The Complexity of the Management of Hypertension and its Comorbidities

HIGHLIGHTS

Fondazione
Internazionale
Menarini

Barcelona (Spain)
November 26 -28, 2015

HIGHLIGHTS

Welcome to Barcelona

Professor Coca, President of the meeting, opened the congress at the School of Medicine of the University of Barcelona. Why an international Symposium on the complexity of the management of hypertension and its comorbidities? Hypertension is the main risk factor of cardiovascular disease and it is the result of the interaction of a series of other risk factors as physical inactivity, diet high in sodium, obesity. The close link between hypertension and other comorbidities is at the base of its complexity. The aim of the Symposium is to study the many interactions between these comorbidities and the triggered physiopathogenetic mechanisms causing heart damage and slow transition from hypertension to heart failure.

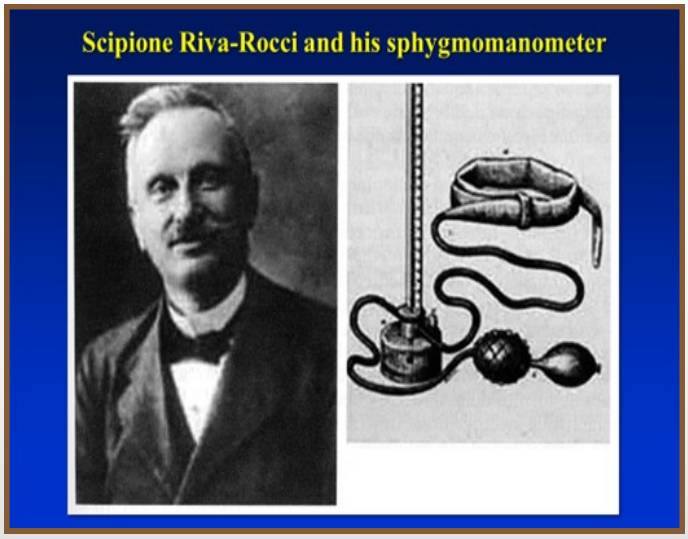
Antonio Coca
(Barcelona, Spain)

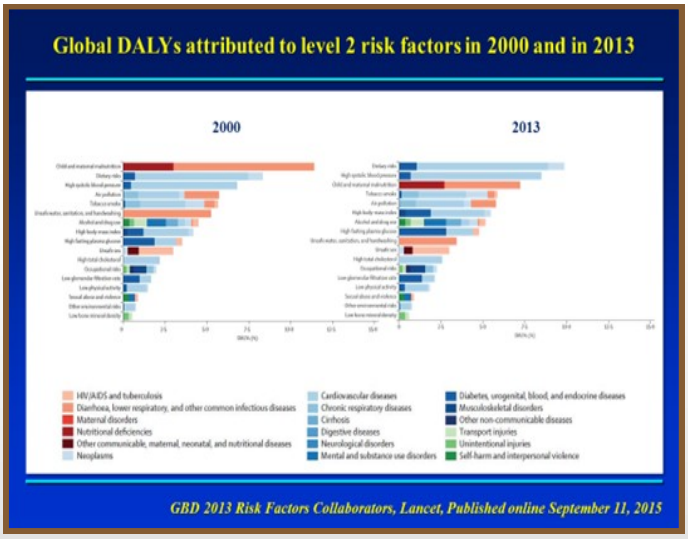
To follow the presentations of this congress click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.

Hypertension Treatment: Past, Present and Future

Alberto Zanchetti
(Milan, Italy)

Professor Zanchetti from Milan opened the symposium with the inaugural lecture on past, present and future of the hypertension treatment. It all began in 1800 when Scipione Riva-Rocci discovered the spygmomanometer to determinate, for the first time ever, the blood pressure values, particularly the systolic values. Only in the '60, the first indications on diastolic pressure levels appeared with George Pickering, who, for the first time, classified hypertension as a combination of high systolic and diastolic blood pressure. In the twenty following years, the treatment of hypertension was guided exclusively by the results achieved in reducing the diastolic pressure. The novelty introduced in 1989 was mentioning systolic blood pressure levels as "a factor influencing initiation of anti-hypertensive treatment". At this point of the speech, Professor Zanchetti introduced a main topic that is still intrinsically linked to the history of hypertension: what are the benefits resulting from lowering blood pressure? In other words, do hypertensive subjects receive real benefits from blood pressure lowering therapy? To this question, Professor Zanchetti answered submitting data from randomized clinical trials published in the last twenty years. This suggests that anti-hypertensive therapy was one of the main achievements in medicine during the second half of the 20th century. Thanks to it, specific treatment protocols were developed for specific groups of patients, according to their hypertensive state. What is the challenge for the future? It is to find realistic solutions to the problem of hypertension control. This is a particularly urgent task for the epidemic growth of this disease even in low-income countries, like Africa.



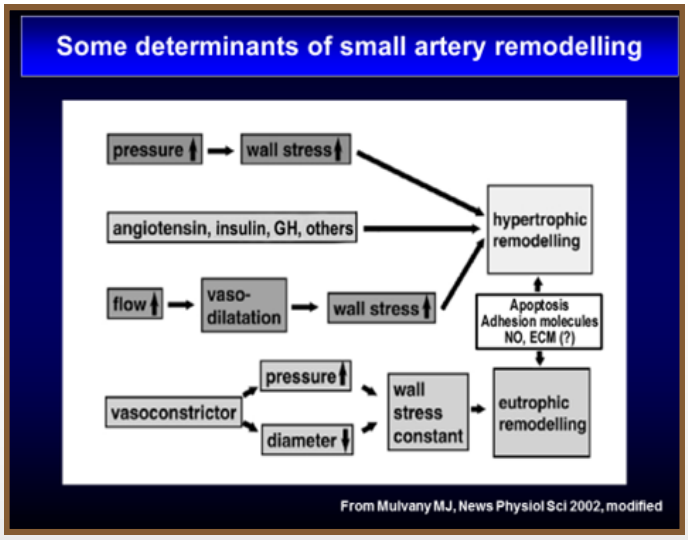


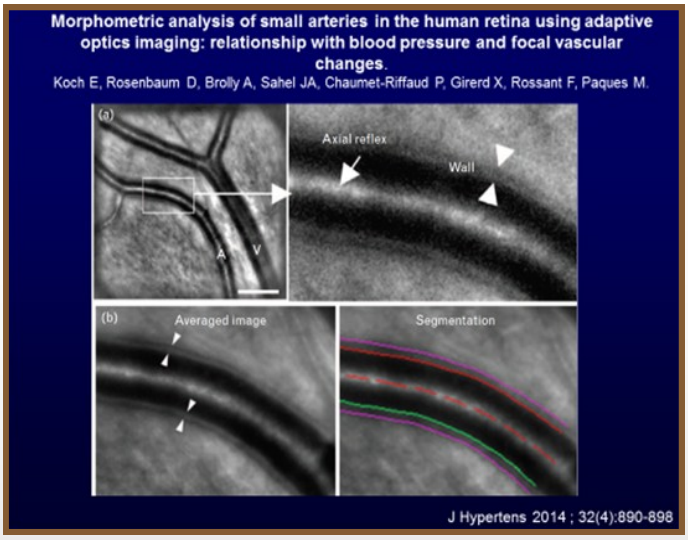
Are there significant differences between the drugs used to treat hypertension? What are the results of the main trials published on the treatment of hypertension? Despite the pharmacological treatments available, why the percentage of treated hypertensive patients remains still unacceptably high?

Small Arteries Disease in Hypertension: what is new?

Enrico Agabiti Rosei
(Brescia, Italy)

Professor Agabiti Rosei from Brescia went into this very topical subject of the correlation between organ damage and small artery remodelling in hypertension. Remodelling is defined as hypertrophic, in presence of severe hypertension. Other pathological conditions, as type II diabetes, could lead to the same hypertrophic remodelling due to vascular wall stress. Pro-inflammatory factors play a primary role among the main patterns responsible for small artery remodelling. The link between T lymphocytes, interleukin-1 production and pathological remodelling seems to be a matter of first importance. The tissue remodelling is responsible for the vasoconstriction, which is the main factor worsening the symptoms of high blood pressure. The increased relationship of wall to lumen ratio is a direct risk factor of cardiovascular events. The relation is also highlighted by the effect of the protective antihypertensive treatment as blood pressure control reduces the incidence of new cardiovascular events. Angiotensin II inhibitors effectively reduce the Augmentation index. A very non-invasive innovatory approach to measure the media/lumen ratio is the morphometric analysis of small arteries in the human retina, using adaptive optics imaging. The arterioles structure in hypertensive treated patients is an independent factor of cardiovascular damage.



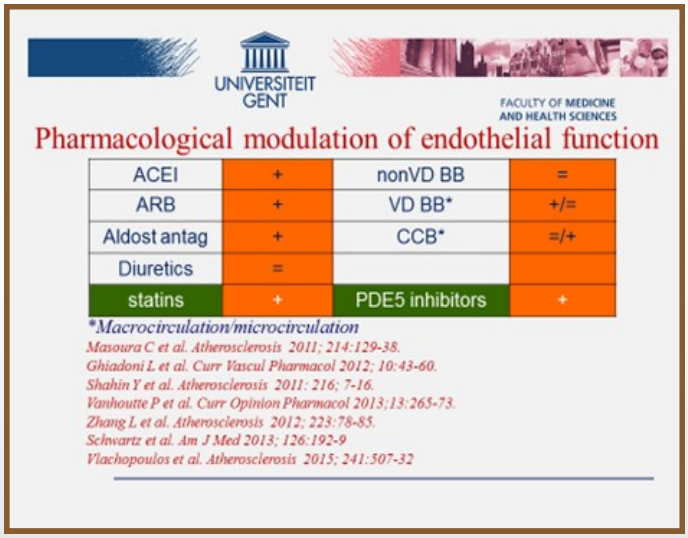


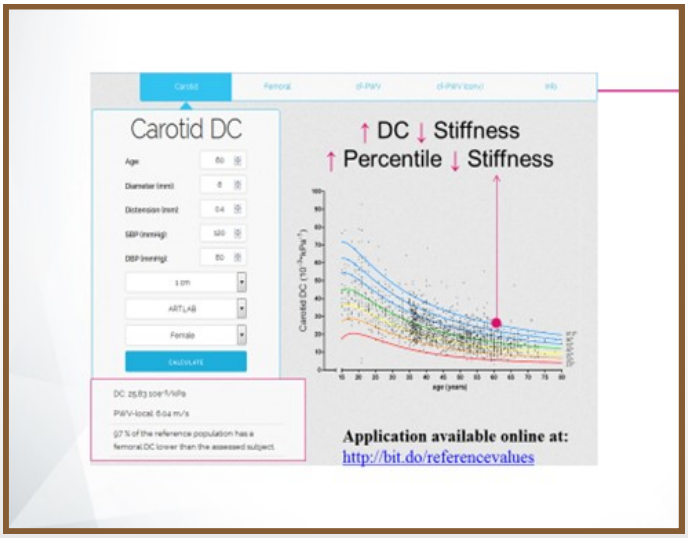
What is the relationship between the reduction of adipose tissue and the pro-inflammatory factors?
To what extent is it possible to normalize the blood pressure in patients affected by cardiometabolic diseases?
What is precisely the "residual risk"?
Which are the most effective drugs to reduce arteriolar remodelling in hypertensive patients?

The Impact of large Artery Damage in Cardiovascular Disease. How can antihypertensive Treatment modify arterial structural Damage?

Luc Van Bortel
(Ghent, Belgium)

Professor Van Bortel from Ghent described the effect of the antihypertensive treatment on the endothelial function, on the carotid intima/media thichness, on the pulse wave reflection/central blood pressure ratio and on the arterial stiffness. As regards the endothelial function, statins and the phosphodiesterase type 5 inhibitors are the drugs with positive effect when they are administered in combination. The drug treatment undoubtedly decreases carotid intima/media thickness but it takes years to be evident. The clinical meaning of this index is associated with the onset of atherosclerosis and it is an independent risk factor of stroke. About the effects of antihypertensive treatment on pulse wave reflection and arterial stiffness, the most effective drugs are nitrates and PDE5 inhibitors. On the contrary, beta-blockers lower heart rate and increase both, the pulse pressure and the systolic pressure. Regarding the arterial stiffness due to hypertension, the ACE inhibitors, the angiotensin II antagonists, the selective β blockers, the calcium antagonists and the direct renin inhibitors are the drugs able to decrease it. There are now numerous novel methods for arterial stiffness measurements and they sufficiently correlate. Some applications, also available on mobile phone, have been developed to easily measure the carotid and femoral pulse wave velocity, the arterial stiffness from a specific subject and to delivers its percentile in reference to a healthy population.



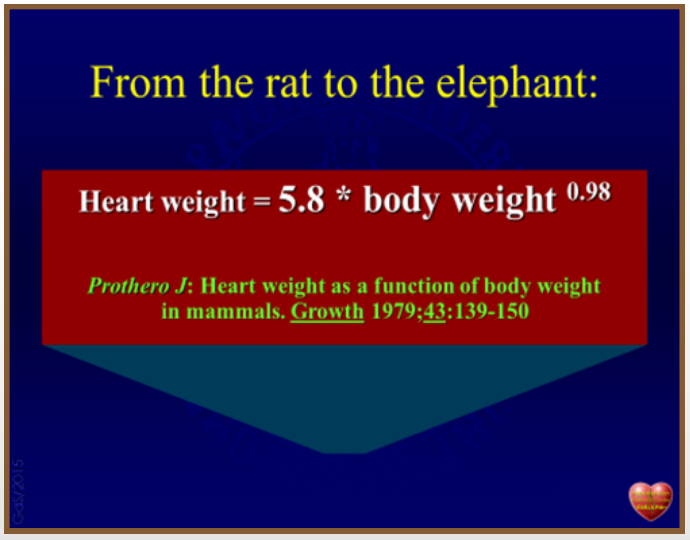


For clinical use, how effective is the index of carotid intima/media thickness for a prognostic evaluation of our patients?
What are the main novel methods to measure arterial stiffness?
How reliable are the blood pressure stiffness indicators for a prognostic evaluation of hypertensive patients?

Defining left ventricular Hypertrophy: why is it so difficult?

Giovanni De Simone
(Naples, Italy)

Professor Giovanni De Simone from Napoli described the main critical steps in determining and interpreting left ventricular hypertrophy. There are problems of imaging-mode acquisition, of conventions of layer measurement and of different calculating formulas of the left ventricular mass. However, the major problems are about the indexing for the body mass. In other words, how to correlate measurements obtained in conditions of abnormal body composition as obesity and anorexia? Both have important alterations of the fat-free mass and they could negatively influence the prediction of the LV mass, as this is closely linked to the fat-free mass. In obese subjects, measurement of left ventricular mass using BSA indicator is likely to produce underestimated data and, on the contrary, it increases the concentric remodelling. In this kind of patients, instead of BSA, the use of heights as normalization parameter is more effective provided the use of allometric and not ratiometric normalization.



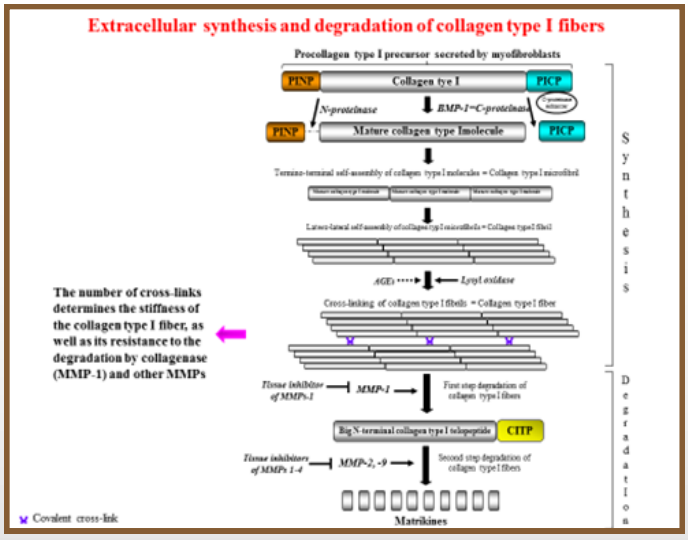
What are the main imaging acquisition patterns?
What are the conventions of correct layer measurements?
How to index the body size in order to calculate the correct LV mass?
How to evaluate the LV geometry?

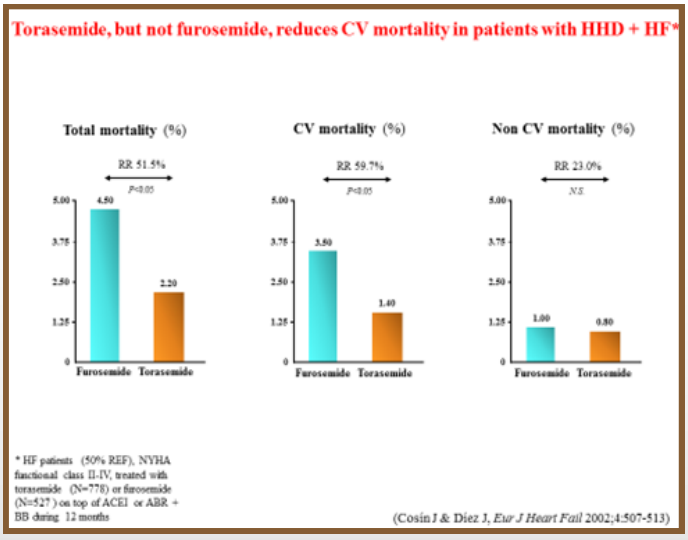
To answer this and other questions click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.

The Transition from Hypertension to Heart Failure

Javier Diez
(Pamplona, Spain)

Professor Diez from Pamplona examined this subject in detail considering that hypertensive patients are at a high risk of developing heart failure also when they are treated with a hypertensive therapy to control the blood pressure. The problem in these patients is the presence of myocardial interstitial fibrosis (MIF) that alters the diastolic and systolic pressure and it is typical also in controlled hypertensive patients. What to do? From a metabolic point of view, it is important to prevent that synthesis of collagen type 1 is predominant on its degradation. To ensure this balance it is important to prevent the cross linking synthesis of collagen, especially through the Lysyl Ossidasi. What to do in terms of clinical? Professor Diez indicated the way to identify new biomarkers that significantly correlate with MIF. This method allows not only to identify patients at high risk of myocardial fibrosis and heart failure but also it would allow for a personalized therapy with existing or novel drugs able to reduce both myocardial collagen type 1 synthesis and cross-linking deposition.





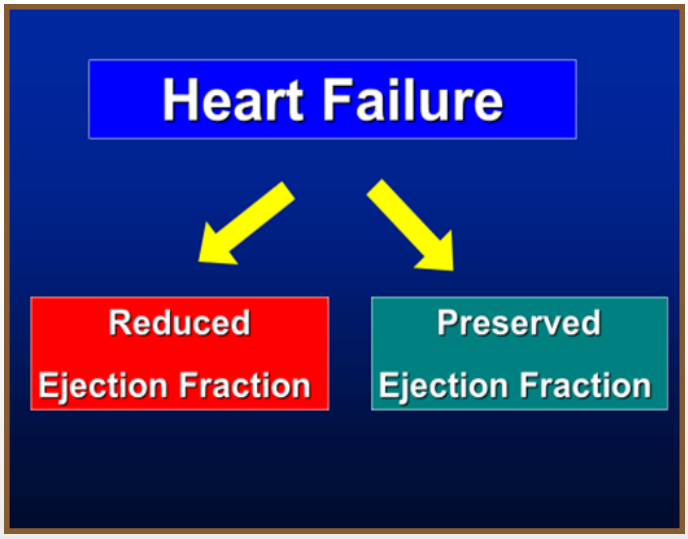
What is the degradation of collagen type I fibres in myocardial cells?
Why hypertensive patients develop myocardial fibrosis?
What are the myocardial fibrosis indicators?
What are the treatments to reduce myocardial fibrosis in hypertensive patients?

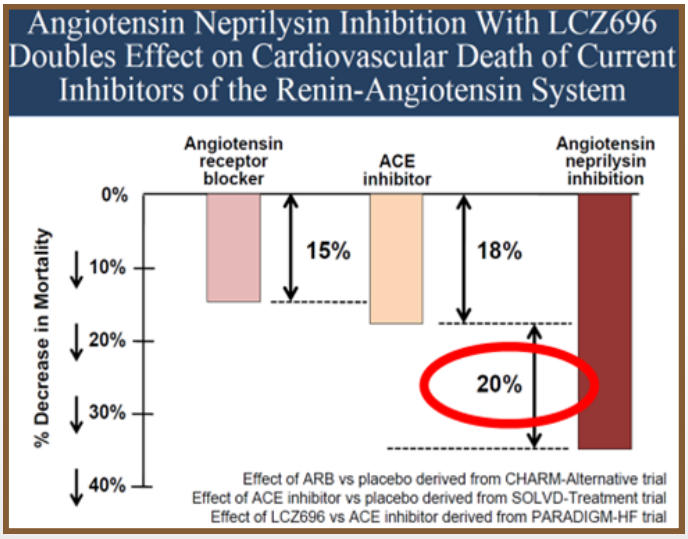
To answer this and other questions click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.

Management of Heart Failure with Preserved Ejection Fraction

Félix Perez-Villa
(Barcelona, Spain)

Professor Perez-Villa from Barcelona examined this subject in detail. Patients with heart failure (HF) can be divided in two main groups: with preserved ejection fraction (EF) and with reduced ejection fraction (EF). Patients with reduced ejection fraction are mostly male affected by heart failure while patients with preserved ejection fraction are mostly women, obese and hypertensive subjects. In recent years, the percentage of patients with preserved EF heart failure is increasing. Their outcome, better than in patients with reduced EF, did not result in significant improvements although numerous tested therapeutic approaches. In other words, no drug treatment has been yet identified to significantly reduce the morbidity and mortality of these patients. Professor Perez Villa analysed the data of the main trials conducted in recent years on patients with heart failure of reduced and preserved ejection failure. In the reduced EF studied population, positive results were obtained from the pharmacological treatment compared to placebo, but not similar results arrived from studies on patients with preserved EF. What to do for this type of patients?





What are the main differences between HF with preserved ejection fraction and HF with reduced ejection fraction?
What are the most effective pharmacological treatments to reduce morbidity and mortality of HF with preserved ejection fraction?
What are the main guideline indications regarding HF with preserved ejection fraction?

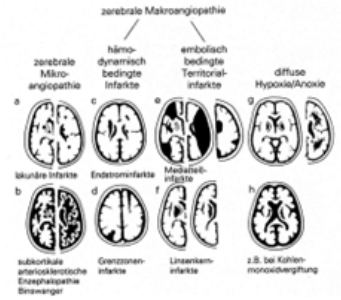
How to manage Blood Pressure in acute Phase of Stroke

Dariusz Gasecki
(Gdansk, Poland)

Professor Gasecki from Gdansk analysed thoroughly this issue starting from the definition of stroke and its subtypes and moving on to describe the vascular pathophysiology of ischemic stroke. In the course of this type of stroke, we can often observe patients with elevated levels of systolic blood pressure. High blood pressure occurs within the first 20 hours after stroke onset. When the early stage of the disease is over, patients tend to move from the state of vascular hypertonia in a state of hypotonia and blood pressure begins to drop spontaneously within the first 10 days after the ischemic event. The presence of cerebral oedema is accompanied by the presence of systolic hypertension for longer periods and this is a negative prognostic factor. The early reperfusion causes a rapid reduction in blood pressure levels. At the beginning of the studies conducted on these patients with systolic hypertension, there were no evidence of any significant benefits related to a pharmacological reduction of blood pressure. Furthermore, the early administration of any anti-hypertensive treatment, taken before the ischemic stroke, seemed to be connected to the increase of disability in the recovery phase. Further studies with patients recruited in the hyperacute phase of ischemic stroke are therefore warranted to find an early treatment of the disease.

Pathophysiology of ischemic stroke

- Stenoocclusion: 90%
  - large vessel 2/3
    - embolus
    - thrombus
  - small vessel 1/3
    - microatheroma
    - arteriolosclerosis
- Low-flow: 10%
  - watershed
  - borderzone



Ringelstein et al. 1982

Conclusion

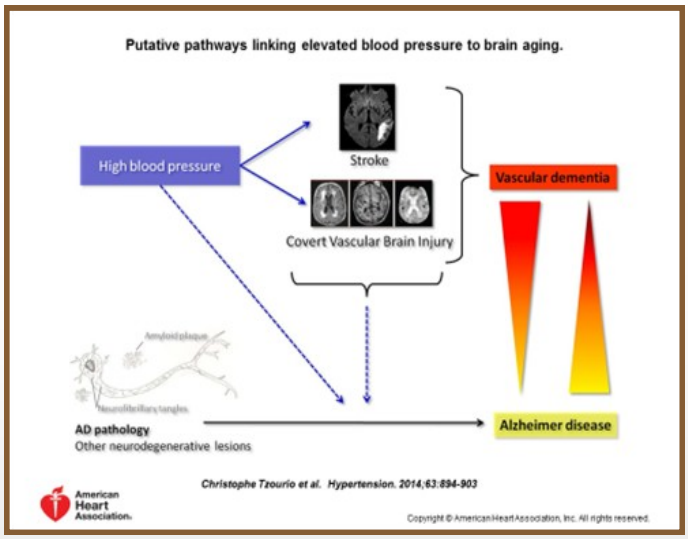
- More research is needed to identify
  - those people who are most likely to benefit from altering blood pressure in acute stroke,
  - the time window in which the treatment is likely to be of benefit,
  - what subtypes of stroke are likely to respond favourably,
  - **the need for phenotyping of population recruited in the hyperacute phase of AIS**

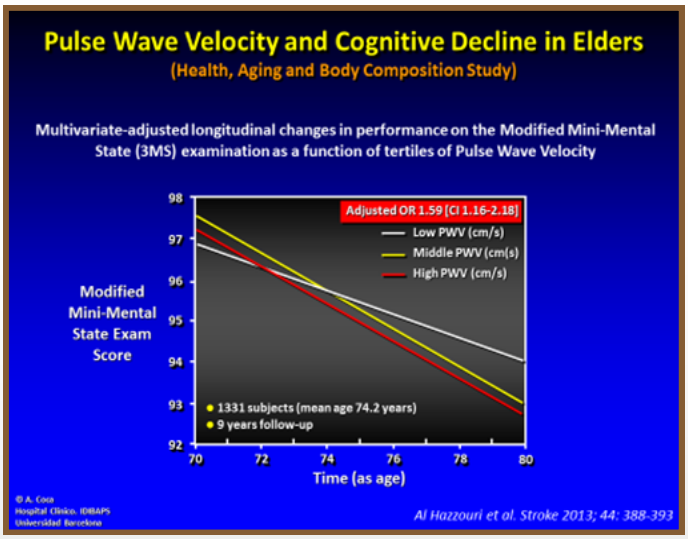
What are the pros and cons in the reduction in blood pressure during the acute phase of ischemic stroke?
Regarding the hypertensive systolic treatment, what are the results of the trials conducted on these kind of patients?
What is the appropriate period to treat systolic hypertension in patients with ischemic stroke?

The interrelation between Hypertension and Cognitive Decline

Cristina Sierra
(Barcelona, Spain)

Professor Sierra from Barcelona explored this issue that is surely topical considering the relation between the increase in life expectancy and dementia cases in the population. Hypertension is associated with a wide variety of cognitive deficits, including impaired memory and reduced abstract reasoning. The link between hypertension and cognitive impairment is related to the onset of hypertension and to its severity. Another important factor is the relationship between dementia and Alzheimer disease. Pathophysiological alterations at the cerebrovascular level, induced by chronic hypertension, will lead, over time, to a reduction in cerebral blood flow and in cholinergic neurotransmission; both factors, in turn, facilitate amyloid accumulation in the brain. Silent cerebrovascular disease is higher than what we can imagine and this is one of the major cause of cognitive impairment in the population.





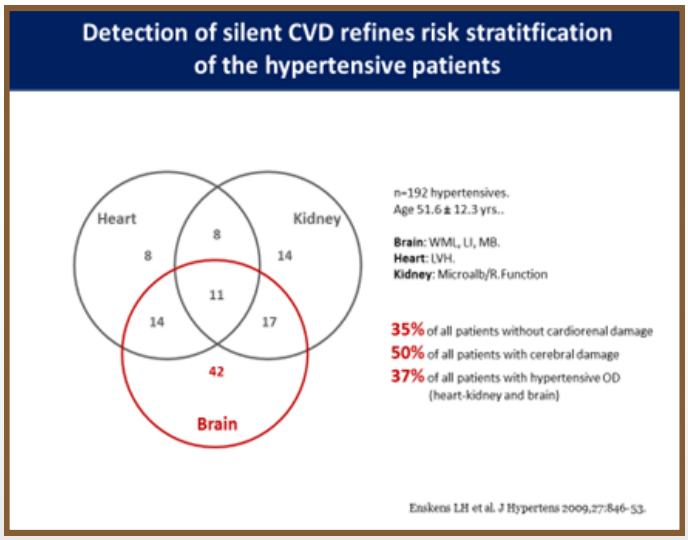
What are the pathophysiological processes relating cognitive impairment to arterial stiffness?
What is the relationship between the pulse wave velocity and cognitive decline in elders?
What are the still outstanding issues in the interrelation between hypertension and cognitive decline?
Are there proper randomized clinical trials to study this interrelation?

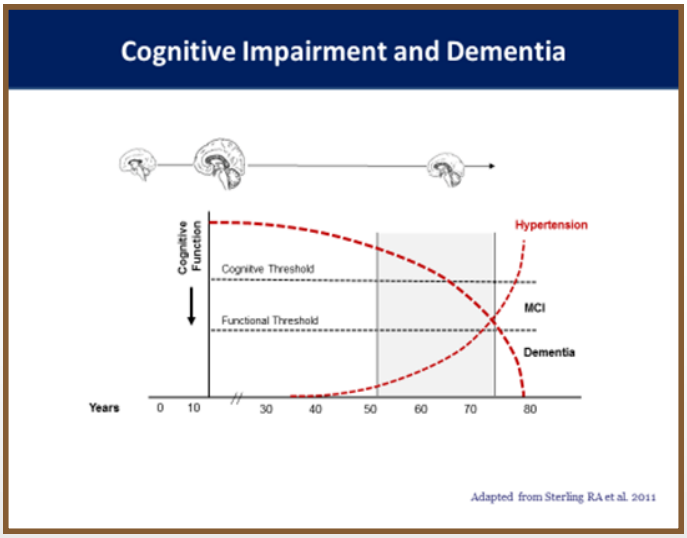
To answer this and other questions click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.

How to assess Cognitive Decline in Routine Clinical Practice?

Augusto Vicario
(Buenos Aires, RA)

Professor Vicario from Buenos Aires addressed this issue starting with the evaluation of the brain organ damage. Hypertension causes important sub-clinical damages to the brain and this factor significantly correlates with the decrease in the cognitive function. It becomes therefore essential to evaluate the cognitive status of patients with vascular brain injury. Professor Vicario submitted data resulting from studies performed in Argentina to approach the cognitive status in hypertensive patients. The resulted data produced a cognitive syndrome known as "executive dysfunction" that is the cognitive domain most and first affected. This function is the ability to perform, quantitatively and qualitatively, testing of different genders as to draw complex shapes. Cognitive impairment is an age-related physiological phenomenon. However, if we analyse the relation between cognitive impairment and increased prevalence of hypertension, we notice that the two phenomena correlate inversely to the increase of blood pressure and as a result, there is a drop of the cognitive performance.





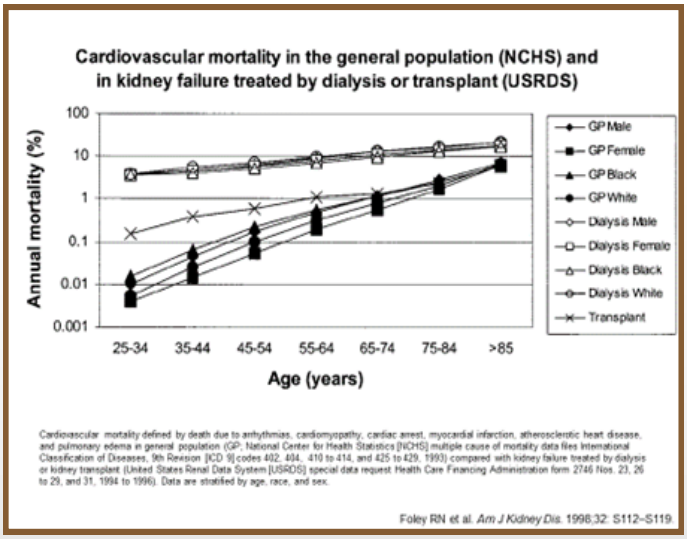
How to evaluate the brain organ damage?
Should we perform cerebral MRI to all patients to identify hypertensive vascular brain injury and stratify their risk?
What is, qualitatively and quantitatively, the most effective test to assess cognitive decline?

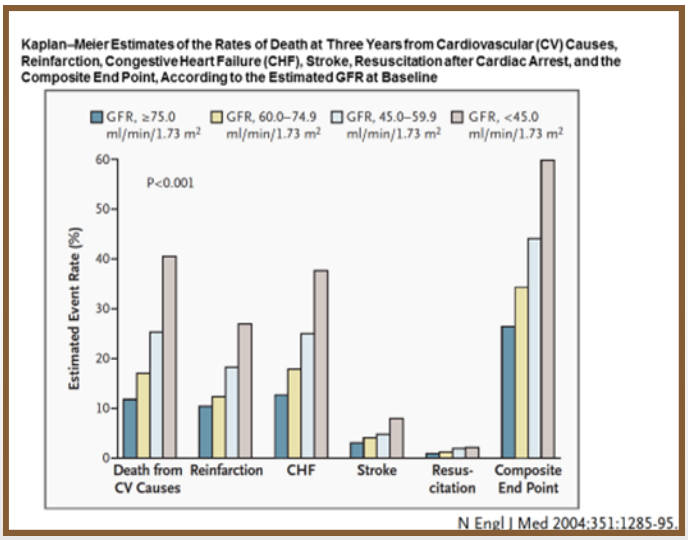
To answer this and other questions click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.

Chronic Kidney Disease in Cardiovascular Disease

Julià Segura
(Madrid, Spain)

Professor Segura from Madrid explained the association between cardiovascular disease and kidney failure. The history began at the end of the last century when the American Journal of Kidney Diseases published a report of the study group of the National Kidney Foundation about the cardiovascular risk in patients with chronic kidney disease. It was stressed that the care of these patients had to start early, before the disease arrived at the end stage when the damage was no longer reversible. It was then specified that these kind of patients were at high risk of developing cardiovascular complications. In the past 15 years, data on tens of thousands of patients were produced actually confirming the article published on the American scientific journal. Professor Segura went on to describe the pathophysiological and metabolic mechanisms that determine the vascular damage: the chronic disease and its clinical implications, the stratification of risk to quantify prognosis, the identification of metabolic markers of chronic kidney disease linked with cardiovascular risk, the interaction between less severe renal failure and cardiovascular risk. The Professor finally closed his presentation with the KDIGO recommendations on the diagnosis and management of patients with chronic kidney disease.





What is the correlation between cardiovascular disease and end-stage renal failure?
What are the metabolic markers that correlate better between vascular damage and chronic kidney disease?
Are there any cut-off values in this correlation?
What suggest the KDIGO recommendations of 2012?

To answer this and other questions click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.

Renal Protection in Diabetic Patient

Michel Burnier
(Losanna, Suisse)

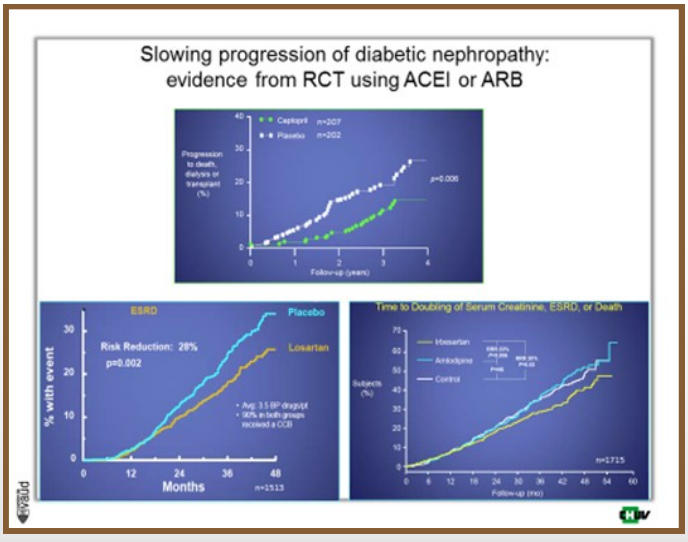
Professor Burnier from Lausanne spoke about the correlation between diabetes and chronic kidney disease. Patients with type 2 diabetes mellitus are however at cardiovascular risk and, if they are affected by chronic kidney disease, the risk increases exponentially. Blood pressure is an important determinant of the progression towards end-stage renal disease and of CV complications. These patients should achieve lower blood pressure level more than others not suffering from kidney disease should. It is not only important to reach specific cut-off blood pressure but it is also essential that, during the 24 hours, no peaks of pressure occur as, they could have a negative impact on the evolution of the disease, if repetitive in time. It is therefore important for this patient to perform, on several occasions, a 24 hours blood pressure monitoring. The speaker went on examining in these patients the effect of the major antihypertensive drugs on blood pressure control. Among combination therapies, blockers of the renin-angiotensin system represent the first line therapy.

GFR and albuminuria and the risk of progression in CKD patients

KDIGO 2012

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+



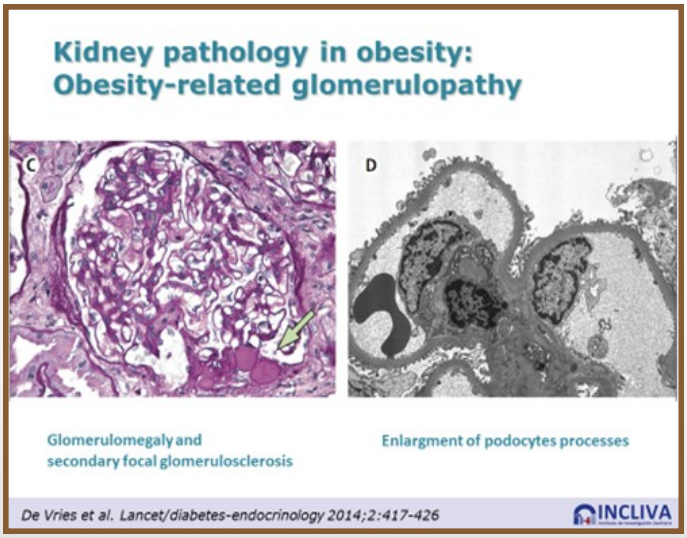
What is the relation between cardiovascular disease and chronic kidney disease?
What are the recommended blood pressure target for these patients?
What are the first line antihypertensive therapies to control blood pressure in these kind of patients?

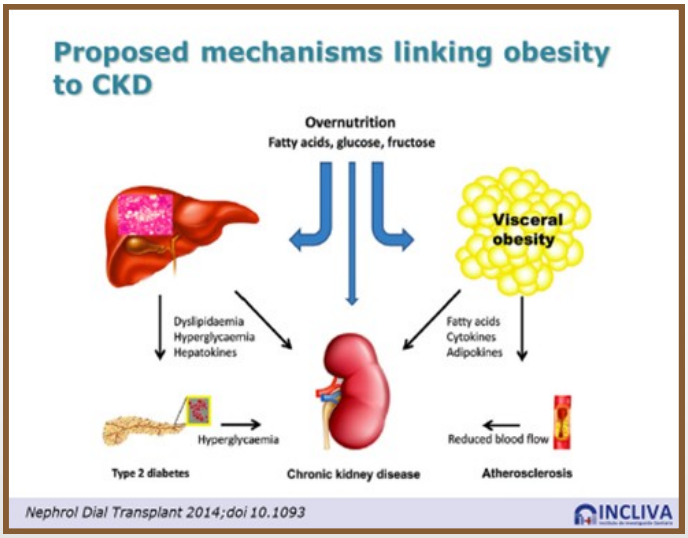
To answer this and other questions click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.

Obesity and the Kidney: what is the Link?

Josep Redòn
(Philadelphia, USA)

Professor Redon from Valencia faced an extremely timely topic: the link between obesity and kidney damage. Obesity is a mounting epidemic around the world and it induces renal damage. The speaker analysed the epidemiology, the pathology, the mechanisms, the clinical impact and the treatment options of this association. Regarding the pathophysiology, obesity is relating to typical glomerulopathy that, in turn, may be the first step for developing kidney disease. The second pathological mechanism is the intracellular lipid droplets in podocytes, mesangial and tubular cells. The third pathological mechanism is the increased sensitivity to sodium. At this point, the speaker presented the potential mechanisms linking obesity to kidney damage. The element that stands out results from the involvement of major organs such as the liver, the pancreas, the vascular bed, the visceral adipose tissue and of course the kidney. We are facing a real global syndrome that involves different and multiple metabolic pathways. The clinical impact could be devastating as the progression to chronic renal failure can appear in about 15-20 years in obese young/adult population also affected by other risk factors associated with obesity. What is the impact of the pharmacological approach? The speaker presented data regarding the main clinical trials conducted on these patients.





What is the link between obesity and kidney damage?
What are the main pathological mechanisms involved?
What is the clinical evolution of these patients?
Are there pharmacological treatments able to block the development of these patients to the end-stage of the renal failure?

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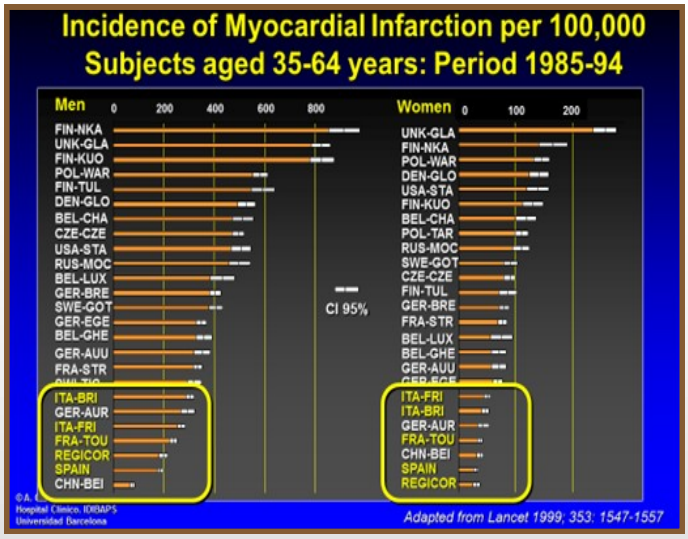
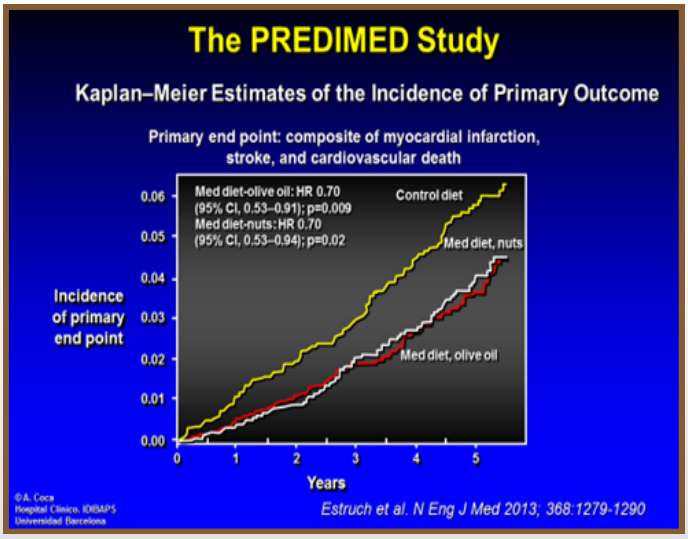
The Diet in the Prevention and Treatment of Cardiovascular Disease

Antonio Coca
(Barcelona, Spain)

Professor Coca from Barcelona submitted interesting data on the prevention and treatment of cardiovascular disease through diet. All hypertension guidelines recommend increasing consumption of vegetables, fruits and low-fat dairy products. The raison d'être of these recommendations is the causal link between high fat diet and cardiovascular disease. The adherence to a healthy lifestyle, regular exercise and a healthy diet reduce significantly the incidence of myocardial infarction and stroke. The incidence of these diseases in Europe is significantly lower in Mediterranean populations. How can we explain this phenomenon? The answer is easy: it is the adherence to the Mediterranean-style diet. Data from cohort studies showed that the Mediterranean diet highly reduces cardiovascular morbidity and mortality in contrast to Western diets characterized by a high intake of butter, red meat and refined grains. Professor Coca presented data from a recent study on groups of Spanish patients affected by type II diabetes, obesity, hypertension and dyslipidaemia. The differences in the groups consisted in two different dietary protocols: the Western diet and the Mediterranean diet. Both groups of study presented cardiovascular risk factors but the cardiovascular and cerebrovascular events were significantly reduced in those subjects with adherence to the Mediterranean diet and not in those on a standard diet.





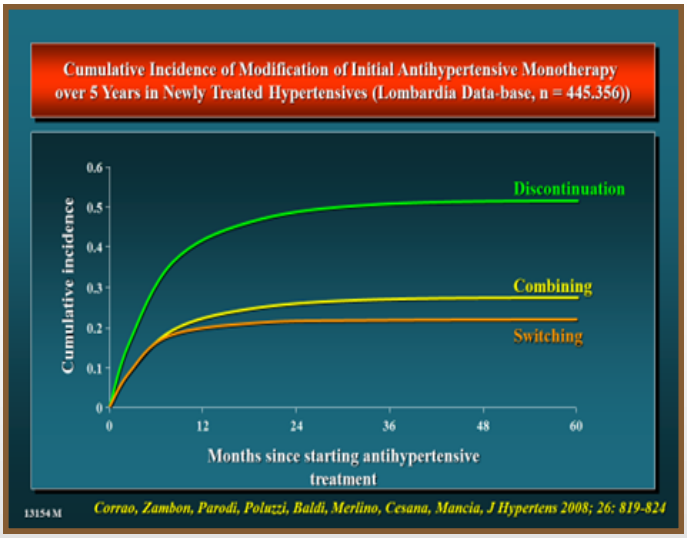
What is the relation between Mediterranean diet and cardiovascular disease?
What is the effect of the Mediterranean diet on hypertension?
What is the beneficial effect of olive oil?
What are the main characteristics of the Mediterranean diet?

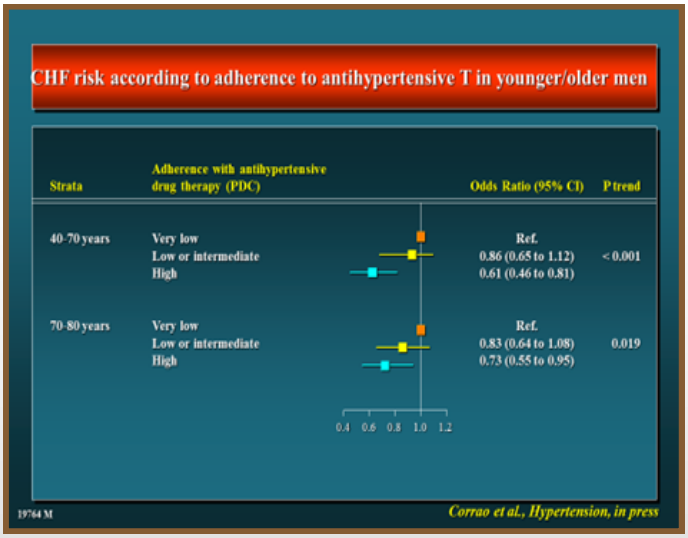
To answer this and other questions click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.

How to improve Adherence to antihypertensive Treatment?

Giuseppe Mancia
(Milan, Italy)

Professor Mancia from Milano examined this very topical issue as there is a high percentage of hypertensive patients who are unable to keep blood pressure under control. What is the adherence to the pharmacological treatment? It is complex to value this phenomenon as there are multiple variables, difficult to control. However, Professor Mancia submitted data from an adherence study based on the requirements of Lombardy region.
Out of approximately 500,000 studied patients, 65% of them discontinued taking medications after 12 months. This is a dramatic result as the adherence factor directly correlate with the incidence of new cardiovascular events. In patients continuing treatments, the risk of coronary/cerebrovascular events were less than in patients characterized by treatment discontinuation. In addition, the incidence of hospitalizations was lower in those patients who were adherent to the therapy. What are the reasons to discontinue an hypertensive therapy? Subjects in combination therapy have a better adherence result than those treated with monotherapy. Other pathologies, as diabetes, increase the adherence to the therapy, perhaps due to a greater motivation by patients. Even lifestyles seem to affect the levels of adherence to treatments: subjects living in metropolitan areas are less adherent than those living in rural areas are. The problem of adherence is also in subjects treated with statins: more than half of them discontinue treatment after only one year from the initial prescription.





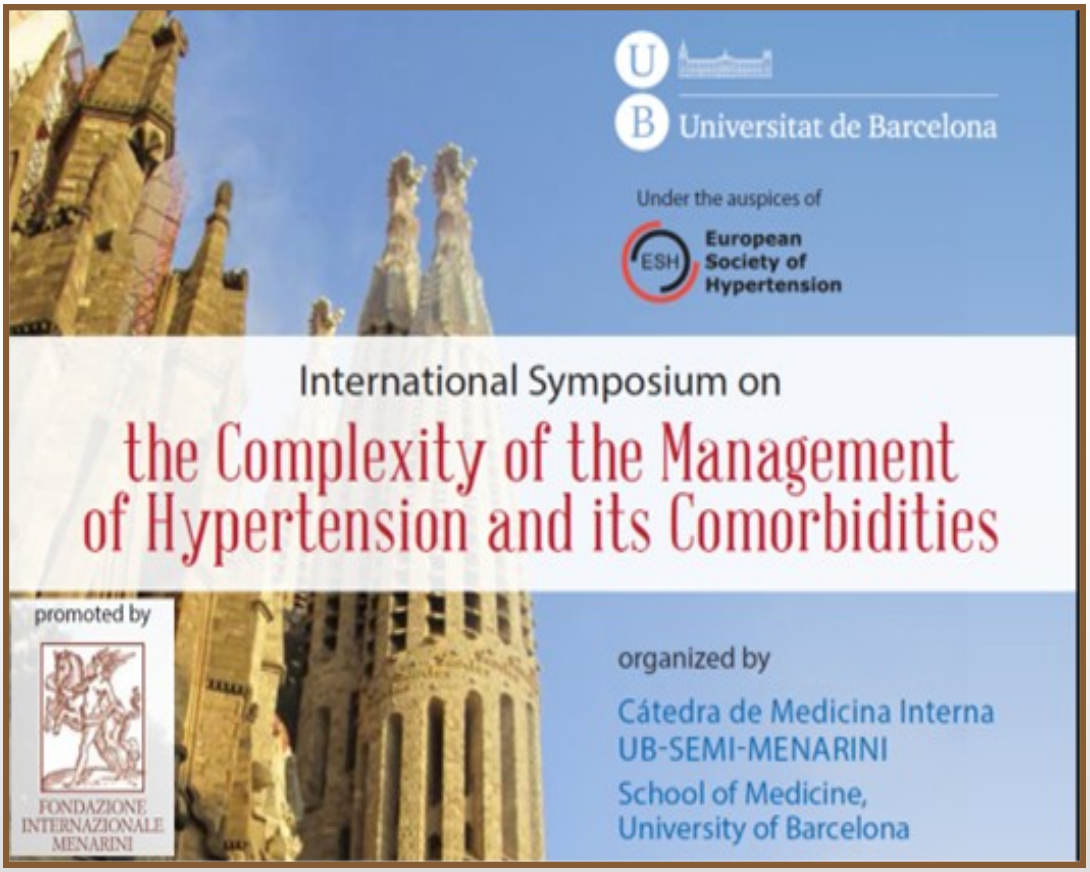
What is the relation between adherence and coronary/cerebrovascular events?
Why a high percentage of patients treated with hypertensive drugs early discontinue medications?
Why subjects living in metropolitan areas are less adherent than those living in rural areas are?

To answer this and other questions click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.

HIGHLIGHTS

These are some of the topics addressed during the congress talks. For more in-depth information, please visit the website of **Fondazione Internazionale Menarini**, which contains the full versions of the congress talks.

To follow the presentations of this congress click on this link: www.fondazione-menarini.it/... and after having logged in, access the multimedia material.



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