective than CEA and the data are limited. Focusing on secondary prevention the risk of adverse events in women during surgery in previous studies has reached up to 10% and was 2.4 times higher than in men. The benefits from this treatment are smaller in female than male patients. That is why some authors recommend to qualify for surgery only women with a stenosis >70%, whilst CEA has shown to be effective in stenoses over 50% in the general population. In women the

decision to refer for surgery also needs to be very prompt, as beyond 2 weeks of the qualifying event the benefit of surgery in females drops dramatically in comparison with men (19)

Previous myocardial infarction increases the risk of stroke. This risk factor occurred more frequently in male patients but 13% of females after myocardial infarction suffer of stroke in 6 year perspective compared to only 9% of men (20). Previous stroke or TIA also increases the risk of a subsequent stroke, but no difference in stroke recurrence has been noted between genders (21, 22). Secondary stroke can be prevented by antithrombotic drugs which have similar efficacy in both men and women (23, 24)

Alcohol increases the risk of stroke by 1.6 to 1.8 times. Women metabolize alcohol slower; therefore it generally acts longer in females. In women in middle age consumption of 5-15 g of ethanol reduces the risk of stroke regardless of the type of alcohol (25). In spite of this finding in the population aged < 35 years the total mortality increases together with the quantity of alcohol consumed even when drunk in small quantities (26).

Overweight and obesity are independent stroke risk factors in women. Their influence on stroke in female is more significant (20). Therefore low-fat, and low-sodium diet as well as physical activity which can reduce obesity and are beneficial in reduction of risk of vascular disease in both genders.

**Do estrogens have a protective role against stroke?**

The importance of the protective role of natural estrogens in females during the fertile part of the women's life has been emphasized over many years. Estrogens have been said to have antiatherogenic and neuroprotective effects and, before menopause, account for a risk profile that is less atherogenic. Estrogen has been widely shown to acutely protect brain from experimental stroke (27-30). One of estrogen's multiple protective mechanisms is the enhancement of postischemic cerebral reperfusion and restriction of vascular endothelial dysfunction. Neurons and glia are also targets for estrogens. Many of them have potent, concentration-dependent lipid antioxidant activity. (31) They also amplify endothelial NO (nitric oxide) and/or cyclooxygenase signaling, reduce intravascular leukocyte adhesion, induce eNOS (endothelial nitric oxide syntase) translocation and activation, increase microvascular cGMP, preserve mitochondrial function (31). Unfortunately the major randomized clinical trial the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal hormone replacement therapy for secondary prevention of cerebrovascular disease showed no overall benefit, and there was an unexpected pattern of increased risk of cardiovascular disease including stroke among women with ischemic heart disease (32, 33). In this trial women were randomly allocated to receive either placebo or a daily hormone replacement therapy (0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate). The Women's Estrogen for Stroke Trial (WEST) compared 17ß-estradiol (1mg/d) to placebo in postmenopausal women with a recent history of TIA or ischemic stroke. The primary aim of the study was to determine whether estrogen therapy reduced the risk of death or recurrent stroke in women enrolled within 90 days of the initial event. Estradiol replacement did not reduce risk of recurrent stroke or death (RR 1.1 in the estradiol group; 95%CI, 0.8 to 1.4). Furthermore subjects allocated estrogen therapy had a higher risk of fatal stroke (RR2.9; 95%CI, 0.9 to 9.0) (34). In the Women's Heath Initiative (WHI) randomized controlled trial hormone replacement therapy (HRT) – conjugated equine estrogens

(0.625mg/d) with medroxyprogesterone acetate (2.5mg/d)was compared to placebo in the context of primary prevention of vascular disease as well as brest and colorectal cancer, and fractures (35). The trial was prematurely terminated because of an excessive risk of coronary heart disease (CHD) (estimated HR 1.29 with 95% CI of 1.02 to 1.63) and an increased risk of breast cancer. Similarly to CHD the risk of stroke was higher among those receiving combined estrogen/progestin therapy (HR 1.41 with 95% CI of 1.07 to 1.85). This data contradicts the use of HRT for the prevention of vascular disease in women (36). It is known that HRT may increase some families of cytokines and C-reactive protein, and these mechanisms are critical in atherosclerosis (37-39) and estrogen can contribute to thromboembolism particularly at moderate to high doses (40).

**Clinical course, mortality and disability after stroke**

Until the age of 55 strokes occurs seldom in both genders, while over 65 years the incidence of stroke increases dramatically. Because the life expectancy for women is about ten years longer than men, the impact of stroke becomes a major issue in elderly women. Up to 16% of women die of stroke compared to only 8% of men (24). Many epidemiological studies showed that stroke has a higher impact in female patients compared to males in terms of severity, subsequent disability and further the need to reside in nursing homes, post-stroke depression, fatigue syndrome as well as post-stroke dementia (42-46). In the International Stroke Trial (IST) a higher proportion of females in comparison with men were unconscious or drowsy (26.7% vs. 20.0%, $p<0.001$) or had a total anterior circulation syndrome (27.4% vs. 20.9%, $p<0.001$) (9). In 2$^{nd}$ Department of Neurology, Institute of Psychiatry and Neurology, in Warsaw from 1996 to 2002 of all 1,232 stroke patients 53.4% where female [47]. In-hospital, 3 month and 1 year mortality was higher in female patients, 22% vs. 17%, 14% vs. 8%, and and15% vs. 7%, respectively. Young women up to 55 years of age had less severe strokes than age-matched men. 80% were alert at admission, compared to 70% men. 2% of females and 17% males had total anterior circulation infarct (TACI). In the age group over 55 more women than men were unconscious (44% vs. 33%, respectively) and more frequently they had TACI (18% vs. 10%, respectively).

**The influence of gender on stroke outcome in thrombolytic therapy**

Differences in stroke management in men and women have been reported. Gargano et al. in a study of 2,566 patients with acute ischemic stroke showed that women received thrombolytic treatment with rt-PA (recombinant tissue plasminogen activator) significantly less frequently than men [48]. Post hoc analysis of approximately 2,000 patients from five pooled randomized clinical trials suggested that women benefit from intravenous thrombolysis significantly more than men (49). A similar result was fund for intra-arterial thrombolysis in an analysis of the PROACT-2 study (50). In the Canadian Alteplase for Stroke Effectiveness Study (CASES) of 1,110 (615 men and 505 women) receiving thrombolysis no effect of gender on 90-day functional outcome was found (51). A normal or near normal (modified Rankin score (mRS) score 0-1) outcome was found in 37.1% of men and 36.0% of women ($p = 0.71$). This remained essentially unchanged after adjusting for differences in baseline characteristics, including age >70, glucose level, hypertension, atrial fibrillation,

hypercholesterolemia, baseline National Institute of Heath Stroke Scale (NIHSS), and Baseline Alberta Stroke Program Early CT Score (ASPECTS) - 35.2% in men vs. 38.2% in women (p = 0.332). Ninety-day mortality was similar in both the adjusted and unadjusted analysis and was 23,3% for males and 19,4% for females (p = 0.168). Symptomatic intracerebral hemorrhage occurred more often in men (5.5% vs. 2.5%, p<0.001). It's worthwhile to mark that another analysis of the GAIN study fund that, among those who received thrombolysis, women were substantially less likely than men to have a good functional outcome, suggesting that they may not benefit more than men from thrombolysis. But even in this trial mortality was lower in women. However, the GAIN study excluded patients who showed major neurological improvement within 1 hour of receiving rt-PA. That suggests that these excluded rapid responders might be a particularly important group to study for gender differences in treatment response. One other study has reported that women are considerably more likely than men to have major neurological improvement in the first 24 hours after rt-PA treatment (n=219, OR 2.4, p = 0.02) (52). The number of women who suffered from stroke and treated with rt-PA should not be smaller than men, because as the above data shows, female answer to trombolysis is similar or even possibly better than with men.

**Unique and specific stroke causes in women**

Fertile women have unique risks related to childbearing potential. These include pregnancy, eclampsia, preeclampsia, and the use of oral contraceptives. Fortunately, the absolute risk of stroke in these young women is low, but a history of preeclampsia during pregnancy or postpartal period may be an indication that the risk persists even in the later years (53, 54). In a systematic review and meta analysis it was shown that women with a history of preeclampsia or eclampsia, compared with women without such a history, had an increased risk for cardiovascular disease, including a fourfold increase in the risk for hypertension, a twofold increase in the risk off ischemic heart disease, stroke and deep venous thrombosis, and 1.5-times higher all-cause mortality (53, 55). The study suggest that affected women may be eligible for preventive therapies at en earlier age, especially if future studies establish the role of preeclampsia as an independent cardiovascular risk factor (54). Similarly to preeclampsia gestational diabetes, pregnancy-induced hypertension has an increased risk of developing type-2 diabetes mellitus and cardiovascular disease including stroke (56).

Another gender specific risk factor is ovarian hyperstimulation syndrome (OHSS) which is the most serious complication of infertility treatment. It is characterized by ovarian enlargement, ascites, electrolyte disturbance, hypovolaemia and haemoconcentration. This results in a higher risk of thrombosis. Ischemic stroke due to middle cerebral artery (MCA) occlusion in a young female with OHSS after pharmacological treatment of sterility has been reported (57). In this case left central hemiparesis due to occlusion of the right MCA occurred suddenly within a few days after the embryo transfer. In this case haemodilution and the anticoagulation therapy were effective and resulted in recanalisation. The patient delivered 2 healthy infants at term. This case emphasizes that the recent advent of ovulation induction and reproductive techniques is a possible cause of cerebral stroke in otherwise healthy females.

In females of childbearing potential 35% of strokes are associated with puerperium and pregnancy. Cerebral infarcts occur most often in the third trimester and in the puerperium. It has been claimed that

pregnancy increases the likelihood of cerebral infarction to about 13 times the rate expected outside of pregnancy. However, the incidence of arterial ischaemic strokes associated with pregnancy or early puerperium was 4.3 per 1000,000 deliveries (95% CI, 2.4 to 7.1) in a large French study, and the rate has not differed from that for all women of childbearing potential (58). The two pregnancy-related causes, choriocarcinoma and amniotic fluid embolism, are rarely responsible for focal cerebral ischemia. Other diseases such as peripartal cardiomyopathy and postpartal cerebral angiopathy were considered as pregnancy-related causes of stroke. Postpartal vasculopathy (PPV) presenting as stroke s a heterogeneous nonatherosclerotic vasculopathy that occurs most likely in the first week postpartum (59, 60). Hypercoagulable state and vessel wall changes associated with pregnancy may play a role in the occurrence of ischemic strokes of arterial and venous origin. Cerebral venous thrombosis has been estimated to occur in 10 to 20 per 100,000 deliveries in developed countries, whereas rate of 200 to 500 per 100,000 have been reported in the developing world. Pregnancy and puerperal state accounts for 5 to 20% of all cerebral venous thrombosis in developed countries; this proportion may reach 60% in developing countries. The occurrence of cerebral venous thrombosis is clearly linked to the puerperal state, suggesting a direct role of the puerperal state (58, 59).

It is also important to remember of syphilis. Its occurrence has increased over the recent years in developed countries. It is known that that syphilis in pregnant women carries a high risk of congenital syphilis. Browning et al. described syphilis in young women in early pregnancy which created a stroke due to meningovascular syphilis. Specific and stroke treatment lead to resolution of the symptoms. Because syphilis is a treatable condition, screening in pregnancy is both cost effective and beneficial. (61).

Other condition predominating in young female subjects is Takayasu's disease. This is a primary autoimmunological granulomatous giant cell panarteritis affecting the aorta and its main branches to the limbs and the head which is much more common in Asians than in Europeans. The main neurological symptoms are syncope and visual disorders, but sometimes also TIA and stroke can occur (62). Treatment of vasculitis complicated by stroke includes steroids combined with or switched to a cytotoxic agent, usually cyclophosphamide, either as continuous oral or in intravenous pulses (63).

Systemic lupus erythematosus (SLE) is an example of secondary vasculitis significantly more frequent in females than males. SLE is the most common cause of stroke among the non-infectious vasculitis group, but usually occurs on average 4 years after disease onset and in active SLE. The treatment is mainly based on immunosuppresion (64).

It is also worth pointing out , that in women under the age of 50 with stroke, in comparison to men fibromuscular dysplasia, antiphospholipid syndrome and SICRET syndrome (Small Infarcts of the Cochlear, Retinal and Encephalic Tissues) (65).

Another stroke-linked disease which occurs more often in women is migraine. Migraine in general has been associated with subsequent risk of stroke, primarily in retrospective case-control studies. In a prospective cohort study conducted among 39,754 US health professional aged 45 and older participating in the Women's Heath Study with an average follow-up of 9 years migraine was not associated with all neither strokes, nor specifically ischemic or hemorrhagic. In subgroup analyses an increased risk of total and ischemic stroke for migraineurs with aura was found. The absolute risk increase was; however, low, with 3.8 additional cases per

year per 10,000 women (66). The analysis of 386 women aged from 15 to 49 years with first ischemic stroke showed that migraine with visual aura was associated with an increased risk of stroke, particularly among women without other stroke risk factors, compared to women with no migraine. Behavioral risk factors, specifically smoking and oral contraceptive use, markedly increased the risk of migraine with visual aura. Women with migraine with visual aura who smoked and were on oral contraceptives had 7.0-fold higher odds of stroke (95%CI, 1.3 to 22.8) than did women with migraine with visual aura that did not smoke nor use oral contraceptives. Also women with onset of migraine with visual aura within the previous year had 6.9-fold higher adjusted odds of stroke (95% CI, 2.3 to 21.2) compared to women with no history of migraine (67).

In summary it can be stated that stroke constitutes a serious socioeconomic and health care problem in women, largely underestimated previously. The incidence of cerebral infarction is lower in females than in males, but only up to menopause, due to natural estrogens which have antiatherogenic and neuroprotective effects. Beyond 65 years of age, the differences between men and women disappear. The risk factors that have higher importance in young women are migraine and oral contraceptive use as well as etiologies specifically associated with pregnancy, birth and puerperium, or even diseases that occur more commonly in women (systemic lupus erythematosus, Takayasu's vasculitis, fibromuscular dysplasia). After menopause typical vascular-disease risk factors play an important role and also others such as hormone replacement therapy. The pharmacotherapy of stroke ought to be similar in both genders, because the effect is similar. On the other hand the benefit from CEA is less in female patients than male, and because of this in women it ought to perform when stenosis of the ICA exceeds 70% and in secondary prevention should be performed as soon as possible. Special attention should be paid to rehabilitation in women because more female patients than men remain disabled after stroke. Gender may have important effect on outcome after stroke. In the future large cohort and experimental studies are needed to establish the actual role of gender in stroke.

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# 8. GENDER ASPECTS OF STROKE

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**Abstract**

Introduction: Recent studies suggest gender-related differences in stroke showing women to have a different profile of vascular risk factors, to respond differently to medical and interventional therapy, and to be less quickly evaluated and treated for stroke. Additionally, female stroke patients show a higher stroke morbidity and a higher degree of disability after stroke.

Methods: In order to provide a national perspective on possible sex differences and stroke, data from the Austrian Stroke Registry for Stroke Units were collected for a comparative analysis.

Results: Our database contained information from 26 stroke units with 13831 (6670 women, 48.2%) prospectively documented cases. Women were significantly older than men (73.4 +/- 13.8 vs. 67.8 +/- 12.7, $p<0.001$), were more likely to have atrial fibrillation (31.1% vs. 20.8%, $p<0.001$) and cardioembolic strokes (19.9% vs. 15.5%, $p<0.001$). Women showed a higher in-stroke-unit risk of death (3.5% vs. 2.4%, $p<0.001$) and a higher 3-month mortality rate (10.9% vs. 7.7%, $p<0.001$). Female patients had significantly ($p<0.001$) more severe neurologic deficits and dependencies at admission (NIH-SS: 7.7 vs. 6.0, Barthel-Index: 52.2 vs. 62.3, Rankin score: 3.1 vs. 2.7), at discharge (NIH-SS: 5.3 vs. 4.2, Barthel-Index: 65.0 vs. 73.9, Rankin score: 2.5 vs. 2.2) and at 3-month follow-up (Barthel-Index: 79.7 vs. 87.7, Rankin score: 2.1 vs. 1.6).

Discussion: This analysis showed significant gender disparities in ischemic stroke patients treated in Austrian stroke units. We also confirmed the prominent role of cardiac disorders especially for female stroke patients.

## Introduction

Stroke is the third most common cause of death in developed countries, exceeded only by coronary heart disease and cancer. Worldwide, 3 million women and 2.5 million men die from stroke every year (1). According to the data from the Framingham study, a statistically significant reduction in stroke incidence for both genders during the last 50 years is documented and a significant reduction in stroke mortality for men from 23 % to 14 %. However, the observed fall in mortality from stroke in women was from 21 % to 20 % (n.s.) (2).

Due to their greater life expectancy, women also suffer from stroke later in life than male stroke patients (3,4). Women with stroke show more severe neurological deficits (4) and a higher degree of disability and institutional living after their stroke (4,5). Female gender was an independent predictor for functional dependence after stroke (6,7). Previous studies report that females are less quickly evaluated and treated for stroke (8), and are less likely to receive stroke care interventions such as carotid endarterectomy and diagnostic tests (7,9,10). According to the data from the Swedish Riks-Stroke Registry, which contains information on 20761 stroke patients, women were less frequently treated with antithrombotic agents both during acute therapy and for secondary prevention, moreover, women with atrial fibrillation less frequently received an oral anticoagulation than men (3).

Women have a different risk-factor profile for stroke and cardiovascular disease compared with men. The relative risk of stroke is significantly higher in women with diabetes, atrial fibrillation and tobacco addiction (11,12,13,14). Cardiac embolism plays a major role in female stroke and is documented as an independent stroke risk factor for women (12). Women with atrial fibrillation have a 4.6-fold higher stroke risk (hazard ratio 1.7, 95% CI 1.0-3.0) than men (hazard ratio 1.7, 95% CI 1.0-3.0) (13). The higher risk of stroke for women with atrial fibrillation (relative risk 3.16 vs. 1.83 in men) was also demonstrated by data from the Framingham Study (14).

In order to provide a national perspective on possible sex differences and stroke, data from the Austrian Stroke Registry for Stroke Units were collected for a comparative analysis.

## Methods

Since 2003 a growing number of Austrian stroke units have documented stroke relevant data in a national register. The register is serviced by the BIQG, a business unit of the Gesundheit Österreich GmbH (GÖG) and was founded in cooperation with the Austrian Society for Stroke Research (ÖGSF) (15). Data entry is online, anonymous and password secured. The register contains epidemiological, clinical, diagnostic and therapeutic data, as well as scores necessary for the compliance with the structure criteria. A questionnaire-based telephone follow-up was performed after three months. Our database contained information from 26 stroke units with 15746 prospectively documented cases collected during the period January 2003 - February 2007 for descriptive statistical analysis.

### Statistical methods

The computer used to process statistics was an R 2.4.1 (The R Project) (16). The Mann–Whitney and Kruskal-Wallis rank sum tests were used to calculate the statistical significances of comparisons. The chi-square test was used to determine the independence of factors. Non-parametric tests were used for group comparisons (without assuming the distribution of data). The Wilcoxon rank sum test, corresponding to the Mann–Whitney test, was used to compare two groups. The Kruskal–Wallis rank sum test was chosen to compare more than two groups. The chi-square test was used to test factors for independence. Tables containing basic statistics (mean

value, median, standard deviation, quantiles) were produced in order to present the results including group comparisons where appropriate.

**Results**

13831cases (6670 women, 48.2 %, 7161 men, 51.8 %, n.s.) were classified as ischemic stroke. With a mean age of 73.4 ± 13.8 years, the female patients were significantly ($p < 0.001$) older than the male patients (67.8 ± 12.7 years). 3029 (71.2 %) female and 3216 (71.0 %) male patients completed the 3-month follow-up.

The distribution of cerebrovascular risk factors gave rise to clear gender-specific differences. Women suffered significantly more frequently from atrial fibrillation (31.1 % vs. 20.8 %), men were more likely to show hypercholesterolemia (44.5 % vs. 51.9 %), myocardial infarction (7.3 % vs. 11.5 %), peripheral arterial disease (5.2 % vs. 8.4 %), current smoking (12.3 % vs. 27.3 %) and alcohol consumption (2.9 % vs. 16.6 %). No statistically signi cant difference could be identified in terms of the distribution of arterial hypertension (78.1 % vs. 76.9 %), diabetes mellitus (25.8 % vs. 26.9 %) and prior stroke (25.5 % vs. 26.5 %) (Table. 1).

In most cases, the cause of stroke could not be determined reliably or was uncertain (women: 46.9 % vs. men: 46.6 %, n.s.), small vessel disease was identified as the second most common stroke aetiology (21.5 % vs. 21.8 %, n.s.). Cardioembolic strokes occurred more often in women (19.9 % vs. 15.5 %, $p < 0.001$), while large artery atherosclerotic disease was more common in men (8.8 % vs. 13.6 %, $p < 0.001$).

At admission, at discharge and at 3-month follow-up, female stroke patients were signi cantly more disabled. More female than male patients were already disabled before the event (Rankin scale: 0.9 vs. 0.5, $p < 0.001$). Female stroke patients demonstrated a more severe neurological deficit at admission (NIH-SS: 7.7 vs. 6.0, Barthel-Index: 52.2 vs. 62.3, $p < 0.001$) and were more severely handicapped (Rankin scale: 3.1 vs. 2.7, $p < 0.001$). Additionally, the female patients showed a higher neurological deficit at discharge (NIH-SS: 5.3 vs. 4.2, $p < 0.001$, Barthel- Index: 65.0 vs. 73.9, $p < 0.001$) and a higher handicap (Rankin scale: 2.5 vs. 2.2, $p < 0.001$), and were more significantly disabled and handicapped at 3-month follow-up (Barthel-Index: 79.7 vs. 87.7, $p < 0.001$, Rankin score: 2.1 vs. 1.6, $p < 0.001$).

First cerebral imaging at admission was performed more frequently in females by CT of the brain (94.9 % vs. 92.8 %, $p < 0.001$) and more frequently in men by brain MRI (11.2 % vs. 15.5 %, $p < 0.001$). No gender-specific differences were identified in terms of the frequency of the first basic diagnosis of the presence of an extracranial cerebral arterial obstruction using Doppler (72.7 % vs. 71.8 %) or Duplex (77.2 % vs. 78.1 %) sonography. Only transcranial Doppler sonography (36.6 % vs. 41.7 %, $p < 0.001$) and MRI angiography (8.2 % vs. 10.4 %, $p < 0.001$) were performed less frequently in female patients. However, women received less frequently a transthoracic (28.2 % vs. 31.2 %, $p < 0.001$) and transesophageal echocardiography (7.0 % vs. 10.4 %, $p < 0.001$).

Therapeutic management during the hospitalisation showed no statistically significant gender-related differences concerning intravenous thrombolysis (452, 7.4 % vs. 522, 7.8 %, n.s.) and application of antiplatelets (4687, 76.4 % vs. 5082, 76.2 %, n.s.).

Secondary stroke prevention at 3-month follow-up showed gender-related differences in terms of the choice of medication. Women were treated more often with ASS (41.4 % vs. 39.9 %, p = 0.027). Clopidogrel (21.7 % vs. 23.8 %, n.s.) and the ASS/Dipyridamol combination (6.9 % vs. 8.2 %, n.s.) were administered with roughly the same frequency. The frequency of an oral anticoagulation was similar in both genders (19.4 % vs. 20.6 %, n.s.).

The in-stroke-unit mortality rate (215, 3.5 % vs. 158, 2.4 %, p < 0.001) and 3-month follow-up mortality rate (331, 10.9 % vs. 249, 7.7 %, p < 0.001) were higher for women than for men. Women died more frequently than men due to heart attack (5.2 % vs. 3.7 %) or due to other cardiac diseases (15.2 % vs. 11.1 %), or other intercurrent illnesses (24.7 % vs. 20.6 %). Female stroke patients died less frequently compared to male patients from a recurrent stroke (6.4 % vs. 14.0 %), pulmonary embolism (1.5 % vs. 2.5 %) or other consumptive illness (4.6 % vs. 9.0 %).

## Discussion

This gender-specific analysis of the Austrian Stroke Unit Registry documents 13831 patients with ischemic stroke and shows a variety of gender-related differences which were statistically signi cant, though only few of these differences could actually be classified as relevant. At hospitalisation and at discharge, female stroke patients were signi cantly older than men (73.4 vs. 67.8 years). Almost one third of women presented an atrial fibrillation at admission, compared to one fifth of men. In comparison with epidemiological studies, this result confirms the importance of atrial fibrillation as a primary risk factor for stroke in women. Further results from our analysis confirm previous study results that heart conditions play a greater role for women than for men, women died more frequently than men from heart attacks (5.2 % vs. 3.7 %) or other heart disease (15.2 % vs. 11.1 %).

Our cohort of patients showed statistically highly signi cant differences in terms of clinical presentation, definition of stroke symptoms and death rates. The mortality rate during hospitalisation at a stroke unit (3.5 % vs. 2.4 %) and the 3-month mortality rate (10.9 % vs. 7.7 %) were statistically signi cantly higher for women than for men, which is probably due primarily to the advanced age of the women. At admission and discharge, female stroke patients were affected by a higher neurological deficit and a higher disability and handicap.

These results are consistent with those of earlier multi-centre studies (4,7).

In general, no gender-related differences could be identified in terms of the diagnostic management of ischemic stroke patients admitted to stroke units in Austria. This was true also concerning the frequency of cerebral imaging and testing for obstruction of the extra- and intracranial brain arteries. The less frequent conduct of echocardiographic investigations in women might be due to the higher prevalence of atrial fibrillation at admission and therefore presumed known stroke aetiology.

In contrast to data from the literature that report a less frequent thrombolysis (17) or application of antiplatelets (3) in women, this analysis showed no statistically significant gender-related differences in acute stroke treatment and secondary prevention with antiplatelets. However, despite the higher prevalence of cardiac arrhythmia, female patients did not receive oral anticoagulants more frequently for secondary stroke prevention during the post-hospitalisation phase (19.4 % vs. 20.6 %).

One of the strengths of this study is the wide-ranging data which records all male and female patients who were treated in Austrian stroke units during the observation period. However, these results only concern stroke patients who were treated at stroke units and therefore no general conclusions can be drawn concerning the ischemic stroke management at national level. The results of our data analysis comparing genders revealed that special consideration should be given to issues which are related to women and men and which have important implications not only for management per se but also for healthcare planning.

*Table 1: Prevalence of cerebrovascular risk factors according to gender*

| **Women** | **Men** | **Significance** | |
|---|---|---|---|
| | 6670 (48.2 %) | 7161 (51.8 %) | **Chi-square test** |
| Hypertension | 4742 (78.1 %) | 5068 (76.9 %) | p = 0.130 |
| Diabetes | 1557 (25.8 %) | 1771 (26.9) | p = 0.155 |
| Hyper-cholesterolemia | 2577 (44.5 %) | 3277 (51.9 %) | p < 0.001 |
| Atrial fibrillation | 1872 (31.1 %) | 1366 (20.8 %) | p < 0.001 |
| Myocardial infarction | 430 (7.3 %) | 745 (11.5 %) | p < 0.001 |
| Other heart disease | 1249 (22.8 %) | 1395 (23.4 %) | p = 0.445 |
| Prior stroke | 1504 (25.5 %) | 1715 (26.5 %) | p = 0.196 |
| Peripheral arterial disease | 292 (5.2 %) | 509 (8.4 %) | p < 0.001 |
| Current smoking | 694 (12.3 %) | 1655 (27.3 %) | p < 0.001 |
| Alcohol consumption | 167 (2.9 %) | 998 (16.6 %) | p < 0.001 |

## Acknowledgments

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# 9. ISCHEMIC STROKE IN YOUNG ADULTS

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According to the World Health Organization, stroke is the third most common cause of death in developed countries (1). Although more common in older adults, stroke also occurs in children and young adults, resulting in significant morbidity and mortality.

Stroke in young adults is rare but can be devastating for the affected individuals and their families. Recently, there has been increasing interest in this topic owing to increasing stroke rates in the younger age group and improved patient evaluation and treatment options.

There is general agreement that young adults have better chances of surviving a stroke than older individuals. However, the majority of survivors have emotional, social or physical sequel that impair their quality of life (2).

According to results of some studies, annual incidence rates of arterial ischemic stroke in children range from 3.4 to 11.3/100000 people per year (3).

## RISK FACTORS AND ETIOLOGY

The number of studies about ischemic stroke in young adults is limited. There are only few studies with data on risk factors in young adults with stroke. Risk factors include vasculopathy, cardiac defects, recent pregnancy, hypercoagulable states, drug use, premature atherosclerosis, and possibly migraine.

In one study, which included 324 patients with ischemic stroke, traditional risk factors were not uncommon. The most common risk factor was smoking (56%), hypertension (23%), dyslipidemia (15%), and diabetes mellitus (2%). Cardioembolic cause of stroke was found in 34%, hematological in 12%, vasculopathy in 14% and atherothrombotic in 12% of patients. [4]

In a prospective study which included 107 young adults with stroke, 13% had dissection, 28% had PFO or arterial septal aneurysm, 7% used oral contraceptives and 5% had elevated anticardiolipin antibodies (5).

### Cardiac cause of ischemic stroke

Myocardial infarction and ischemic stroke are rare in young adults and etiology is often uncertain, with no cause found in 30% to 40% of cases. Many of these cryptogenic strokes in young adults might be caused by

paradoxical embolism, and a higher prevalence of patent foramen ovale (PFO) has been reported in young adults suffering ischemic stroke (6).

A meta-analysis of these case-control studies, which were often small and poorly designed, confirmed a significant association between PFO and IS in adults below 55 years of age. A PFO was identified on postmortem in 35% of all adults dying under 30 years of age but in only 22% of older persons (7).

Acquired cardiac lesions, including endocarditis, cardiomyopathy and prosthetic valve placement are risk factors for stroke (8).

**Hematological cause of ischemic stroke**

The most common cause of stroke in children is sickle cell disease. The incidence of acute ischemic stroke in young patients with sickle cell disease is 0.44 per 100 patients per year. [9]

Many inherited or acquired prothrombotic disorders have been associated with pediatric stroke. The most usual are anemia (particularly iron deficiency), abnormal activated protein C resistance, protein C and S deficiency, antiphospholipid syndrome, elevated lipoprotein and homocysteine, often associated with homozygous mutation of the methylenetetrahydrofolate reductase (MTHFR) gene (10).

According to the results of studies, in young adults with ischemic stroke, several of these factors are associated with venous thromboembolism but not clearly with ischemic stroke. (11)

**Vasculopathy**

Vasculopathy are one of the most often cause of acute ischemic stroke in young adults. They can be divided into inherited or aquired and noninflammatory or inflammatory according to the etiology (12).

**Dissection**

Internal carotid artery dissection is the most common vascular abnormality in some young adult's studies. Fig. 1. It can be caused by major or minor trauma or it can be spontaneous in which case genetic, familial and/or heritable disorders are likely etiologies. The predisposition to arterial dissection is connective tissue disorders such as vascular Ehlers-Danlos syndrome or Marfan syndrome (12).

Carotid artery dissection begins as a tear in the tunica intima or between the tunica media and tunica adventitia. The blood under arterial pressure dissects along the artery to create an intramural hematoma, which can either narrow the carotid artery lumen or cause an aneurismal dilatation.

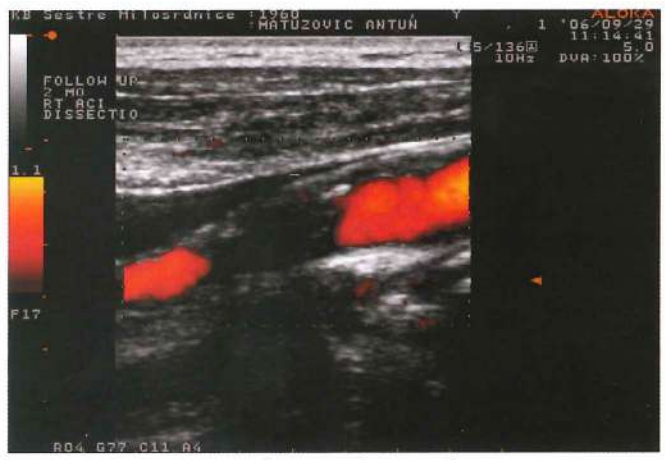

*Figure 1. Dissection of internal carotid artery*

Patients with internal carotid artery dissection can present with nonspecific complaints and in all settings. Pain is the initial symptom of a spontaneous internal carotid artery dissection presenting to a physician. Head, neck or facial pain ipsilateral to the dissection is common. In less than half of patients presenting with a carotid artery dissection, unilateral oculosympathetic palsy, or a partial Horner syndrome, may develop, and these patients will experience miosis, visual disturbances and mild ptosis (13).

### Vasculitis

Vasculitis are inflammatory changes in cerebral vessels and can be divided into primary and secondary. Primary vasculitides are Takayasu arteritis, giant cell arteritis, polyarteritis nodosa, Kawasaki disease and primary angiitis of the central nervous system. Secondary vasculitides are caused by collagen vascular disease or by infections (14).

### Genetics of ischemic stroke

There are few mendelian and mitochondrial disorders which are associated with ischemic stroke in young adults. For some of them, like Fabry disease or sickle cell disease, specific diagnosis is important because there are proven disease-specific treatments. A major goal for genetic discoveries is that they lead to improved methods for identifying individuals who are in the early stages of, or at high risk for, stroke or other diseases of interest. The specific diagnosis is important for all genetic diseases, because a diagnosis has prognostic value and avoids exposing patients to unnecessary, potentially harmful therapeutic agents and diagnostic tests.

### FABRY DISEASE

Fabry disease is an X-linked storage disorders caused by mutation in the α-galactosidase A gene. Patients with Fabry disease cannot metabolize globotriaosylceramide (Gb3) normally. The result is progressive accumulation of Gb3 in the lysosomes of vascular endothelial cells and smooth muscle cells. Progressive accumulation of Bg3 within endothelial and smooth muscle cells of the vascular system, dorsal root ganglia and cells of the autonomic nervous system, result in the neurological manifestation of the disease. (15,16). These include peripheral neuropathy and cerebrovascular complications in affected males and females carriers.

Peripheral neuropathy causes an almost constant discomfort of the hands and feet, with paroxysmal burning pains of the palms and soles. Recurrent painful episodes may be triggered by stress, fever, heat, joint pain or exercise (17,18).

Cerebral involvement, due mainly to vasculopathy and a dilatative arteriopathy in affected males and female carriers, may lead to TIA, stroke, aneurysms, acute blindness and accumulation of symptomatic and asymptomatic white latter lesions (19).

Strokes usually involve the posterior or vertebrobasilar regions.

The most common cerebrovascular symptoms in hemizygotes included hemiparesis, vertigo, dizziness, diplopia, dysarthria, nystagmus, nausea, head pain and ataxia of gait. Heterozygotes have memory loss, dizziness, ataxia, hemiparesis and hemisensory symptoms. The mot common angiographic and pathologic features were elongation, ecstasies and tortuosity involving the vertebral and basilar arteries (19).

Diagnosis is often delayed, especially in heterozygous females. Affected males are readily diagnosed by determining the level of α-galactosidase activity in plasma or peripheral leukocytes. Females have normal to very low levels of α-galactosidase activity, necessitating a genetic diagnosis in females (15).

There is no cure for Fabry disease. However, treatment with recombinant alpha-Gal A is available and should be considered for eligible individuals. Two formulations of recombinant human alpha-Gal A have been developed: agalsidase alpha (Replagel) produced in a genetically engineered human cell line, and agalsidase beta (Fabrazyme) produced in a Chinese hamster ovary cell line.

Enzyme replacement therapy reduced neuropathic pain and improved creatinine clearance (20) Further studies are required to determine whether enzyme replacement treatment in Fabry disease will result in a reduction in clinical outcomes such as stroke, ischemic heart disease or end-stage renal disease.

**MELAS**

Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS) is a maternally inherited syndrome caused by mutations in mitochondrial DNA. he mitochondrial mutations that result in MELAS cause defects in respiratory chain enzymes, particularly complex I. Substitution of an adenine for guanine at nucleotide position 3243 in the gene encoding tRNA Leu accounts for 80% of the cases.

The hallmark of this syndrome is the occurrence of stroke-like episodes that results in hemiparesis, hemianopia, or cortical blindness. Clinical diagnostic criteria for MELAS are stroke before the age of 40 years, encephalopathy characterized by seizures or dementia, and blood lactic acidosis or ragged red fibers in skeletal muscle biopsy specimens (21). Fig.2

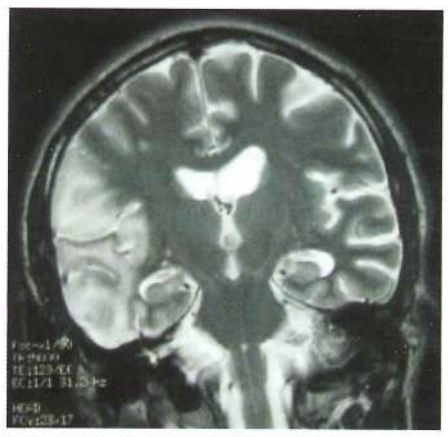

*Figure 2. MRI in patient with MELAS syndrome*

**CADASIL**

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by a mutation in the Notch3 gene, which leads to progressive degeneration of smooth muscle cells in the vessel wall. The function of the human Notch 3 receptor is not precisely known. Studies in animals suggest that the Notch 3 gene is involved in development of the CNS.

Stroke, dementia, psychiatric illness, and migraines are common features of CADASIL. The level of disability from the disease varied considerably, both within and among pedigrees. Fewer than half of patients older than 60 years could walk without assistance.

MRI of the brain is an essential screening test for CADASIL and presymptomatic carriers of a CADASIL mutation. Abnormalities in the white matter can be observed on MRI long before patients present with stroke or TIA. Several CADASIL mutations have been identified, and a genetic test is commercially available for the most common n mutations. However, this test currently has a false-negative rate of at least 20% because it screens only few mutations.

The diagnosis of CADASIL can also be approached pathologically. Vascular osmophilic granules can be seen on electron microscopy in skin, muscle, and peripheral nerves (22).

Even asymptomatic patients with minimal abnormalities on brain MRI can have characteristic granules in or near the outer side of thickened basal lamina of vessels in the dermis. Skin biopsy, although practical, can be falsely negative.

Until now, there is no treatment of CADASIL. Patients use Aspirin and related drugs in the hope of preventing thrombotic occlusion of thick-walled narrow cerebral blood vessels. Micro bleeds can be seen on brain MRI in more than half of CADASIL patients, suggesting that even daily aspirin might place patients at risk for intracranial hemorrhage (23).

## HOMOCYSTINURIA

Homocystinuria is an autosomal recessive disease characterized by marked increase of homocysteine in plasma and urine. Elevated levels of homocysteine are an independent risk factor for stroke. The characteristic clinical phenotype includes mental retardation, thromboembolism, premature atherosclerosis, ectopia lentis, osteoporosis, and skeletal abnormalities. Homocystinuria can be caused by severe deficiency of methylenetetrahydrofolate reductase (MTHFR) or by homozygous defects in the gene encoding the enzyme cystathione β-synthase. Patients are treated by pyridoxine, folic acid and vitamin B12 (24).

## MOYAMOYA DISEASE

Moyamoya disease is an extremely rare disorder characterized by progressive intracranial vascular stenoses of the circle of Willis, resulting in successive ischemic events. Fig.3.The condition leads to irreversible blockage of the carotid arteries to the brain as they enter into the skull. It is disease that tends to affect children and adults in the third to fourth decades of life. In adults it tends to cause bleeding or strokes.

The clinical features are cerebral ischemia, recurrent TIAs, sensorimotor paralysis, convulsions and/or migraine-like headaches.

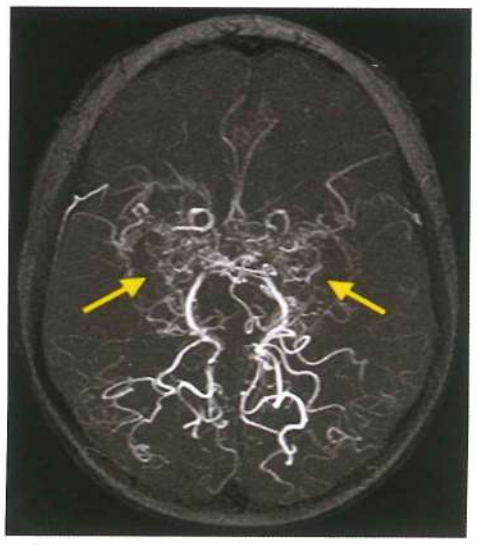

*Figure 3. Angiography in patient with MoyaMoya syndrome*

## DIFFERENTIAL DIAGNOSIS OF STROKE IN YOUNG ADULTS

In young adults with ischemic stroke, differential diagnosis includes seizure and postictal deficits, migraine, systemic infection, psychiatric disorders, brain tumor, toxic-metabolic abnormalities, cranial neuropathy, transient global amnesia and syncope or presyncope.

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# 10. ULTRASONOGRAPHY AS A DIAGNOSTIC AND THERAPEUTIC TOOL IN STROKE

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## Extracranial color Doppler in the evaluation of stroke

### Carotid stenosis

Advances in performance and interpretation of extracranial cerebrovascular sonographic studies over the last 20 years (1) have been driven by technological improvements in gray scale and color-coded duplex Doppler sonography (CDDS) examinations, resulting in wide clinical applications and technical performance of carotid and vertebral sonographic examinations (2).

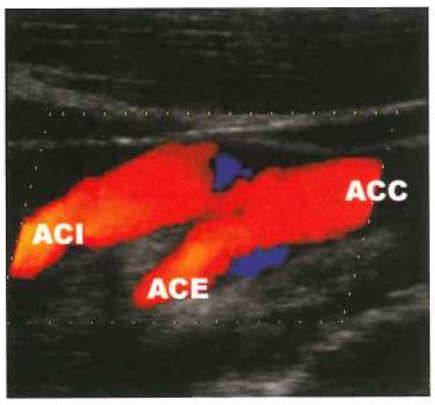


*Figure 1. Normal appearance of the carotid bifurcation on Color Doppler (Duplex) Flow Imaging.*

The benefit of carotid endarterectomy in stroke prevention in advanced carotid stenosis was proved in large studies (European Carotid Surgery Trial - ECST and North American Symptomatic Carotid Endarterectomy Trial - NASCET), using different angiographic methods of estimation of carotid stenosis measurement (3,4); (Figure 1,2). Asymptomatic Carotid Surgery Trial (ACST) (5) in primary prevention to reduce the risk of stroke, was based on ultrasonographic findings. Although peak systolic velocity PSV is the most important component of the carotid Doppler examination (6), the grading of carotid stenosis with ultrasound should not be limited to this parameter only (6-9). As a screening test, carotid ultrasound should have an optimal tradeoff

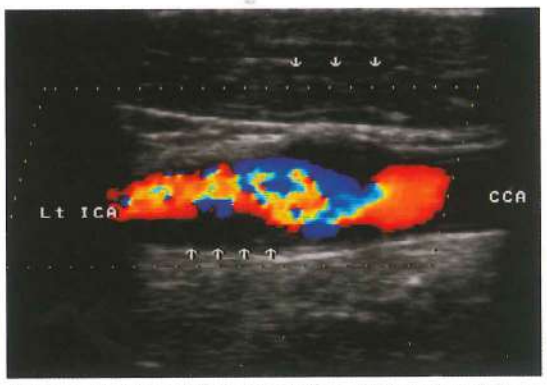


*Figure 2. Carotid stenosis (moderate grade) on Color Doppler (Duplex) Flow Imaging.*

between sensitivity and specificity with the aim of identifying the highest percentage of patients with the potential of having a severe carotid stenosis. Since ultrasound grading of carotid stenosis is operator dependent and relies on different and individually validated criteria despite the use of similar equipment (10,11), and also depends on plaque characteristics (12), a combination of criteria of ultrasound screening specific to each laboratory should be applied. Such criteria must be accurately defined, and tested in prospective studies (13-15). Among different techniques of noninvasive estimation of carotid stenosis, CCDS showed lowest interobserver variability (9). A high correlation between angiography and CCDS in detecting various degrees of carotid stenosis has been proven; for example CCDS enables visualization of pseudo-occlusion thus being superior to angiography (13). Furthermore, ultrasound is more sensitive in detecting the category of severe stenosis (near occlusion, pseudo-occlusion).

The use of CCSD (B-mode) is valuable in atherosclerotic plaque characterization and is useful in the assessment of the vulnerability of the atherosclerotic lesion (12,16). In The Second International Consensus Meeting (16), criteria for the classification of unstable or "dangerous" plaques were determined: Plaque compositions are thus characterized in five steps as follows: 1. Uniformly anechogenic plaques, with the high risk for stroke, 2. Predominantly hypoechoic plaques with hypoechoic areas of more of 50% of plaque structure, 3. Predominantly hyperechoic plaques with hypoechoic areas of less than 50% of plaque structure, 4. Calcified plaques, with the 2.,3.,and 4. types of lower stroke risk, and 5. Calcified plaques with the acoustic shadow, making the vessel lumen evaluation impossible, in which the risk for stroke is still under investigation.

Recent studies have provided good evidence that lipid-rich plaques are more prone to rupture and suggest that an association between intraplaque hemorrhage and a high lipid content as revealed in B-mode ultrasound may support this theory (17). The presence of hypoechoic ICA plaques has also been reported as an independent risk factor for cerebrovascular events (18,19).

**Vasculitis, vasulopathies, dissections**

Vasculitis of the nervous system includes a group of disorders characterized by the histological feature of inflammation of blood vessels. The use of CCDS may help in noninvasive visualization of the disease (20), by direct visualization if the location of the disease is present in a segment that is accessible to the ultrasound investigation, i.e. affection of the branches of the aortic arch (21), by indirect signs in hemodynamic of the carotid or vertebral arteries, or by visualizing dark halo around the pin like color-coded flow in temporal artery (22) or occipital artery (23). Vasculitis affecting smaller arteries, may alter intracranial hemodynamic, that can be measured as impaired vasoreactivity as a marker of smaller vessel involvement.

Among vasculopathies, Moya-Moya disease (24) and fibromuscular dysplasia (25) can be displayed, and may predispose to dissection. Dissections are lately more often recognized as relatively common causes of stroke, particularly among young patients. Dissections lead to ischemic strokes through artery-to-artery embolism or by causing significant stenosis and occlusion of the proximal vessel, and in some cases, dissections may lead to formation of a pseudoaneurysm, which can also serve as a source of thrombus formation. Intracranial dissections in the vertebrobasilar territory have a higher risk of rupture, leading to subarachnoidal hemorrhage (SAH). Dissections may appear as different findings in color-coded Doppler mode (26-30), (Figure

3). When extending from aortic arch, double lumens can be seen. Bifurcation stenosis may dissect leading to the formation of color-coded flow in the plaque base. In younger persons dissections are usually affecting distal parts of the internal carotid or vertebral arteries. Hypoechoic stenosis of the vessels in distal parts can be seen, or when located intracranial leading to complete occlusion, the indirect signs of distal occlusions are present. Such signs include dampened flow, with high resistance pattern, and possible inversed hemodynamic during diastole. The goals of the therapy, when treating patients with dissections and ischemic stroke, are to prevent further ischemic strokes and to promote healing of the dissected vessel, and CCDS may help in monitoring of the vessel healing, parallel with the emboli detection that may show reduction in embolic signals (31-33).

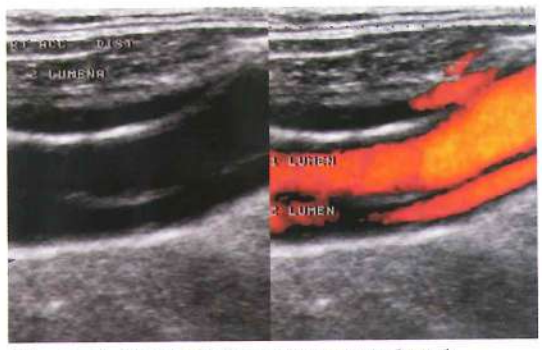

*Figure 3. Carotid dissection visualized by power Doppler.*

The detection of rare causes of ischemic stroke, such as dissections, intimal hyperplasia and other less frequent etiologies is facilitated by the systematic use of ultrasound studies.

**TCD as a diagnostic tool in stroke**

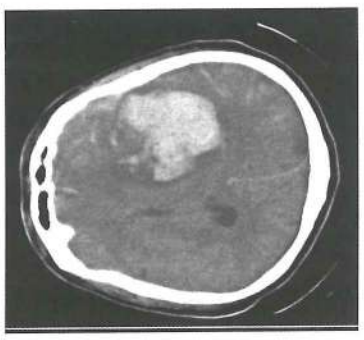
*Figure 5. Parenchymal haemorrhage vizualized by CT scan (same patient as on Figure 4).*

Transcranial Doppler (TCD) is a convenient non-invasive diagnostic method, that evaluates cerebral blood flow in real and may be repeated in sucsession if needed. TCD enables the detection of hypoperfusion, arterial stenosis, occlusion, and recanalization, may assess the collateral blood flow and vasomotor reactivity, TCD helps in right-to-left shunt detection; it also serves as an excellent method for follow-up of stroke patients. In the neurointensive care unit, TCD is useful for detecting increased intracranial pressure, for monitoring of patients with subarachnoid heamorrhage and for confirmation of cerebral circulatory arrest. Transcranial color coded sonography (TCCS) is a modality that is useful in the evaluation of brain parenchyma such as detection of parenchymal haemorrgahe, (Figure 4,5), brain tumor, vascular abnormalities (Figure 6) and discrimination of Parkinson's disease from other movement disorders (34-42).

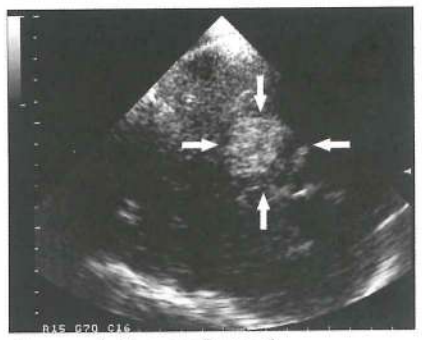
*Figure 4. Parenchymal haemoorhage vizualized by TCCS*

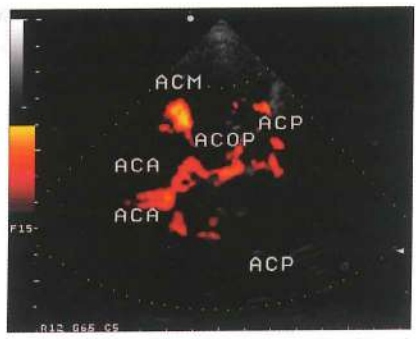

*Figure 6. Circle of Willis visualized by TCCS power Doppler.*

Furthermore, TCD can detect microembolic signals, which are characterized by unidirectional high intensity increase, short duration,

random occurrence, producing a „whistling" sound. Microembolic signals have been proven to represent solid or gaseous particles within the blood flor and can be detected in a number of clinical settings: carotid artery stenosis, aortic arch plaques, atrial fibrillation, myocardial infarction, prosthetic heart valves, patent foramen ovale, valvular stenosis, during invasive procedures (angiography, percutaneous transluminal angioplasty), surgery (carotid, cardiopulmonary bypass, orthopedic), and in certain systemic diseases (43).

Recently TCD has been recognized particularly suitable for the evaluation of intracranial haemodynamics in emergent cases, such as stroke. Urgent detection, localization and assessment of the severity of obstructive arterial lesions by grading systems help triage patients with acute cerebral ischemia and select patients for the most adequate therapy or invasive angiography. A grading system of arterial patency has been developed to detect the localization and extent of vessel occlusion or stenosis; the previously established TCD patterns of occlusion and recanalization have been redefined into the Thrombolysis in Brain Ischemia (TIBI) system according to the dynamic nature of acute occlusion and recanalization process taking place in acute stroke in patients receiving rt-PA (44). The TIBI classification consists of 6 grades which are based on the combination of waveform analysis and flow velocity differences (as compared to normal and flow in the contralateral MCA). Complete MCA occlusion is defined by absent (TIBI 0) or minimal (TIBI 1) flow signals detected at one or more localizations in the range of MCA insonation. The insonation of the MCA is performed through the transtemporal window at the depth of 40-65 mm, the MCA may further be divided into the proximal (M 1) part (46-65 mm depth) and distal (M 2) part (< 45 mm). In cases of TIBI 0 or TIBI 1, either terminal internal carotid artery (ICA) or posterior carotid artery (PCA) flow signals must be identified from the ipsilateral window (to exclude inadequate US insonation through the bone). Partial MCA occlusion is diagnosed when blunted (TIBI 2) or dampened (TIBI 3) signals are detected. A blunted flow signal is characterised by delayed (> 0.2 seconds) systolic flow acceleration with a pulsatility index (PI) < 1.2, which indicates low resistance flow diversion to branching vessels or a residual positive end-diastolic flow at the site of MCA occlusion. A dampened flow signal is identified when normal systolic flow acceleration is present in the pulsatile MCA waveform with mean flow velocities < 70% of the contralateral MCA and positive end-diastolic flow with variable PI values. Complete recanalization is diagnosed if low-resistance stenotic (TIBI 4) or normal (TIBI 5) signals are detected through the MCA and with no other signs that would indicate distal persisting occlusion (dampened distal signal or flow diversion).

The TIBI flow grades represent the first systemic classification of residual flow determined by TCD for major intracranial vessels and can be used to quantitate residual flow appearance and assess the vessel patency and its relation to stroke severity. The TIBI grading system has a good correlation with angiography with a sensitivity and specificity of > 90% for the MCA territory and > 86 % for the vertebrobasilar territory (45,46).

TIBI 0 : absent – no detectable flow signal despite varying degrees of bacground noise

TIBI 1:minimal – systolic spikes of variable velocity and duration; absent diastolic flow during all cardiac cycles based on a visual interpretation of periods of no flow during end diastoli; in certain cases reverberating flow may be detected which is a type of minimal flow

TIBI 2:blunted – flattened systolic flow accelerations of variable duration compared to control (other MCA); positive end diastoic velocity and pulsatility index < 1.2

TIBI 3:dampened – normal systolic flow acceleration; positive diastolic velocity; decreased mean flow velocities (MFV) by > 30% compared to control

TIBI 4:stenotic – MFV of > 80 cm/s AND velocity differences > 30% compared to the control side; or if both affected and comparison sides have MFV < 80 cm/s due to low end-diastolic velocities, MFV > 30% compared to the control side AND signs of turbulence

TIBI 5:normal - < 30% mean velocity differences compared to control; similar waveform shapes compared to control

Figure 7: TIBI grading system

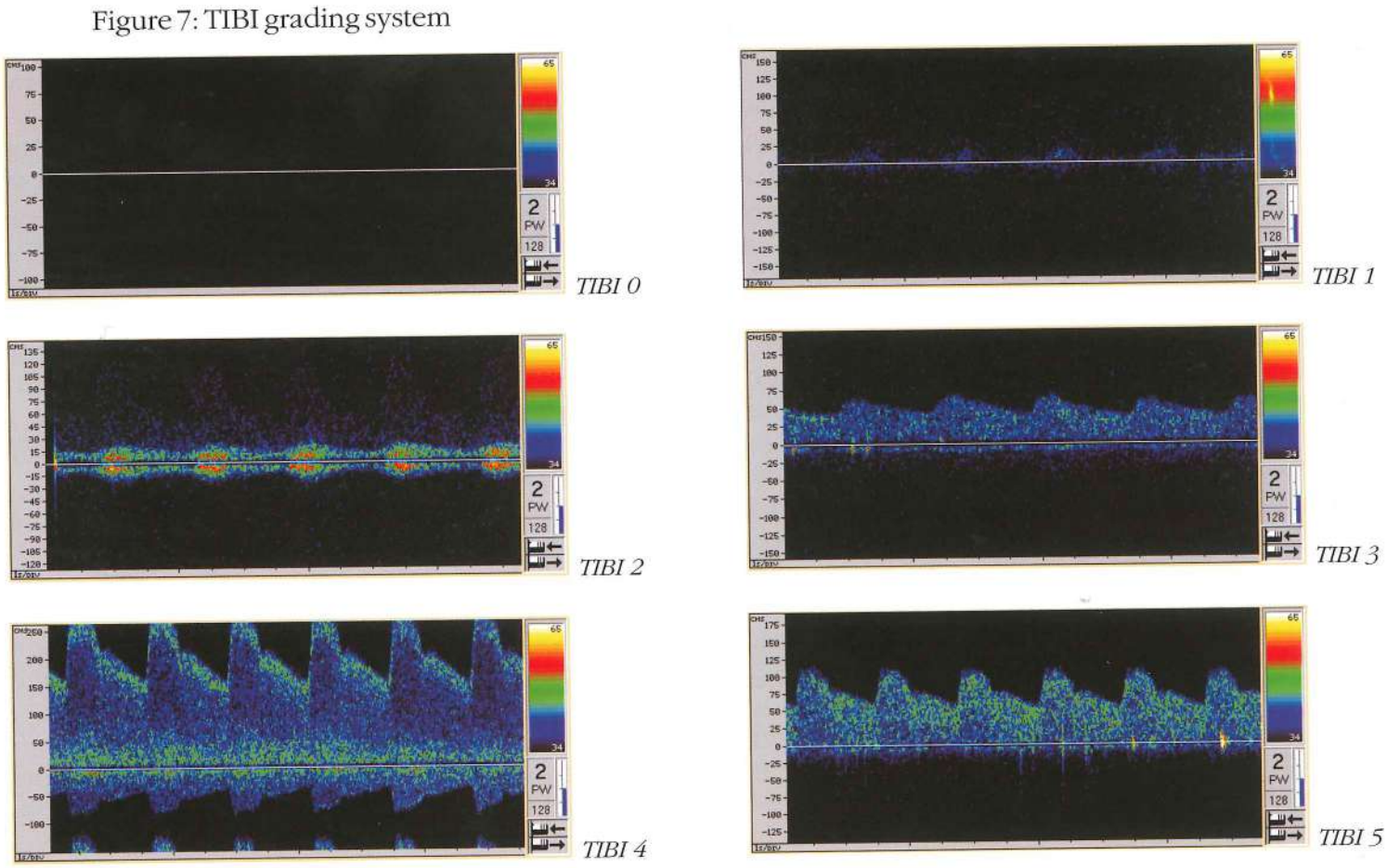


*Figure 7. TIBI grading system.*

The TIBI grading system is mostly used in the assessment of MCA occlusion, and proximal and distal vessel occlusion may be diagnosed according to the following criteria:

A) Proximal MCA occlusion is defined as the presence of minimal flow signal throughout the MCA at an insonation depth from 46 to 65 mm, accompanied by flow diversion in the ipsilateral anterior cerebral artery and posterior cerebral artery.

*B) Distal MCA occlusion is defined as blunted or dampened signals (TIBI 2 or 3) in the symptomatic artery with < 30% flow compared with the contralateral MCA and flow diversion signs in ipsilateral neighbourghing arteries.*

Additional studies are needed to test the TIBI grading system for other vascular territories than MCA. Moreover, the TIBI grading system has so far been used only in patents receiving rt-PA and its prognostic value can not be applied to patients not receiving thrombolytic therapy.

**TCD as a tool for patient selection**

Furthermore, TCD may help to rapidly identify patients who are targets for additional intra-arterial thrombolytic or mechanical interventions (patients with TIBI 0 and I grade). The recanalization rate of 25 % to 30 % observed with proximal large vessel occlusion may explain the limited effect of systemic thrombolysis alone (47,48), and intraarterial thrombolytic therapy may result in better recanalization rates. TCD may serve as a screening tool to predict outcome and identify a proximal arterial oclussion that requires intra-arterial lysis using the mean flow velocity (MFV) ratio of the MCA billateraly (affected MCA-to-contralateral MCA MFV ratio) (49). In this study the ratio < 0.6 had a sensitivity of 94 % and specificity of 100 %, positive predictive value of 100 % and negative predictive valuse of 86 % for identifying proximal occlusion in the anterior circulation compared with standard cerebral angiography (49). Since TCD is operator dependent „blind" method, it can only serve as a screening test for evaluation of the presence of intracranial artery occlusion, therefore angiography (CTA, MRA) is mandatory for the selection of patients that might require additional intra-arterial interventions.

**Combined TCD and extracranial Doppler in stroke diagnosis**

Recent studies have shown that the combined usage of TCD and extracranial Doppler (duplex) may help in patient selection for best treatment option (50). The presence of proximal ICA occlusion may warrant other treatment approaches in addition to iv. rt-PA since clinical experience has shown that recanalization of the proximal part of ICA almost never occurs with this therapy (51,52). Carotid and vertebral duplex and TCD examination compared with digital subtraction angiography (DSA) can predict the presence of vascular lesions with 100 % sensitivity and 100 % specificity, although individual accuracy parameters for TCD and carotid duplex specific to occlusion location ranged 75 % to 96 % because of the presence of tandem lesions and 10 % rate of no temporal windows (50). Carotid duplex alone in comparison with DSA, has a high sensitivity and specificity if performed in cerebrovascular laboratories with high clinical experience (53).

The so-called tandem ICA/MCA occlusion (severe carotid stenosis or occlusion ipsilateral to MCA occlusion) due to its specific haemodynamic changes that produces, requires special attention when a stroke patient with a suspected tandem lesion is assessed. The advantage of TCD is that it can detect residual flow in the

sub-occluded artery and detect as well the major collateral pathways in the anterior and posterior circulation. Therefore specific TCD criteria have been established which include 3 major and 3 minor criteria; acute ICA/MCA occlusion is diagnosed if abnormal (or asonic) TIBI waveforms in the MCA is present with one major or two minor findings (54,55). In acute stroke patients, these TCD criteria have shown sensitivity of 79% and specificity of 86% in comparison with angiography (the „gold" standard) to detect severe ICA stenosis or occlusion (54).

Major criteria include:

Collateral flow signals in the anterior or posterior communicating artery or ophthalmic arteries

Abnormal ICA siphon or terminal ICA signals (TIBI grading system: absent, minimal, blunted, dampened or stenotic waveforms)

Delayed systolic flow accelerations in the MCA or terminal ICA (maximum frequencies arrive late in the systole with normal velocity range)

Minor criteria include:

Decreased pulsatility flow index (> 0.6 or interhemispheric difference > 30%)

Flow diversion signs to branching or contralateral vessels (velocity: PCA > MCA; PCA > ICA and contralateral ACA > MCA)

Compensatory velocity increase in branching or contralateral vessels (> 20% increase in the contralateral hemispheric vessels or vertebrobasilar arteries)

In consecutive ischemic stroke patients, isolated MCA occlusion may be found in 51% of patients and tandem ICA/MCA occlusion in another 17 % of patients (55); in this study lower NIHSS scores were detected in both groups of these patients when associated with positive diastolic flow at the MCA origin assessed with TCD and detectable 2 major collaterals whereas patients with NIHSS scores 20 had no diastolic flow at the M1 part of the MCA origin and one or no detectable major collaterals indicating occlusion of perforating arteries and probably greater overall thrombus burden (55).

When combined with carotid duplex sonography, the presence and total number of arteries with suspected steno-occlusive lesions by TCD in TIA or stroke patients, were associated with poor outcome (56) an increased risk of further vascular events and death within 6 months (57). Such combined stroke patient evaluation can identify lesions amendable for interventional treatment (LAIT) in patients with acute cerebral ischemia (58) achieving 100% accuracy.

**TCD in stroke therapy**

The results of clinical trials exploring new treatment modalities have shown to be promising, particularly the use of continous TCD monitoring while administering rt-PA and even more recently, the co-administration of microbubbles with rt-PA and TCD monitoring.

The Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic TPA (CLOTBUST) trial (phase II) has recently demonstrated that continous 2-MHz TCD monitoring of an intracranial artery occlusion enhances systemic thrombolysis in acute stroke patients, may improve outcome, and which is most important, this enhanced ultrasound (US) monitoring seems to be safe (59). US enhanced thrombolysis in previous research studies has shown that US has the ability to accelerate the transport and penetration of rt-PA into the clot by creating plasma microstreams within the fibrin rich thrombus, thus resulting in faster and more successful clot disruption (60). A randomized multicenter, double blind, controlled clinical trial called CLOTBUST (**C**ombined **L**ysis **o**f **T**hrombus in **B**rain ischemia using transcranial **U**ltrasound and **S**ystemic **t**-PA) suggests that continuous 2MHz, single-element pulsed-wave TCD ultrasonography that is aimed at residual obstructive intracranial blood flow may help expose thrombi to rt-PA and enhance the thrombolytic activity of t-PA (59). Among 126 patients randomly assigned to receive continuous ultrasonography (63 patients) or placebo (63 patients), complete recanalization or dramatic clinical recovery with 2 h after the administration of a t-PA bolus occurred in 31 patients in the treatment group (49%), compared with 19 patients in the control group (30%; p=0.03). The CLOTBUST Trial showed a trend toward sustaining complete recovery at 3 months (41.5% versus 28%, modified Rankin Scale scores 0 to 1), moreover, trends toward better clinical outcomes at 24 hours and long term were also noted in sonothrombolysed patients. SICH occured in 4.8% in both treated groups. This was a subject for a pivotal phase III trial.

However, the use of US in acute stroke patients may be potentialy harmful, as results of the Transcranial Low-Frequency Ultrasound Mediated Thrombolysis in Brain Ischemia trial (TRUMBI) trial have shown (61). In the TRUMBI trial low frequency US has been used (300 kHz), however, low frequencies may cause mechanical distortion of human brain microvessels leading to vessel disruption, and this was the probable reason for high SICH of 35% in this study. High SICH rate (including bleeding in brain areas not affected by ischemia) and no signal of efficacy on early recanalization or clinical outcome at 3 months were the reasons for premature trial cessation.

Administration of microbubbles (MBs) further accelerates the US-enhanced thrombolysis in acute stroke, leading to an even more complete recanalization of the artery, as recent studies have shown (62-65). Microbubbles are small air- or gas-filled microspheres, whose acoustic impedance largely differs than from the body fluids (blood), thus increasing the reflection of ultrasound – this is the main acoustic property how microbubbles serve as an US contrast agent. In the setting of clot disruption, MBs act as cavitation nuclei, and during the application of high-acoustic-pressure US, MBs continously absorb the energy until they explode, releasing the absorbed energy; this is the theoretical presumtion that has shown to be effective in the recent study tested on acute stroke patients (62). The study combined the standard administration of rt-PA (group rt-PA), plus 2-hour continous 2-MHz TCD monitoring of the occluded artery (group rt-PA/US), results from previous trials (59) plus the iv. administration of MBs (group rt-PA/US/MB): 3 boluses of 400 mg/dL of the galactose-based MBs (Levovist) given at 2, 20 and 40 minutes after rt-PA administration. Two-hour recanalization was seen in 39%, 68% and 71% in the rt-PA, rt-PA/US and rt-PA/US/MB group respectively. Two-hour complete recanalization rate was significantly higher in the rt-PA/US/MB group (54.5%) compared with the rt-PA/US group ( 40.8%) and the rt-PA group (23.9%). Symptomatic intracranial haemorrhage was observed

in 5.5%, 2.7%, and 2.6% in the rt-PA, rt-PA/US and rt-PA/US/MB groups respectively, indicating that SICH appeared unrelated to US monitoring or MB administration, despite the fact that asymptomatic intracranial haemorrhage (in all cases in deep MCA territory) has been detected on control CT in 16%, 19% and 23% of patients who recieved rt-PA, rt-PA/US and rt-PA/US/MB respectively. Moreover, the co-administration of Levovist (3 boluses) during rt-PA infusion was well tolerated in all patients without systemic complications. At 24 hours, 31%, 41% and 55% of rt-PA, rt-PA/US and rt-PA/US/MB respectively treated patients improved > 4 points in the NIHSS score (median score at addmission was 18). Although this study was non-randomized, sample size was small, and the study was focused on patients with MCA occlusion, the results of the study are encouraging for further trials in this direction.

Recent study randomized fifteen stroke patients treated with perflutren microspheres and TCD, within 3 hours and abnormal TIBI residual flow grades 0-3 before tPA on TCD. Patients were randomized 3:1 to target group (tPA+TCD+2.8 mL microspheres) or control (tPA+TCD). It was a safety study, and after treatment, asymptomatic ICH occured in 3 target and 1 control subject, and sICH was not seen in any study subject, thus reaching the primary endpoint (66). Microspheres reached MCA occlusion in all target subjects at velocities higher than surrounding residual red blood cell flow ($p<0.001$). In 75% of subjects, microspheres permeated to areas with no pretreatment residual flow, and in 83% residual flow velocity improved at a median of 30 minutes from start of microspheres infusion (range 30s to 120 minutes) by a median of 17cm/s (118% above pretreatment values). In order to provide perspective for further investigation, the study recanalization rates were compared with the tPA control arm of the CLOTBUST trial: complete recanalization in this study was 50% versus CLOTBUST 18%, partial 33% versus 33%, none 17% versus 49%, $p=0.028$. At 2 hours sustained complete recanalization was 42% versus 13%, $p=0.003$, and NIHSS scores 0 to 3 were reached by 17% versus 8%, $p=0.456$. Perflutren microspheres reached and permeated beyond intracranial occlusion with no increase in sICH after systemic thrombolysis suggesting feasibility of further microspheres dose-escalation studies and evelopment of drug delivery to tissues with compromised perfusion.

**TCD in assessment of stroke outcome**

Intracranial arterial occlusions detected by TCD are associated with poor neurological recovery, disability, or death after 90 days (67) whereas normal results predict early improvement (68). In patients with acute ICA territory stroke, TCD findings, stroke severity at 24 hours, and CT lesion size were independent predictors of outcome after 30 days (69).

The most effective therapy for stroke is rt-PA, however, only 1-8.5 % of hospitalized stroke patients in receive rt-PA because of many exclusion criteria primarily due to late hospital arrival (70). Furthermore, in patients who do recieve rt-PA, less than 50% recanalize, there is a substantial risk of symptomatic heamorrhagic transformation (SICH), and re-occlusion occurs in part of the treated patients.

During the last few years, mounting evidence from continous TCD-monitoring studies confirmed initial clinical findings in stroke patients. The dynamic process of thrombus dissolution during thrombolytic therapy has been accurately delinated by continous TCD monitoring, showing in real time all stages of recanalization

and characteristic embolic signals indicating thrombus fragmentation (71). The speed of clot lysis during continuous TCD monitoring was categorized into sudden recanalization indicating rapid and complete restoration of flow (abrupt appearance of a normal or low-resistance signal), stepwise (gradual flow improvement over 1-29 minutes) or slow (flow improvement in > 30 minutes) which reflect reflect proximal clot fragmentation, downstream embolization and continuation of clot migration distaly. The pattern of sudden clot lysis has been associated with a higher degree of neurological improvement and better long-term outcome than stepwise and slow recanalization, although sudden recanalization has been observed in only 8-12 % of patients treated with rt-PA (71).

The treatment with rt-PA has been found to be effective in different stroke subtypes (72), however, the response to the treatment widely varies, most probably depending on the size, composition and source of the thrombus. Platelet rich, well organized and presumably old thrombi are found to be more resistant to thrombolysis than fresh, fibrin- or red cell- rich clots formed in conditions of stasis (73,74). In a recent TCD study of stroke patients with proximal MCA occlusion who were treated with rt-PA, early recanalization was shown to be more frequent, faster and more complete in strokes presumably to be cardioembolic (CE) in origin as compared with other stroke subtypes: one-hour recanalization was observed in 59% of CE patients as compared with 8% in large vessel disease group or 50 % in patients with stroke of undetermined origin (75). Rate of complete recanalization was 50 % in CE group as compared with 27 % in other stroke subtypes. Furthermore, sudden clot lysis during rt-PA administration has been identified in 81% of patients with cardiac sources of emboli.

The in vitro and clinical studies indicate that faster recanalization occurs in cases of cardioembolic strokes that are more fibrin-rich red clots. Since the rt-PA has a high binding affinity for fibrin, rt-PA penetrates and distributes more homogeneously in fibrin-rich clots and thus enabling more rapid and complete clot dissolution as observed by TCD in the pattern of sudden or stepwise recanalization. Distribution of rt-PA in well organized, platelet-rich clots is limited which may result only in clot shrinking (since the rt-PA acts mostly on clot surface), movement to more distal parts of the vessel and prolonging ischemia. In these cases the presence of distal artery occlusion is correspondent with TIBI 3 grading system (dampened flow signlas, increased resistance to flow in the distal circulation), indicating slow and incomplete recanalization, which is associated with worse long-term outcome (75).

Clinical recovery from stroke can be predicted by the timing of arterial recanalization after rt-PA therapy evaluated by TCD; the majority of rt-PA induced recanalizations occur during the first hour after treatment: at 1 hour partial recanalization was observed in 28% and complete in 17 % of patients, at 2 hours partial recanalization was observed in 22 % and complete in 31 % of patients, which indicates that only 19 % of patients presented with flow improvement at 2 hours (47). Recanalizations during the following hours occur in less percentage, however, the clinical improvement if achieved within 6 hours from onset does not significantly differ in early versus late recanalization groups.

Early re-occlusion has been recognized as a cause of clinical worsening and poor outcome in stroke patients treated with rt-PA, and has been documented on continous TCD monitoring in ranges from 12 % to 34 % of patients (76,77). Reocclusion was more frequent after partial (60%) than after complete recanalization and

after stepwise (53%) and slow (40%) as compared with sudden recanalization patterns. NIHSS 16 at baseline and the presence of ipsilateral severe carotid stenosis or occlusion were significantly associated with reocclusion (77).

TCD findings in the setting of acute stroke has the utility to predict clinical outcome which has been shown to be in the correlation with TIBI grading system and NIHSS score (44); the 24-hour NIHSS scores were higher in follow-up in patients with TIBI grade 0 or 1, in this group 35 % of patients improved to grades 4 or 5 in comparison with 52 % of patients with initial TIBI 2 or 3.

A recently published article on ultra-early Doppler sonography for stroke in a multicenter trial (Neurosonology for Acute Ischaemic Stroke –NAIS) (7), as a part of standard patients assessment, provided additional functional prognostic information in the hyperacute phase of anterior circulation strokes. The study included 361 patients with moderate to severe clinical deficits (National Institutes of Health Stroke Scale score 5-20). Out of those, 34% had a normal MCA, 48% had branch occlusion, 2% had severe MCA stenosis, and 16% had a main-stem MCA occlusion. 88% of patients with main-stem occlusion were dead or dependent 3 months after stroke. An occlusion of the main-stem of the MCA within 6 h after stroke was an independent predictor for poor outcome (p=0.0006). Good outcome was found in 50% of patients with ultrasonographic diagnosis of branch occlusion and 63% with normal MCA. The authors concluded that neurosonology technique can be used to identify patients with high risk for poor functional outcome.

TCD-detected M1 MCA occlusions within 6 hours of stroke onset may be an independent predictor of spontaneous hemorrhagic transformation, with a positive predictive value of 72% (59), since a delayed (>6-hour) spontaneous recanalization was independently associated (odds ratio [OR] = 8.9, 95% CI = 2.1 to 33.3) with hemorrhagic transformation (79).

The follow up of changes in the TIBI flow grading system enables the physicians to assess the longterm outcome and to facilitate discharge planning in means of discussing early rehabilitation options and everyday life adjustments for the stroke recoveries with family members. Due to many advantages the TCD offers, this technique should be incorporated into the standard acute stroke examination, and serve as a helpful guide for treatment desicions and follow up of patients.

**TCCS in stroke therapy**

In the sonothrombolysis study in stroke patients 6 hours within the stroke onset, not suitable for iv thrombolysis showed that patients treated with 2 MHz transcranial color coded Doppler sonography (TCCS) had better stroke outcome (80). After 1 hour recanalization rate (TIBI 2-5) was 62.5% in the target group compared to 0 in the control group, and after 24 hours 57.1% in the target group compared to 33.3% controls, visible by amalioration of the NIHSS ≥4 points in 62.5% in the target group compared to 14.3% in the control group. The need for hemicraniectomy due to malignant MCA infarction was not need in any target group patients compared to 42.9% controls. The outcome, measured by mRA (0-1) after 3 months, was better in the target group: 25% compared to 0 controls. In a randomized study including 37 stroke patients with acute MCA occlusion, all patients were treated with iv. t-PA, and the target group was additionaly treated during one hour

with TCCS with the 1.8 mHz probe (81). Recanalization rate was obtained 57,9% in the target group compared to 22.2% controls ($p<0.045$), resulting in amelioration of the neurologic outcome measured with mRA (0-1) (4 compared to 0, $p=0.106$) and Barthel index ($\geq 95$) (8 compared to 0, $p=0.003$). SICH was more frequent in the target group (15.8%) compared to control (5.6%), $p=0.6$.

In conclusion, transcranial and extracranial Doppler besides wide diagnostic possibilities, can be used in multimodal selection of patients eligible for thrombolysis. The combination of these techniques may help to identify patients who will have better outcome if treated with additional intra-arterial or mechanical interventions. According to recommendations for stroke treatment, clinical examination and CT scan are most important criteria for selection of patients for treatment with rt-PA, however, proven usefullnes of TCD and carotid duplex in urgent treatment of neurovascular diseases has incorporated these techniques into the recommendations for comprehensive stroke centers (82,83). Ultrasonographic and radiological imaging methods combined with clinical presentation help in the establishment of algorythms needed for more appropriate and safer treatment desicions in acute stroke patients as well as the prediction of short- and long-term outcome.

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# 11. TREATMENT OF ACUTE STROKE - REVIEW 2009

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Stroke is among the three most frequent causes of death and morbidity. Mortality of stroke declined during the last decade, from about 20 % within three months in many countries to five percent in most advanced centers. Both better treatment of stroke, and better prevention strategies of the major risk factors account for this decline. This review focuses on acute treatment of stroke, and its improvement in the last ten years.

**Stroke Units**

Stroke units were introduced in England and Scandinavia in the eighties, and in Germany, Italy and Croatia in the nineties. Stroke units reduce three months mortality and invalidity by about 6 % (10). They are characterized by

1. a multidisciplinary team of physicians, nurses and therapists dedicated only to stroke
2. a geographical place within the hospital with 4-21 beds and
3. immediate start of treatment, both medically and physiotherapeutically.

In recent years, different types of stroke units evolved: the older English and Scandinavian data mainly stem from rehabilitation stroke units. Patient were admitted there within days after stroke, received standardized medical treatment with aspirin and blood pressure control and usually stayed for a mean of three weeks with daily physiotherapy. Germany introduced the intensive care stroke units, with admission within hours after stroke and monitoring of vital parameters for one to three days. Meanwhile, many countries have developed comprehensive stroke units, a combination of intensive care and rehabilitation stroke units.

Importantly, stroke units work, even if they do not use thrombolysis frequently (6) In a telemedically controlled network of 15 stroke units in Bavaria, the proportion of patients with a severe handicap was reduced by 10 % in comparison to traditional, non-specialized treatment (3). Only 5 % of patients were treated with rtPa. The benefit is even seen 2 years after stroke, when fewer patients from the TEMPiS network needed nursery homes or permanent assistance (4). Stroke units are beneficial for severe and less severe strokes, young and

very elderly patients, ischemia and hemorrhage. An acknowledged quality goal is that 80 % of all patients within 24 hours of ischemia are treated on stroke units irrespective of age and stroke severity. This also adopts to patients with transitory ischemic attacks (TIA).

It is not clear what produces the beneficial effects of stroke units. Monitoring and multidisciplinary team is believed to prevent complications such as hypertensive crisis, heart failure, and tachyarrythmias and fever (11). There are a couple of rules which distinguish stroke patients from other vascular patients:

- Stroke patients require high blood pressure during the first one or two days. Thus, antihypertensives are usually stopped and restarted after 2 or 3 days, with the exception of ß-blockers and drugs which recompensate heart failure. Blood pressure peaks up to 220 /120 mmHg are tolerated. This only applies to ischemic stroke, however. Brain hemorrhage is likely to expand with high pressure. A clinical study currently explores the therapeutic effect of rapid normalization of blood pressure in haemorrhages (1).
- High and very low blood glucose is likely to impair outcome. Therefore, glucose levels should be maintained between 90 and 150 mg/dl. Ultra early and aggressive lowering of blood glucose, however, by the use of glucose-potassium-insulin (GKI) infusions has not been shown to improve outcome (8). GKI has the side effect of a drop in mean blood pressure of about 10 mmHg. This may have counteracted neuroprotection.
- Almost all stroke patients have bacterial infections within hours of stroke onset, in particular pulmonary and urinary tract infections. The cause is ß-sympathetic activation and pituitary dysfunction by stroke. Clinical signs of those infections should be treated early by IV antibiotics and physical cooling. Prophylactic antibiotic treatment is currently under study.
- Mobilization on day 1 is likely to improve outcome even in severe ischemic and hemorrhagic stroke (5). First mobilization on the bed rim, however, should by accompanied by a physiotherapist and by monitoring of vital functions (heart rate, oxygenation). In order to enable early mobilization, invasive catheterization (IV lines, bladder catheter) should be cut to the required minimum. Falls are the most frequent and serious complication soon after stroke and specialized staff training is required to mobilize and protect the patients at the same time (11).

**Thrombolysis**

Intravenous thrombolysis with rtPA (Actilyse$^{R}$) is admitted for stroke treatment because the NINDS trial in 1996 showed a 13 % risk reduction for death and dependency when treatment starts in a three hours time window (2). Recently, ECASS III showed persisting benefit in a time window of 4.5 hours, with an absolute risk reduction of about 7 % (9). The earlier rtPA application starts, the better the treatment effects. The number needed to treat (NNT) to avoid death and dependency increase from 4 in the first 90 minutes to 9 at 180 minutes and to 14 at 270 minutes (2, 16). There is a bleeding risk, but symptomatic bleeding is infrequent (1.7 %/ 24 h in SITS MOST (16) and hemorrhagic transformation of large ischemic core zones does not harm the patients.

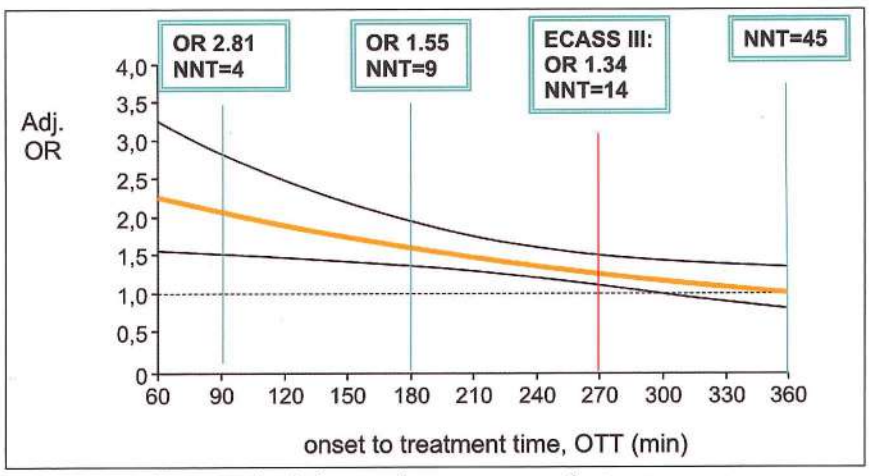


*Figure 1: Odds ratio (OR) for good outcome in relation to onset to treatment time (OTT) in pooled thrombolysis trials*

Short prehospital ambulance times, and short in-hospital „door-to-needle" times, as required to shoot rtPa as soon as possible, are hard to achieve and warrant reorganization of the neurological emergency system. Potential patients need to learn the warning signs of stroke, rescue dispatchers need to treat stroke as emergency similar to myocardial infarction, and a network of stroke centers with transport times less than 30 minutes need to be made known both to patients and dispatchers. Stroke centers are characterized as emergency rooms staffed with stroke experienced neurologists, internists and radiologists, in association to a stroke unit. Where not available due to long distances or spare population, telemedicine may help (3).

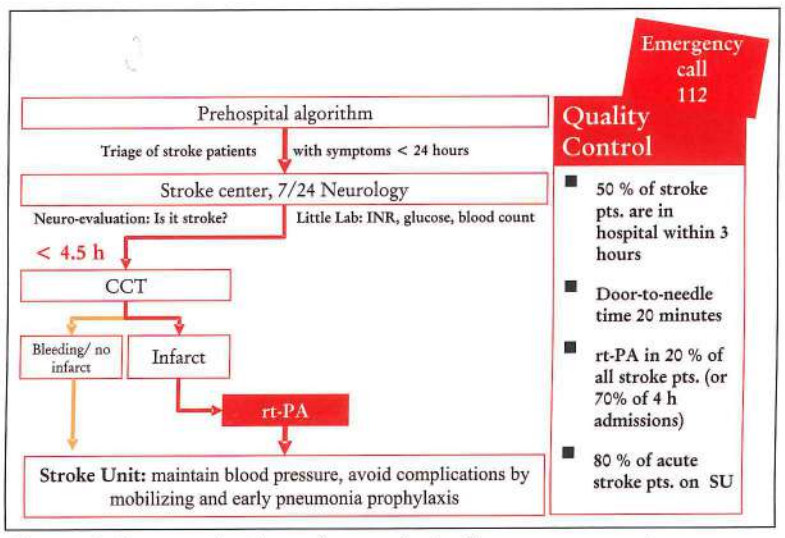


*Figure 2: Reorganization of neurological emergency systems*

There are other endeavours to increase the rate of stroke patients who receive thrombolysis. MR techniques have been elaborated which allow to distinguish the penumbra of stroke irrespective of time windows, the mismatch of diffusion weighted and perfusion weighted imaging. There are no clinical trials, however, which show that selection of patients by mismatch is superior to time and CT criteria. Recently published DIAS II trial was not supportive. Intraarterial recanalization devices, even used before systemic thrombolysis since the late eighties, are priorized by some centers that have access to neuroradiological interventions, but there is no study powered by enough patients which shows that IA treatment achieves positive clinical results as frequently as IV thrombolysis.

Thus, IV thrombolysis should be used in all patients who arrive within a 4.5 hours time window, have signs of stroke they do not want to live with, and have a CT scan without signs of bleeding or demarcated fresh infarction. There are restrictions of application, which are more or less obeyed in different countries. Age limit of 80 years is a relative restriction, since a number of studies shows that thrombolysis is safe and efficacious beyond 80 years. Stroke with improving clinical signs and very severe stroke is also a relative restriction, because the metaanalysis demonstrated benefit also in those patients (2).

**Early prevention after stroke**

The recurrence risk after stroke is high: large artery disease in particular of the carotids produces 25 % recurrencies within 3 months, re-stroke risk of atrial fibrillation is about 15 % in the first month, and intracranial stenosis is associated with 20 % re-strokes in the initial year. Recent publication showed that recurrent stroke after TIA is in a similar range. The impact of risk after TIA is well described by the $ABCD^2$ score (12) as depicted in Table 1. The practical consequence is that stroke prevention has to start on day 1 after stroke (14).

Risk stratification of TIA: $ABCD^2$-Score

| | | |
|---|---|---|
| • **A**ge | ≥60yrs | = 1 |
| • **B**loodpressure | >140 syst. and/or >90 diast | = 1 |
| • **C**linicalfactors | palsyononeside | = 2 |
| | aphasia | = 1 |
| | other symptoms | = 0 |
| • Duration | ≥60 Min. | = 2 |
| | 10-59 Min. | = 1 |
| | < 10 Min. | = 0 |
| • Diabetes | | = 1 |

| | Stroke risk | | |
|---|---|---|---|
| | 2days(%) | 7days(%) | 90days(%) |
| All | 3,9 | 5,5 | 9,2 |
| 0–3points (34%) | 1,0 | 1,2 | 3,1 |
| 4–5points (45%) | 4,1 | 5,9 | 5,9 |
| 6–7points (21%) | 8,1 | 11,7 | 17,8 |

Currently, only aspirin is admitted for early stroke prevention. The recommended dose is unclear, but many centers start with 300 mg on the day of stroke and continue with 100 mg thereafter. Clopidogrel and aspirin plus extended release dipyridamole has not been tested very early after stroke. Heparin and coumadins have no general indication, although coumadins are recommended to be started in cardioembolic stroke within the first week unless there is bleeding in the CT scan or the infarction is quite large. Following IV thrombolysis, all anticoagulants including aspirin and low molecular weight heparins (LMWH) should be used with caution in the first 24 hours. LMWH have no indication due to stroke, but only due to prophylaxis of deep vein thrombosis and pulmonary embolism in immobilized patients.

Usually, all stroke patients receive a statin in secondary prevention. Evidence of protection against recurrent stroke and cardiovascular events stems from the SPARCL trial which used atorvastatin 80 mg in non-cardioembolic stroke patients when LDL cholesterol was 100-190 mg/dl (15). The protection by statins within days of stroke is not proven. We start the statin within the first week after stroke. Pre-treatment with statins should not be terminated or interrupted during the acute phase of stroke, because statin withdrawal promotes thrombotic processes. All statins should be avoided in primary brain hemorrhages.

Carotid surgery and carotid stenting have a clear indication in all symptomatic stenosis $\geqslant 70$ %. Largest benefit by recanalization is seen when the intervention is done early within 2 weeks (13). There is also an evolving indication of stents in tight symptomatic intracranial stenosis, which have high recurrency rates when treated with high dose aspirin or warfarin (7, 17).

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# 12. MANAGEMENT OF HYPERTENSION AND HYPERGLYCEMIA IN THE ACUTE ISCHEMIC STROKE

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Several observations have demonstrated spontaneous elevation of blood pressure in the first 24-48 hrs after stroke onset with a significant spontaneous decline after a few days (1,2,3). Despite of increased prevalence of hypertension following stroke, optimal management has not been yet established. Several arguments speak for lowering the elevated BP: risks of hemorrhagic transformation, cerebral edema, recurrence of stroke and hypertensive encephalopathy. On the other hand, it may be important to maintain the hypertensive state due to the damaged autoregulation in the Ischemic brain and the risk of cerebral hypoperfusion exacerbated by the lowered systemic blood pressure.

Two prospective studies (4,5) demonstrated a U-shaped relationship between baseline systolic blood pressure and both early death and late death or dependency. Both high blood pressure and low blood pressure were independent prognostic factors for poor outcome

On the other hand, the GAIN study (6) demonstrated that baseline mean arterial pressure was not associated with poor outcome. However, variables describing the course of BP over the first days have a marked and independent relationship with 1- and 3-month outcome.

In a Cochrane systematic review (7), death was found to be significantly associated with elevated mean arterial BP and high diastolic BP.

Several observations, including the NINDS-tPA trial (8,9), found association between high blood pressure on admission, and its prolongation, with poor outcome and mortality. Although in one study no such association was found in alert patients, stroke patients with impaired consciousness showed higher mortality rates with increasing blood pressure (10). The association between elevated blood pressure and recanalization was evaluated after intraarterial thrombolysis (11). The study demonstrated that the course of elevated systolic blood pressure, after acute ischemic stroke was inversely associated with the degree of vessel recanalization. When recanalization failed, systolic BP remained elevated longer than when it succeeded.

The theory that elevated systemic BP may compensate the decrease cerebral blood flow in the ischemic region led to the attempts to elevate blood pressure as a treatment for acute ischemic stroke. In animals models the mild induced hypertension was found to increase collateral flow and oxygenation and to improve cerebral metabolic rate of oxygen in the core and penumbra (12). Several small studies in humans have addressed these questions and administrated vasopressors to patients with acute stroke (13,14,15). Despite of documented improvement in CBF (16), the concept was abandoned because of the increased risk of hemorrhage and brain edema. In a systemic review of 12 relevant publications including 319 subjects the small size of the trials and the inconclusive results limits conclusion as to the effects on outcomes, both benefits and harms. A randomized controlled trial is needed to determine the role of pressors in acute ischemic stroke (17).

According to a systemic review of the literature (3) no conclusive evidence to support the lowering of blood pressure in the acute phase of ischemic stroke was found and more research is needed to identify the effective strategies for blood pressure management in that phase (3).

Although the controversy in the management of BP in the acute phase, the benefit of blood pressure reduction as a secondary prevention of stroke is well established and was demonstrated in many studies. However, in most of these studies antihypertensive agents were administrated several weeks after stroke onset. Only few trials were performed in the acute setup. The ACCESS trial (18) was a prospective, double blind, placebo controlled, randomized study evaluating the angiotensin receptor blocker cadesartan vs. placebo in the first week following stroke. Although no difference was found in stroke outcome in 3 months, significantly lower recurrent cardio vascular events rate and lower mortality after 1 year was documented in the treatment group. On the other hand, treatment with telmisartan in 1360 patients with acute mild ischemic stroke and mildly elevated blood pressure in the recent ProFess trial (19) was not associated with better functional outcome or lower recurrence and mortality rate.

Despite of the somewhat confusing and unclear data the current European Stroke Organization (ESO)-2008 guidelines (20) recommend that blood pressure up to 200 mm Hg systolic or 110 diastolic may be tolerated in the acute phase without intervention unless there are cardiac complications. According the American guidelines (21) it is generally agreed that patients with markedly elevated blood pressure may have their blood pressure lowered in not more than 15% during the first 24 hours after the onset of stroke. There is an indication to treat blood pressure only if it is above 220 mm Hg systolic or if the mean blood pressure is higher then 120 mm Hg. No data is available to guide selection of medication for the lowering of blood pressured in the setting of acute Ischemic stroke. The recommended medication and doses are based on general consensus. More studies are needed to identify the optimal strategy for BP management. Several on going clinical trials such as the The Efficacy of Nitric Oxide in Stroke (ENOS) trial may help answer the remain questions.

It has been well established that elevated glucose levels play a major role in microvascular and macrovascular morbidity and in hematological abnormalities as well. Several processes were found to be associated with theses conditions including impaired vascular tone and flow, disruption to endothelial function, changes at the cellular level, intracellular acidosis and increased aggregation and cougolability. Some animal studies (22,23) have demonstrated the relations between acute ischemic stroke and hyperglycemia. In

these models the administration of glucose to animals resulted in worsen brain ischemia. Pre treatment with insulin was found to limit the Ischemia.

As mentioned, 30-40% of acute stroke patients are found to have elevated glucose levels on admission, about half of them have known diabetes, and the others are newly diagnosed or suffer from stress induced hyperglycemia (24).

Hyperglycemia on admission (25) was correlated with decreased neurological improvement and the risk of hemorrhagic transformation in reperfused thrombolysed patients but not in nonreperfused tPA-treated patients. On the other hand, in the NINDS study, glucose level on admission was not associated with altered effectiveness of thrombolysis. All of these findings suggest that glucose level is an important risk factor for morbidity and mortality after stroke. However, it is not clear whether hyperglycemia itself affects stroke outcome or reflects, as a marker, the severity of the event due to the activation of stress hormones such as cortisol or norepinephrin. Diffusion-perfusion MRI analysis supports the first hypothesis. Higher hyperglycemia levels in patients with perfusion diffusion mismatch, shown on Diffusion Weighted Imaging-Perfussion Weighted imaging (DWI –PWI) MRI, was associated with higher lactate production and with reduced salvage of mismatch tissue and increased conversion of tissue „at risk" to infracted tissue comparing with patients that arrived with lower values (26).

Among the factors found to contribute to the post acute stroke hyperglycemia (27) are the involvement of the insular cortex which is known to play a role in sympathetic activation, involvement of the internal capsule, pre-existing diabetes, elevated systolic BP and NIHSS higher than 14 points.

The previous data raises the question how, and especially to what extent, should post acute stroke hyperglycemia be treated. Intensive insulin therapy administrated IV and aimed to maintain blood glucose levels at 4.5-6.1 mmol/L in surgical intensive care set up was found to reduce mortality by more than 40%.(28). Similar results were documented among patients after myocardial infraction (29). The question remains regarding the application in acute stroke pts. The GIST-UK trail (30), published recently, addressed this question. The study was conducted among hyperglycemic acute stroke pts who received glucose-potassium-insulin infusion versus placebo. In the treatment group significantly lowered glucose and blood pressure values were documented, however, no clinical benefit was found among the treated patients. There are variety of methods of insulin administration including continuous intravenous (IV) infusion, repeated subcutaneous dosing and IV infusion containing insulin and dextrose with potassium supplementation (31). A randomized, multicenter, blinded pilot trial, Treatment of hyperglycemia in ischemic stroke (THIS) (32), compared the use of aggressive treatment with continuous intravenous insulin, with no glucose or potassium in the insulin solution, with insulin administrated subcutaneously in acute stroke patients. The aggressive-treatment group was associated with somewhat better clinical outcomes which was not statistically significant Ongoing trials, such as The Glucose Regulation in Acute Stroke Patients Trial (GRASP), address the role of IV insulin for hyperglycemic stroke patients (33).

According to the ESO 2008 recommendations (20) a blood glucose of 180 mg/dL (10 mmol/L) or higher, is an indication for treatment with IV insulin. According the American guidelines (21) even lower serum glucose

levels possibly between 140-185 mg/dL should trigger administration of insulin. Despite of the current recommendation, a more aggressive approach is advised, especially in pre-thrombolysis patients.

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KLINIKA ZA NEUROLOGIJU
KB „Sestre milosrdnice"

# 13. VASCULAR COGNITIVE IMPAIRMENT AND VASCULAR DEMENTIA

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**Summary**

Dementia is a neurological disease that is associated with aging. The incidence and prevalence of dementia is increasing as the population continues to age. The two most common forms of dementia are Alzheimer's dementia (AD) and vascular dementia (VaD). Although these two forms of dementia represent different pathologies and different clinical presentations, they share similar risk factors. Vascular dementia is an important and often overlooked form of dementia in the elderly. Growth of the elderly population and a rising incidence of vascular disease could cause vascular dementia to become the most common form of dementia. Diagnosis of vascular dementia could lead to prevention of dementia by appropriate control of vascular risk factors. Primary prevention of vascular dementia depend on early identification and appropriate control of vascular risk factors, while secondary prevention must include energetic therapy to prevent stroke recurrence.

## Introduction

Dementia is defined as a neurological syndrome consisting of impaired cognition that is severe enough to interfere with social or occupational functioning (1). Vascular dementia is the most common form of dementia in the elderly after Alzheimer's dementia (2). The term vascular dementia identifies patients with severe cognitive loss from cerebrovascular disease, either after large ischemic or hemorrhagic strokes, lacunes, and microscopic cortical infarcts, or from cardiac and circulatory disorders causing incomplete white matter infarction (3).

Mild cognitive impairment is considered the earliest clinical manifestation of Alzheimer's dementia (4). A similar concept was proposed for vascular dementia under the name vascular cognitive impairment (VCI) (5, 6). The concept of VCI includes patients with classic vascular risk factors and some degree of cognitive loss, but not dementia. The term vascular cognitive impairment (VCI) has been used to refer to all forms of mild to severe cognitive impairment that are associated with a vascular insult, whether they meet criteria for vascular dementia or not (7-11). This form of impairment includes those who have cognitive dysfunction associated with stroke, multiple cortical infarcts, multiple subcortical infarcts, silent infarcts, strategic infarcts, multiple small vessel

disease with white matter lesions, and lacunar infarcts. There is believe that appropriate prevention measures and treatment of the vascular risk factors could prevent the progression of VCI to vascular dementia (10-11), because it was recently demonstrated in the Canadian Study on Health and Aging (12) that some patients with VCI improved spontaneously after a 5-year follow-up, indicating that VCI does not always have to progres to vascular dementia.

In an attempt to approach the heterogeneity of the pathophysiology associated with VaD, a number of researchers have subclassified vascular dementia according to the pathophysiology of the lesion that causes the cognitive deficit. One simplified subclassification includes post-stroke dementia, subcortical VaD, and AD plus VaD (mixed dementia) (10). Post-stroke dementia is defined as a cognitive impairment resulting from a thromboembolic or hemorrhagic event causing cognitive symptoms severe enough to impair social and occupational functioning. Subcortical VaD is caused by lacunar infarcts and white matter lesions.

## Epidemiology and Risk Factors

Population-based epidemiological studies and neuropathology data have confirmed that vascular dementia is responsible for about 20% of cases of dementia and that vascular lesions are commonly found in patients with AD. The role of vascular risk factors and strokes in AD is an area of intensive research (13-17), and decreased incidence of AD and vascular dementia was observed with control of hypertension (18), and with the use of statins (19).

Age is the most significant risk factor for any dementia; however, other factors associated with health status earlier in life may predispose older adults to developing VaD. Atherosclerotic risk factors such as smoking, hypertension, myocardial infarctions, hyperlipidemia, and diabetes mellitus predispose older adults to cerebrovascular disease causing VaD (20). Additionally, the presence of stroke-related factors as a consequence of hemorrhagic, ischemic, or embolic events in the brain may also cause VaD (21). The location and size of the stroke can also cause significant cerebral tissue loss and white matter disease, leading to VaD (20).

Based on projected figures for the growing proportion of elderly persons and increased incidence of ischemic heart disease and stroke, it has been postulated that vascular dementia may become the most common cause of dementia in the near future because it affects 30% of ischemic strokes and 26% of patients with congestive heart failure due to hypoperfusion (4, 22). On the other hand, post-stroke dementia (multi-infarct dementia) often remains underecognized (23), and it is rare to diagnose vascular dementia after congestive heart failure, after major surgery in the elderly, or after coronary artery bypass graft.

Subcortical ischemic vascular dementia results from small-vessel disease, and produces lacunar strokes and incomplete white matter infarction (24) having relatively poor prognosis of lacunes in terms of cognitive outcome (25). Furthermore, silent lacunar strokes appear to double the risk of dementia (26). It has been postulated that chronic brain edema from damage of the blood-brain barrier could explain their poor outcome (27). Lacunes are markers of small-vessel disease and should prompt a search for diagnosis and treatment of relevant risk factors.

## Pathophysiology

Vascular dementia results from brain injury caused by stroke and cerebral ischemia. Single ischemic or thromboembolic infarcts occurring in strategic areas of the dominant hemisphere (eg, angular gyri, mediodorsal thalamus, anterior thalamus) may cause a dementia-like syndrome without the involvement of large volumes of cerebral matter. In general, volume of tissue loss is a poor predictor of the severity of the cognitive impairment. More commonly, progressive cognitive deficits and dementia can result from multiple temporally placed small cerebral infarcts. Frontal subcortical regions supplied by small penetrating arterioles may be especially prone to degenerative changes in patients with poorly controlled hypertension, diabetes mellitus, or both. A less common cause of vascular dementia is global hypoxic-ischemic injury (eg, following cardiac arrest). Irreversible cognitive impairment is frequently observed following coronary bypass surgery (28).

Whether chronic cerebral ischemia associated with carotid artery stenosis (CAS) may alter cognitive function has not been conclusively demonstrated and remains a controversial concept. Neuropsychometric evaluation of patients undergoing carotid endarterectomy has not conclusively shown cognitive impairment or reductions in the probability of developing dementia in the long term.

An ill-understood form of vascular dementia is Binswanger encephalopathy, causing mostly subcortical dementia features. Postmortem, myelin loss is observed and is most prominent in the hemispheric deep white matter. Axonal drop out is also observed with little or no signs of inflammation. Neuroimaging shows decreased white matter density on CT scanning and decreased white matter intensity on MRI. Frequently, but not invariably, lacunar strokes are also observed.

Dementia associated with cerebrovascular disease is also observed in a rare genetic condition, ie, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy - CADASIL (29). Affected patients often present with migraines with aura. Recurrent strokes start when the patients are aged 30-50 years. Multiple lacunar infarcts, mainly in the frontal white matter and basal ganglia, lead to progressive cognitive decline and finally dementia. However, cognitive decline is thought to begin even before strokes occur, suggesting that chronic cerebral hypoperfusion in the absence of overt stroke might be sufficient to cause significant neuronal circuit disruption.

Lastly, cognitive decline has been reported in association with several other vasculopathies such as temporal arteritis, polyarteritis nodosa, primary cerebral angiopathy, lupus erythematosus, and moyamoya disease.

## Diagnosis

A diagnosis of VaD would be appropriate for an individual who presents with an acute onset and stepwise progression of cognitive impairment (30). Three specific elements are required for a clinician to diagnose an individual with VaD (Table 1) (30, 31, 32). First is demonstration of cognitive impairment. Many individuals with VaD have a generalized cognitive deficit with less striking memory loss than is found among

individuals with AD (6, 9). In fact, a more common form of cognitive impairment associated with VaD is compromised executive functioning, which involves goal-directed behaviour, initiation of sequences, and problem-solving abilities (6, 33). Cerebrovascular subcortical lesions in the prefrontal cortex resulting in subcortical VaD can often cause cognitive impairments associated with executive functioning. To determine if executive impairments exist in individuals with VaD, specific neuropsychological tests of executive functioning such as the Trail-Making Test, the Executive Interview, and the Clock Drawing Test may be used (6). Second, there are several nonspecific clinical symptoms associated with vascular dementia. Individuals with typical subcortical lesions may display extrapyramidal symptoms and instability leading to falls. Urinary frequency and incontinence, as well as dysarthria and dysphagia, are common symptoms (10). The Hachinski Ischemic Scale accounts for factors associated with vascular development of dementia such as the onset of the cognitive impairment, the risk factors related to stroke, behavioural abnormalities such as depression and emotional incontinence, and focal neurological symptoms (21). A score lower than 4 renders a diagnosis of AD, whereas a score of greater than 7 is classified as multi-infarct dementia (9, 34), while score of five to six may suggest the so called mixed dementia - Alzheimer's dementia and vascular dementia. A final factor required for the diagnosis of VaD is for the cognitive impairment to have occurred within three months of the cerebrovascular event. This temporal criterion is being disputed in some recent discussions of taxonomy (6, 8). Third, the individual must demonstrate some form of cerebrovascular pathology as displayed by brain imaging studies (computerized tomography or magnetic resonance imaging). Brain imaging studies demonstrate vascular lesions that may differ in size depending on the degree of vascular pathology. These lesions range from a single lacunar stroke to multiple cortico-subcortical strokes and periventricular white matter ischemia (6, 9).

Since the memory deficits may be mild in vascular dementia, the National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (30, 35) for dementia require the presence of involvement of memory plus two or more cognitive areas (31).

*Table 1. Criteria for diagnosis of probable vascular dementia*

1. Dementia
2. Cerebrovascular disease
3. A relationship between the above two disorders
    a) Onset of dementia within three months of a recognized stroke
    b) Abrupt deterioration in cognitive functions or fluctuating, stepwise progression of cognitive deficits

II. Clinical features consistent with the diagnosis of probable vascular dementia

1. Early presence of gait disturbances
2. History of unsteadiness and provoked falls
3. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease
4. Pseudobulbar palsy

5. Personality and mood changes

III. Features that make the diagnosis of vascular dementia uncertain or unlikely

1. Early onset of memory deficit and progressive worsening of memory and other cognitive functions in the absence of corresponding focal brain lesions on imaging
2. Absence of focal neurological consequences other than cognitive disturbances
3. Absence of Cerebrovascular damage on brain imaging

**Clinical findings**

Patients with VaD are cognitively impaired in executive functioning activities such as organizing, planning, and initiating sequential events. Patients with VaD have relatively mild memory loss but usually have early executive dysfunction, and loss of executive control function is characterized by lack of planning, disorganized thought, behavior, or emotion (36-39). Therefore, it is very similar to subcortical neurogedenerative dementias, sometimes called dysexecutive cognitive impairment. Complex activities such as cooking, dressing, and housekeeping are predominantly affected in patients with.(39 - 40). However, most of the current tests for assessment of dementia are relatively insensitive to executive function, leading to underdiagnosis of vascular dementia. Executive dysfunction is relatively common among elderly people living in the community, affecting one in six non-demented individuals (40 - 44). Loss of executive function is an important cause of disability in non-demented community-dwelling individuals (41-44), as well as in patients with vascular dementia (45-49), and Alzheimer's dementia (50). Other cognitive domains such as memory, language, visuospatial skills and motor speed, or demographic features such as age, education and health status, have minimal contribution to activities of daily living (ADL). Similar conclusions were reached using two tests of executive function, the EXIT25 and a simple clock-drawing task (51, 52). Mini-mental state examination made no contribution to the regression model, while depression and physical illness contributed little additional variance to the model.

Apathy and depression frequently occur as a consequence of disruption of prefrontal circuits in patients after stroke and these symptoms are an important component in the development of VaD. Vascular depression is currently recognized as an independent condition (53, 54). A study of post-stroke patients in Finland (55) confirmed that executive dysfunction was the main determinant of abnormalities in both basic and instrumental ADL suggesting that executive function including instrumental ADL may be more sensitive for the diagnosis of vascular dementia and could accurately measure the effects of potential therapies. Instrumental ADL appear to be an appropriate examination for executive function in patients with post-stroke cognitive decline (56-59). Apathy and depression, although there is no total agreement with this concept (60).

In addition to the above, other typical clinical features of vascular dementia include cases with sudden onset and slow or stepwise progression, often increasing in severity with each ischemic event; fluctuations are common and memory is only mildly affected. In VaD gait is typically disturbed, shuffling and with short steps, and often resembles that of patients with Parkinson's disease (61, 62).

## Treatment

A number of medications have been used for the symptomatic treatment of VaD, including vasodilators such as niacin, calcium channel blockers, pentoxifylline, antiplatelet agents, and nootropic agents such as memantine. More recently, the cholinesterase inhibitors donepezil, galantamine, and rivastigmine have been studied in controlled clinical trials in vascular dementia. Cholinergic deficits in the condition may result from ischemia of the nucleus basalis of Meynert or from interruption of cholinergic pathways by vascular lesions.

Compared with placebo, donepezil treatment groups showed statistically significant improvement in cognition, global function, and both basic and instrumental ADL (63-65).

Study of galantamine in vascular dementia showed a significant improvement in the behavioral symptoms in the treated group versus placebo (66).

The change from baseline on the neuropsychiatric inventory score at 22 months showed that the rivastigmine group improved while the aspirin group deteriorated. Also, the rivastigmine group showed significant improvements in executive function, behavioral symptoms, and caregivers' relative stress score relative to the aspirin group (67, 68).

Two trials of memantine in patients with mild to moderate vascular dementia the mean ADAS-cog and the mini-mental state examination scores improved significantly with memantine compared with deterioration with placebo and the nurses' observation scale for geriatric patients' disturbed behavior also showed differences in favor of memantine. Memantine therapy resulted in stabilization of patients with vascular dementia, compared with placebo controls (69, 70).

## Primary and Secondary Prevention

The classic modifiable risk factors for vascular dementia include hypertension, cardiac abnormalities such as atrial fibrillation, smoking, lipid abnormalities, diabetes, and elevated homocysteine levels. Modifying and treating vascular risk fastors leads to stroke prevention and lower the risk of Alzheimer's dementia and VaD.

In the extension of the Systolic Hypertension in Europe Study (SYST-EUR) long-term antihypertensive therapy reduced the risk of both Alzheimer's dementia and post-stroke vascular dementia by 55% with the treatment with the calcium-channel blocker nitrendipine (18). Antihypertensive treatment reduced the odds of incident cognitive impairment by 38% in a 946-participant cohort of African Americans and it was associated with a 28% reduction in the risk of recurrent stroke and a 38-55% reduction in the risk of dementia (71).

In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) blood pressure lowering in patients with previous stroke or transient ischemic attack significant reduction of cognitive decline and dementia was documented in the active treatment group, compared with the placebo (72, 73).

The Mediterranean diet, with its high content of fish, seafood, grains, vegetables, citrus fruits and olive oil, appears to be protective against vascular disease, as well as moderate physical activity. (74, 75). Finally, effortful mental activities appear to be protective against dementia, both Alzheimer's and vascular (76, 77).

## Mixed dementia

Mixed dementia, or mixed Alzheimer's dementia and cerebrovascular disease, is an overlap between AD and VaD. There are currently no specific established criteria to make a proper diagnosis. As mentioned, the risk factors for AD and VaD are similar. Furthermore, there is a strong association between the pathologies of AD and VaD, both of which have been shown to synergistically affect cognitive functioning (30). However, scarce epidemiological evidence exists to support the diagnosis of mixed dementia, which could have an incidence of 20-40% (78). This wide variation in incidence is likely due to the difference in recruitment biases among the different studies, the different age populations that were set within each study, and the lack of specific diagnostic criteria for determining mixed dementia (78).

## Conclusion

Vascular dementia is an important and often overlooked form of dementia. Projections indicate that it may become the most common form of dementia in the elderly affected by ischemic heart disease and stroke. Most cases of vascular dementia present with a subcortical form of dementia with prominent executive dysfunction that is usually not recognized as dementia by relatives or caregivers. Cholinergic treatment may improve the prognosis of the condition. Primary prevention of vascular dementia appears to depend on early identification and appropriate control of vascular risk factors. Secondary prevention, after clinical stroke or silent lacunes, must include energetic therapy to prevent stroke recurrence.

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# 14. APHASIA

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## Aphasias

### Definition and etiology

There are different definitions of aphasias, but the most widely accepted neurological and/or neuropsychological definition is that aphasia is a loss or impairment of verbal communication which occurs as a consequence of brain dysfunction. It manifests in impairment of almost all verbal abilities—abnormal verbal expression, difficulties in understanding spoken or written language, repetition, naming, reading and writing (1,2,3).

Diseases affecting blood vessels of the brain are the leading cause of aphasia in about 80% of adults. Ischemic stroke (embolic or thrombotic) as well as hemorrhagic (intracerebral hemorrhage) in the area of anterior cerebral circulation, especially in a territory of the left middle cerebral artery, is a common cause of aphasia syndromes. Temporary aphasia may also be found in patients with transient ischemic attack (TIA- in this case neurological deficit as well as disturbance of speech withdraws within 24h). The main characteristic of aphasia of vascular origin is sudden occurrence and possibility of partial or complete recovery of speech (4,5,6,7,8). In our study, witch included almost 1000 patients, aphasia was diagnosed in 21%. The most frequently it was global aphasia (45%), then Broca's (23%), anomic (16%) and Wernicke's (9%) (9).

Other, and less frequent, couses of aphasias are head injuries, degenerative diseases and dementias, poisoning, metabolic disorders, infective diseases and demyelinisation diseases with involvment of the left cerebral hemisphere (4,10,11,12,13,14).

### Classification

Both, traditional and modern classification of aphasias are based on elementary clinical characteristics of dichotomies ( motoric- sensoric, expressive- receptive, fluent or non fluent). Classification based on fluency of spontaneous speech is widely accepted and enables an easy way to diagnose a type of aphasia. Main characteristics of non-fluent aphasia include difficulties of articulation, forming short non grammatical sentences and prosody disorders. On the other hand, fluent spontaneous speech, long grammatically shaped sentences and preserved prosody abilities are basic features of fluent aphasia (1,4,15,16).

During the history, many classifications of aphasia syndromes were established. However, all of these had some limitations, so even today there is no generally accepted classification. Clinical classifications based on fluency of speech, language comprehension and ability to repeated speech seems to be the most practical (Table 1) (1,17).

*Table 1. Classification of aphasias based on fluency, language understanding and preserved repeated speech*

| **Aphasia** | **Fluency of speech** | **Language understanding** | **Repeated speech** |
|---|---|---|---|
| Brocka's | Non- fluent | Intact | Disrupted |
| Transcortical motor | Non- fluent | Intact | Intact |
| Global | Non-fluent | Disrupted | Disrupted |
| Mixed transcortica l | Non fluent | Disrupted | Intact |
| Anomic | Fluent | Intact | Intact |
| Conductive | Fluent | Intact | Disrupted |
| Wernicke's | Fluent | Disrupted | Disrupted |
| Transcortical sensory | Fluent | Disrupted | Intact |
| Subcortical | Fluent or non-fluent | Variable | Preserved |

Widely in use, and still practical, classification is one that classifies aphasia syndromes in groups of speech disorders associated with neurological sings and neuroanatomical localizations of lesions. The main anatomical classification is on perisylvian and extrasylvian aphasias, witch means is the localization of brain lesion „around" or „away" of Sylvian fissure (Table 2) (1,2).

*Table 2. Aphasia syndromes*

| **Syndromes** | **Fluency of speech** | **Paraphasias** | **Repetition** | **Understanding** | **Naming** | **Hemiparesis** | **Hemisens. disorders** |
|---|---|---|---|---|---|---|---|
| **Perisylvianaphasia** | | | | | | | |
| Brocka's | Non fluent | Rare-literal | Disrupted | Preserved | Disrupted | Extensive | Rare |
| Wernicke's | Fluent | Extensive-mixed | Disrupted | Disrupted | Disrupted | Rare | Occasional |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Conductive | Fluent | Extensive-literal | Disrupted | Disrupted | Disrupted | Rare | Extensive |
| Global | Non fluent | extensive-mixed | Disrupted | Disrupted | Disrupted | Rare | Extensive |
| **Extrasylvianaphasia** | | | | | | | |
| Exstrasylvian motor | Non fluent | Rare | Preserved | Preserved | Disrupted | Occasional | Rare |
| Aphasia of supplementary motor area | Non fluent | Rare | Preserved | Preserved | Disrupted | Extensive / crural | Occasional |
| Extrasylvian sensoric | Fluent | Extensive-mixed | Preserved | Disrupted | Disrupted | Occasional | Extensive |
| Extrasylvian mixed | Non fluent | Rare | Preserved | Disrupted | Disrupted | Extensive | Extensive |
| Anomic | Fluent | Rare | Preserved | Preserved | Disrupted | Rare | Rare |
| Subcortical | Fluent or non fluent | Extensive | Preserved | Variable | Disrupted | Extensive | Extensive |

## Broca's aphasia

Broca's aphasia is also known as motoric aphasia, efferent of kinetic aphasia, verbal or syntactic aphasia and expressive aphasia. However, the most frequently used terms are motoric or Broca's aphasia. Lesions which cause Broca's aphasia are located in the lower frontal gyrus, forward towards the motoric tract, including premotoric and posterior prefrontal regions (Figure 1).

This type of aphasia is characterized by non-fluent, scarce production of speech, with poor articulation in the form of short sentences with only a few words. Grammatical suffixes are usually not used in words, verbs and adjectives, while the use of nouns remains relatively good. Speech expression is disprosodic because of impairment of rhythm, melody and stress. The way these patients speak sounds similar to telegrams („telegramatism").

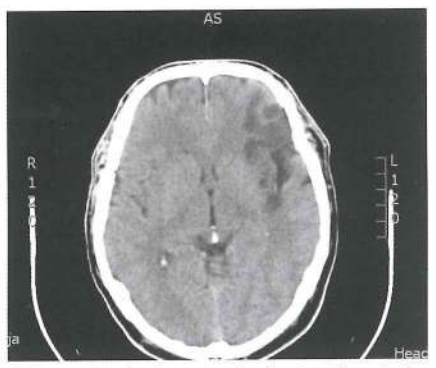


*Figure 1. Ischemic stroke in frontal lobe (by computed tomography) in patient with Broca's aphasia*

Auditory understanding is here maintained, and is usually much better than expressive speech. However, understanding of complex grammatical structures and serial orders is usually impaired. The most frequent difficulties are found in understanding of function words and verbs. Relational words are also difficult to understand, such as above/below, bigger/smaller and sentences expressing communication relations such as „sister's mother" or „mother's sister."

Repetition is poor, usually less impaired than spontaneous speech. Difficulties especially occur in repeating complex sentences. The patient simplifies grammar in a sentence. He also shows phonemic distorsion and phonemic paraphasia, omitting some phonemes and words. Naming is impaired, as opposed to showing the objects named which is maintained. Difficulties in naming the objects are usually the consequence of articulatory disorders, not from the loss of lexical knowledge. In some patients, a combination of lexical and articulatory disorders is possible. Most patients are not able to read aloud or to understand the text they read to themselves. Aphasic writing is also present. Agraphia is manifested in writing large, inappropriately written letters, with literary paragraphy and agrammatism, or „telegram writing" (1,2,3,17).

The majority of patients with Broca's aphasia have some additional neurological symptoms such as right side hemiparesis or hemiplegia, ideomotoric apraxia of the left arm, and disartria.

**Wernicke's aphasia**

The most frequently used synonym for Wernicke's aphasia is sensory aphasia, and some other names are also used, e.g. acoustic-amnestic aphasia, receptive aphasia and verbal agnosia.

This aphasia is characterized by easy speech production, and is therefore classified as a fluent aphasia with a normal or sometimes above normal speech production. Some patients are so logorrhoeic that they can be stopped only by energetic reaction of the interlocutor. Therefore, spontaneous speech in this case has well-preserved articulation and prosody. Speech is characterized by long sentences, which seem grammatically correct, but is more or less incomprehensible due to a small or a large number of literary and verbal paraphasia and neologisms.

A person with this kind of aphasia has a very poor understanding of the interlocutor and poor repetition. Repetitive speech is generally impaired in proportion with the degree of auditory understanding. In the highest degree of this syndrome, the content of the speech is completely incomprehensible to the interlocutor—then we usually say that the patient neither understands what he said nor is understood. This is opposed to motoric aphasia where the examiner has the impression that the patient understands him, but cannot speak correctly or answer the question properly. Communication of a person with sensory aphasia can be compared to a person who is in a foreign country whose language he does not understand or speak (1,2,3).

Naming (objects and events) is impaired, usually to the degree of anomia, and the patient describes the objects he wants to name. Reading is alexic, and writing agraphic. His writing has the same features as his spoken language—he uses long sentences which are regularly shaped, but with paraphasia or neologisms.

Unlike motoric aphasia, most patients with sensory aphasia have no neurological symptoms. However,

when they are present, it is usually upper quadrantanopsia, or sometimes homonymous hemianopsy, hemihyperesthesia, or a mild hemiparesis. Wernicke's aphasia is usually caused by a lesion in the dominant temporal lobe, especially in the auditory area in the back upper part of the first temporal gyrus (Figure 2).

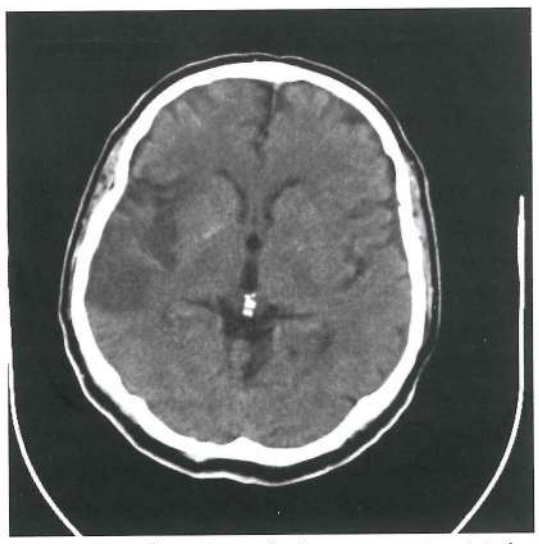

*Figure 2. Ischemic stroke in temporoparietal region (by computed omography) in patient with Wernicke's aphsia*

**Conductive aphasia**

Conductive aphasia is also called afferent or kinesthetic motoric aphasia, efferent conductive aphasia and central aphasia. This is a relatively rare type of aphasia, 5-10 percent of all aphasias are conductive. It is characterized by easy production of speech with dominant literary paraphasia. Understanding of the interlocutor is relatively good, and so understanding of the text read, but repetition is outstandingly impaired. Naming is also impaired. Writing is agraphic, and reading alexic, contaminated by paraphasic symptoms (1,17).

This aphasia is clearly different from Wernicke's aphasia because understanding is much better than repetition. It is different from Broca's aphasia because production of spontaneous speech is fluent. Ideomotoric apraxia, which includes buccofacial and limb activities, is widespread but not a rule. Neurological symptoms include a possible, but temporary hemiparesis. Conductive aphasia usually occurs because of a lesion in the back of the perisylvian area of the dominant hemisphere, usually immediately below supramarginal gyrus (Figure 3).

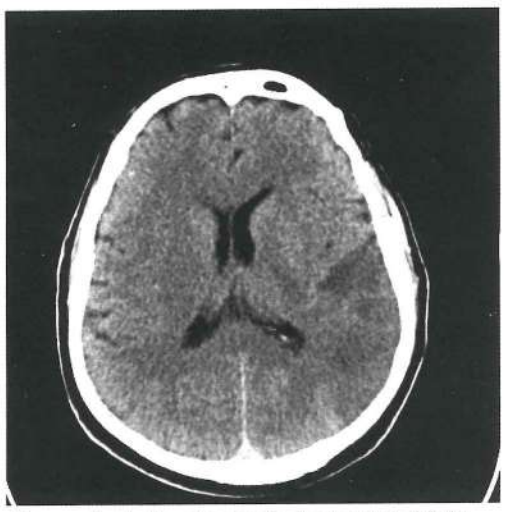

*Figure 3. Ischemic stroke in parietal lobe (by computed tomography) in patient with conductive aphasia*

**Global aphasia**

This is a relatively frequent aphasia, 10-40 percent of all aphasias. It is also called complete aphasia. Global aphasia is the most serious form of speech disorder. All aspects of speech are impaired, and the patient can usually pronounce just a few words or neologisms. Spontaneous speech is non fluent, understanding of the interlocutor poor, poor repetition or no repetition at all, and the patient is unable to name objects, read or write (usually complete alexia and agraphia). Speech disorders are usually accompanied by right-sided hemiplegia or hemiparesis, and hemisensory disorders (1).

The degree of verbal dysfunction and localization of pathology that causes it may vary. It is usually a lesion of a large area of left hemisphere (infarction in irrigation region of the middle cerebral artery) (Figure 4).

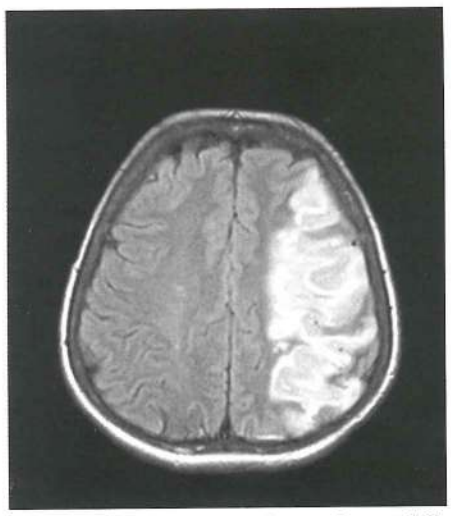

*Figure 4. Ischemic stroke in the middle cerebral artery territory (by magnetic resonance) in patient with global aphasia*

**Transcortical motor aphasia**

Transcortical motor aphasia or extrasylvian motoric aphasia is a non fluent aphasia which occurs in damage of the dominant hemisphere outside the speech area or Sylvian fissure, which is characterized by a relatively well-preserved ability to repeat. All aphasias which are caused by lesions outside the Sylvian fissure are called transcortical. They are usually caused by vascular insufficiency or infarction in the border zone between the middle, anterior and posterior cerebral artery of the left hemisphere. It can occur also as a consequence of tumor, hemorrhage, infection and in Alzheimer's disease (1,2,17).

Transcortical motor aphasia is also called dynamic aphasia. The lesion which causes this type of aphasia may be located in the left hemisphere in front of or behind Broca's area, in the left medial frontal region, affecting also supplementary motoric cortex or connections of white matter between these two areas. The main features of this aphasia are difficulties in spontaneous speech production, relatively or well preserved understanding of speech, unimpaired repetition, impaired naming, impaired reading aloud with good understanding of the read text and impaired writing.

**Transcortical sensory aphasia**

This fluent aphasia is characterized by a fluent (easily produced) spontaneous speech with paraphasias and echolalia. Echolalia is the basic symptom of this syndrome and this is why it is often misdiagnosed as a psychiatric disease (psychosis).

Understanding of spoken language is considerably impaired, but repetition is intact. Naming, reading and writing are usually considerably impaired. Present variability in reading aloud and impaired understanding of the read text. Combination of neurological symptoms varies depending on localization and depth of the lesion. Pathological process that causes this aphasia is usually located in the left parietal and temporal lobe, behind perisylvian area, often in the lower part of the parietal lobe (1,17).

**Mixed transcortical aphasia**

This non fluent extrasylvian aphasia is also called the syndrome of isolation of speech area. It is very rare compared to other types of aphasia. It is a combination of motor and sensory varieties of extrasylvian aphasia with symptoms of global aphasia, except preserved ability of repetition of spontaneous speech.

Spontaneous production of speech is impaired (non-fluent) and echolalic. There is a poor understanding of spoken language, poor naming, relatively preserved repetition, impaired reading aloud and understanding of the read text, aphasic writing. Neurological symptoms are often present, but not constant.

Lesions that cause this aphasia affect frontal and posterior borderline zones (between middle cerebral artery on the one side, and anterior or posterior cerebral artery at the other side) of the left hemisphere. Numerous pathological states accompanied by hipoxia and hypoperfusion of the brain in this region, such as intoxication with carbon-monoxide, accute carotide artery occlusion, acute hypotension, cardiac arrest may cause mixed transcortical aphasia (1,2,17).

**Anomic aphasia**

In most aphasias, patients have difficulties in finding words. However, in anomic aphasia, naming is the main and the most frequent symptom. It is also called nominal aphasia or amnestic aphasia. It is classified as a fluent aphasia with preserved repetitive speech.

Production of spontaneous speech is easy, but the speech is „empty" with long sentences in which the patient tries to replace the missing words with others (circumlocution). Understanding of spoken language is good, and repetition is good, too. There is some variability in reading aloud, but understanding of the text is intact. Writing can be aphasic. Location of the lesions which cause this syndrom varies, and anomia can be a consequence of a pathological process located anywhere in the linguistic zone, and in some cases it is even a consequence of processes located in the right hemisphere. If anomic aphasia is combined with alexia and agraphia and Gertsmann's syndrom (right-left disorientation, agnosia of fingers, acalculia and agraphia) the lesion usually affects the dominant angular gyrus (Figure 5).

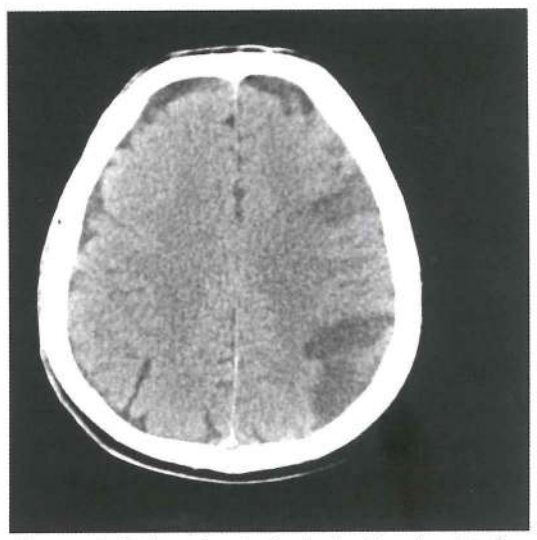

*Figure 5. Ischemic stroke in posteroparietal region (by computed tomography) in patient with anomic aphasia*

**Subcortical aphasia**

This is one of the recently discovered aphasias. It was possible only after the apperance of computed tomography in diagnosis of brain damages. Oscillations in symptoms and relatively good outcome with fast recovery of speech impairements are the main features of this aphasia.

The symptoms vary considerably depending on the location of affected subcortical structures. In acute subcortical aphasia, the patient is always mute (without any ability to speak), recovering slowly to hipophonia

with a slow and poor articulation. Spontaneous speech is contaminated with paraphasias, which disappear when the patient is requested to repeat the sentences spoken by the interlocutor.

Furthemore, other verbal properties are also affected, depending on subcortical pathology. There is a strict tendency of disappearance of verbal disorder and this transience may be accepted as one of the main diagnostic characteristic. However, if the lesion has affected verbal cortical areas, recovery is not complete. Subcortical aphasia is usually caused by ischemia or hemorrhage in the area of irrigation of terminal deep branches of the middle cerebral artery (paraventricular white matter, basal ganglia and thalamus). This is why symptoms look like transcortical aphasia with good recovery of speech impairments (1,4).

**Diagnosis of aphasias**

Recognition of aphasic disorders is important part of neurological examination. Precise diagnosis of aphasia should be made as soon as possible, which unfortunately is not always the case. One of the reasons is limitation of neuroimaging techniques in all centers and, in the other hand, somewhat deficient knowledge in this field among neurologists and neurosurgeons. Furthermore, not many Departments of Neurology or Neurosurgery have a privilege to have qualified speech therapists. Therefore, early recognition and particularly precise diagnosis of aphasias and early rehabilitation of speech disorders sometimes are missing (1,2,17).

Boston test is one of the most precise and widely used aphasia tests in developed diagnostic centers. Boston test examines conversation and fluency of speech, language comprehension, speech expression, repetition, naming, reading and writing. This battery of tests is especially designed for therapy planning and can be useful to monitoring the recovery and efficiency of speech rehabilitation. One of the limitations of the test is the length of the examination, which is about three hours. Porchov index of communication skills is a simpler test having also shorter duration (maximum 90 minutes). Test consists of 18 subtests which are grouped in verbal, graphic and gestual categories. International test of aphasia (Schuell-Benton) evaluates naming, repetition, fluency of speech, language comprehension, reading, writing and articulation as modalities of speech.

**Tretment of aphasias**

Treatment of aphasias is multidisciplinary and depends on the symptoms, localization of the brain lesion, etiology and knowledge of the remaining speech and cognitive abilities (1,17).

Many speech impairments have a tendency of spontaneous recovery. Recovery of aphasias caused by ischemic stroke occurs sooner, and it is the most intensive in the first two weeks. In aphasias caused by hemorrhagic stroke, spontaneous recovery is slower and occurs in the period from the fourth to the eighth weeks after the stroke. The course and the outcome of the aphasia depend a lot on the type of aphasia. Global aphasia has a poor prognosis, unless it is the initial phase of subcortical aphasia. Recovery from Broca's and Wernicke's aphasia varies. Conductive, anomic and transcortical aphasia have relatively good prognosis. In spontaneous restitution of aphasias, the initial syndromes are transformed into other clinical forms in 30-60 percent of patients (1,5).

Regardless of the fact that a significant number of aphasias spontaneously improves, it is necessary to start the treatment as soon as possible. Different rehabilitation procedures are developed, depending of the type of aphasia. Our hospital based studies in post stroke aphasias showed the best results of speech therapy in patients with Broka's and anomic aphasia, than in those with Wernicke's, and the poorest recovery was found in patients with global aphasia. Continuous speech treatment significantly contributed to recovery of post stroke aphasias, regardless to the type of stroke and sex, and showed better results in the younger stroke patients (18).

Early treatment of aphasia is important not only because of speech recovery, which is crucial for everyday communication, but also because of the entire rehabilitation of patients with neurological symptoms accompanying speech impairment. Rehabilitation of motoric impairments is more complex and slower in persons with aphasic syndromes, especially if the patient is not treated by parallel rehabilitation of neurological deficit and speech impairments.

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