FORMACIÓN CONTINUADA

Multi-organ protection and the kidney. From nephroprotection, cardioprotection, neuroprotection to multi-organ protection

Gh. Gluhovschi, Gh. Bozdog, L. Petrica, A. Schiller, V. Trandafirescu, S. Velciov, C. Gluhovschi y F. Bob
Dept. of Nephrology, University of Medicine and Pharmacy «Victor Babes», Timisoara

Lately in the literature some protection measures have been discussed, which are targeted against different risk factors that determine functional disturbances and organic lesions of the main organs: heart, kidney and brain. As a consequence, the terms of cardioprotection, nephroprotection and neuroprotection have been adopted.

The surprise of multicentric studies has been that despite the presence of some observations that prove the concomitant damage of the three organs, it has not been always approached as a whole. One or the other of the analyzed organs is mentioned only briefly. The Framingham study, for example, is focused on cardiovascular lesions, the cerebral ones are mentioned, but the kidney is not very privileged in this study.

Although sometimes a complex treatment is applied, which consists of measures of nephroprotection, cardioprotection and neuroprotection, this treatment is not defined by a single term, as a treatment that approaches many organs and, as a consequence, its results are not followed up equally. The cardiologist will talk about cardioprotection, the neurologist about neuroprotection, while the nephrologist will talk about nephroprotection.

When the nephrologist has been obliged to deal with heart injuries, which occur frequently in renal diseases, measures of cardioprotection in the renal patient have been mentioned, for example in chronic renal failure. On the other hand, lesions of different organs interconnect.

Recibido: 12-IV-2004.
En versión definitiva: 18-IX-2004.
Aceptado: 27-IX-2004.

Correspondencia: Prof. Dr. Gheorghe Gluhovschi
Calea Aradului, 8, Ap. 16
1900 Timisoara (Romania)
E-mail: ggluhovschi@yahoo.com - cbob@mail.dnttm.ro

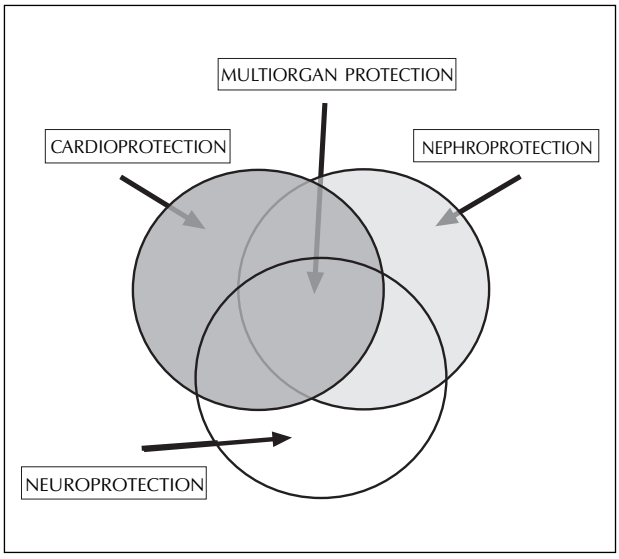

Fig. 1.—The concept of multiorganprotection with reference to kidney, heart, brain.

Stepwise it has been observed that an organism with chronic disease can benefit from nephroprotection in case of renal injury, cardioprotection, when the heart is affected, and neuroprotection when we deal with neurological injuries. The most typical example is given by the diabetic patient, who suffers from nephropathy, which needs nephroprotection, ischaemic heart disease, which is approached through cardioprotection, as well as atherosclerotic cerebral lesions, which suggest the need for neuroprotection.

Like the definition of multiple organ sufferance in pathology, which includes the pathology of an organism with multiple organ injuries, the problem of multi-organ protection has been raised. This latter term has originally been used in multi-organ failure, an acute injury of multiple organs that benefits from

a complex therapy, which has the objective of finding solutions to the numerous problems that occur in this disease. The term of multi-organ protection in these situations is beginning to be used.

Although chronic diseases lead to multiple organ injury, they are not defined as multiple organ sufferance, and the protection measures are approaching every organ as a part, such as: nephroprotection, cardioprotection, neuroprotection.

The objective of this article is to analyze the prerequisites for defining multi-organ protection, and the advantages that derive from here.

The three organs: kidney, brain and heart can be affected concomitantly under many circumstances. The kidney, heart and brain have a rich vascularization. The injury of the cardiovascular system can be produced by common pathological processes in the course of hypertension, vasculitis, as well as by vascular risk factors, which through the lesions they produce, have direct effects against the cardiovascular system.

The kidney, heart and brain have a rich blood supply. High blood pressure afflicts the kidney, heart and brain concomitantly causing vascular lesions with resultant pathological and functional consequences.

Patients with essential hypertension could also show plurivascular arterial lesions (cardiac, renal and cerebral) due to atherosclerotic processes.

Lipid metabolism disturbances that are involved in atherogenesis are common to the vessel compartment of the three organs.

Carbohydrate metabolism disturbances are common to all three organs during the course of diabetes.

Other metabolic disturbances, disorders of acid-base balance, as well as oxidative stress can affect the three organs, as well as the body as a whole.

Sometimes the simultaneous deposition of some pathological components can afflict many organs, including the kidney and the heart, as can be seen in amyloidosis.

The hypoxia that accompanies anaemia can affect the brain and the heart simultaneously with direct consequences on their function.

Increased salt intake is involved in blood pressure control bearing on the vessel compartment as a whole, as do hyperhomocysteinaemia, coagulation abnormalities and smoking.

Chronic inflammatory processes are encountered in many disorders. They consist of the release of various cytokines and inflammatory proteins whose actions will influence the target organs. Sometimes the inflammatory process in one of the three organs leads to the response of the entire body, as is the case with the kidney during renal failure.

Uraemia is considered a microinflammatory state. Zimmermann y cols. consider that inflammation enhances cardiovascular risk and mortality in haemodialysis patients[2].

The protective measures which attempt to address these abnormalities will be common to the kidney, heart, and brain, thus producing multi-organ protection. They include:

- blood pressure control, ACE inhibitors playing a major role,
- lipid metabolism corrections,
- carbohydrate metabolism control,
- reduced salt intake,
- smoking cessation,
- low-dose aspirin.

Besides the above-mentioned factors, the three organs will be subjected to other potential risk factors, which will also need to be addressed during multi-organ protection: metabolic disturbances, anaemia and oxidative stress etc.

Apart from these common measures responsible for multi-organ protection, other specific therapies will be aimed at depending on the circumstances. They concern the kidney, heart and brain during nephro-, cardio- and neuroprotection.

In a patient with heart disease, arrhythmias will determine the necessity for specific therapy in addition to the common multi-organ protective measures. The correction of rhythm abnormalities will improve cardiac activity and, consequently, blood flow in the circulation.

Proteinuria control is part of the nephroprotective measures. It diminishes hypoproteinaemia and directly contributes to correction of lipid profile abnormalities, which occur during the nephrotic syndrome. Thus, it will exert a beneficial effect on the blood vessels, with main implications for the kidney, heart and brain.

It seems that some organ-specific measures will thus influence other organs as well.

Other measures, which target the nervous system selectively, such as treatment of degenerative nervous disease, have limited effect on other systems.

Multi-organ protection should comprise measures that address the three organs simultaneously, as well as those specific to one organ, as each body part can suffer from 2 insults, one specific to it, and one common to the other two. Very often the preponderant involvement of an organ requires the adaptation of the protection measures.

Factors that pertain to the kidney are as follows:

- proteinuria;
- insufficient eritropoetin secretion- an important contributor to anaemia, with consequences for other organs;

– retention of nitrogen products with secondary inflammation and toxic effects;
– phosphorous and calcium metabolism disorders; parathormone is a putative uraemic toxin;
– disturbances of the intrarenal circulation.

Factors specific to the heart:

– arrhythmias - atrial fibrillation can reduce cardiac output by 20%;
– myocarditis.

Factors specific to the brain, exerting an effect through the following:

– neurotransmitters;
– glutamate flow;
– neurotrophic growth factors: FGFb, GDNF, VEGF.

Organ protection measures will address all factors which retard the progression of the disease. Protection measures that act on the cellular level define cytoprotection. As an example erythropoetin has a cytoprotective effect on the central nervous system, as well as on the kidney[3]. Other protection measures act at the molecular level. Some of them address the organ level, belonging to organ protection, while most of them affect many organs, belonging to multi-organ protection.

Multi-organ protection and organ protection can be acute or chronic.

As an example, multi-organ system failure requires rapid and extensive multi-organ protection. A single organ affection can also require acute protection.

Acute cardioprotection is applied in acute coronary syndromes, during cardiac surgery and cardiac arrest.

Acute renal failure prompts the need for acute nephroprotection. Its etiology could extend therapy from acute nephroprotection to acute multi-organ protection.

Multi-organ protection could similarly be applied to chronic disorders of the kidney, heart, brain.

We will remark that organ protection utilizes common measures with other organs, that which define

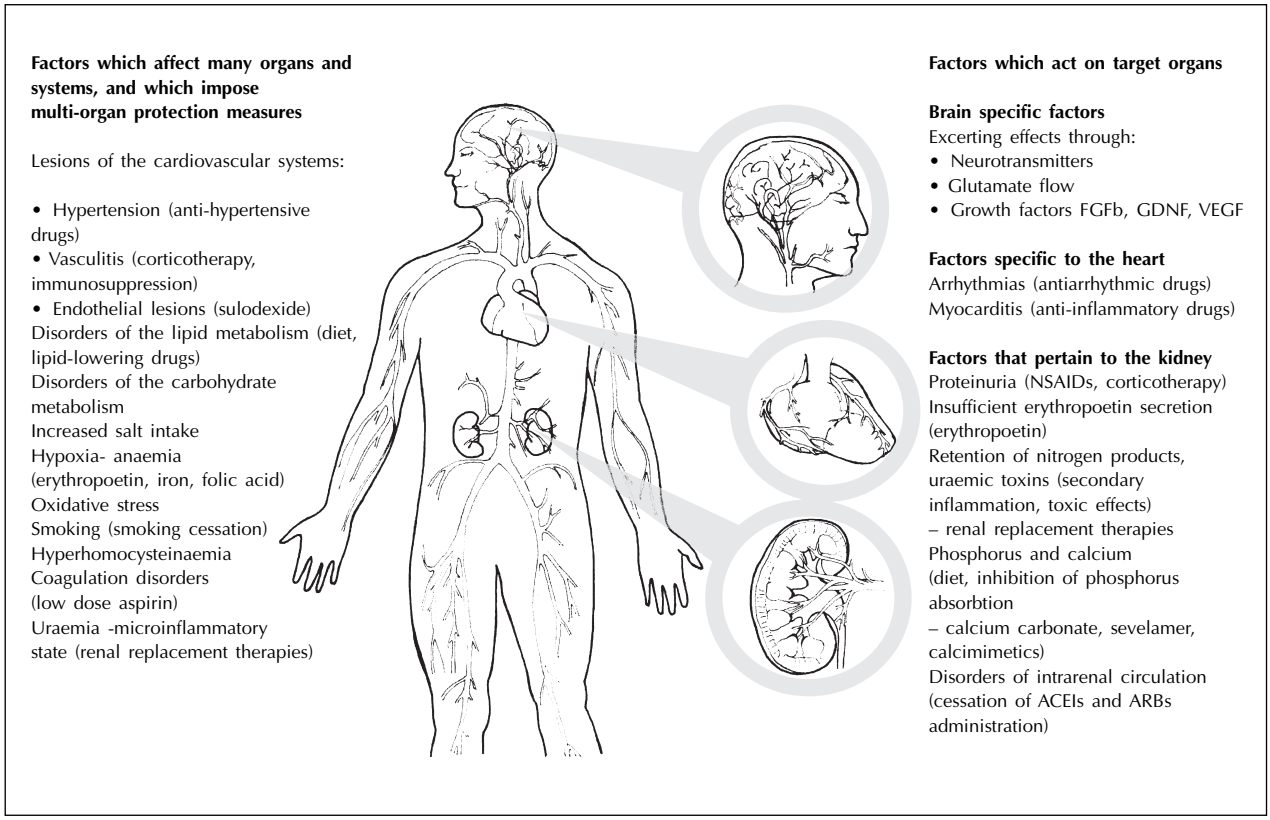

Fig. 2.

Table I. Classification of organ protection

Multi-organ protection: acute chronic	Main organ protection
(Nephroprotection + Cardioprotection + Neuroprotection)	Nephroprotection: acute chronic Cardioprotection: acute chronic Neuroprotection: acute chronic
Cytoprotection Organ protection at the molecular levels	

multi-organ protection. At the same time there are measures that address only to the protection of one organ.

In order to delineate multi-organ protection, we will briefly analyze nephro-, cardio, and neuroprotection, outlining the common, as well as the specific factors of progression.

NEUROPROTECTION FROM THE STANDPOINT OF MULTI-ORGAN PROTECTION

According to the Jain Biotech Report, an agent could be considered neuroprotective, if it prevents

Table II. Measures that combine those addressed to the nervous system with those addressed to other tissues

Drug	Action	Authors	Observations
Anti-hypertensive drugs	Correct cerebral blood supply		Regulate the circulation in different organs including brain, heart and kidneys
Perindopril	A net amelioration of distensibility and compliance of the carotid arteries Lowering of systolic blood pressure	London y cols.,[6]	In hypertensive and renal failure patients treated with perindipril
Perindopril	Cerebroprotective effect	Progress study	In essential hypertension and in normotensive subjects with high risk of stroke (reduce with 20% the risk of stroke)
Trandolapril Quinalapril	Protective effect on stroke in spontaneously hypertensive rats	Richer y cols.[7] Vacher y cols.[8]	Protective effect increases the compliance of coronary vessels
Lipid-lowering therapy (statins, non-statin drugs, diet)	Relative risk reduction of stroke by lipid-lowering therapy by 17% Decrease in the effect of cholesterol Effect on the progression and stability of the plaque in intracranial atherosclerosis	Corvol y cols.[9] Crouse y cols.[10]	Metanalysis- studying the literature between 1996-2001, 38 trials, 83,161 patients, mean follow-up 4.7 years Reduction of incidence of coronary heart disease
– Erythropoetin – Drugs that block free radicals – NO synthesis activation – membrane stabilizers – medication that blocks cellular adhesion – drugs that block proteic destructions – decrease in Na and K flux – anti-inflammatory drugs, especially COX2 inhibitors	Cytoprotective and antiapoptotic effect Act at the cellular level	Vesey y cols.[11] Isenman and Schultz[5] Digicayloglu y cols.[12]	In experimental brain injury and cisplatin induced nephrotoxicity
Neurotrophic factors Gene therapy Inhibition of apoptosis	Neurotrophic action Action at the gene level Neuroprotective action	Jain Pharma Biotech report[4] Robertson y cols.[13]	
Measures targeted against endogenous and exogenous toxic effects	Their toxic effects act not only against the nervous system but also against other organs		Uraemic toxins -typical example
Calcium channel blockers (nimodipin) Calcium channel modulators (flunarisine) Calcium channel chelators	Neuroprotective effect	Isenman and Schultz[5]	

neuronal death by the interference of any one of the following processes: lesion of the central nervous system, ischaemia of an artery or hypoxia of any cause, including the protection against neurodegeneration and neurotoxins[4].

Neuroprotection is targeted to:

– cerebral blood supply;
– traumatic injuries of brain and spinal cord;
– neurodegeneration
– endogenous and exogenous metabolic toxic effects (neurotoxins).

Acute neuroprotection is directed towards acute cerebral vascular events, including stroke. Neuroprotection could be applied to chronic vascular lesions, attributable to diffuse cerebral atherosclerosis or atheromatous plaques, located in different territories, more often in the carotid arteries. These measures are part of chronic neuroprotection.

Ischaemic vascular lesions can lead to thrombosis. Embolic lesions of cardiac origin are sometimes present.

Neuroprotection will address factors specific to the cerebral blood supply, and also measures common to other circulatory territories, such as coronary arteries and renal vessels.

An important role is attributed to blood pressure-lowering therapy. Hypertension leads to cerebral lesions through vessel rupture during acute events or through chronic injuries.

The concomitant use of therapies addressed to vascular processes related to hypertension, such as lipid-lowering agents and smoking cessation, is included in general multi-organ protection measures.

According to Isenman and Schultz, an important neuroprotective role is exerted by the effect on cerebral blood vessels by some calcium channel acting agents: calcium channel blockers (nimodipin), calcium channel modulators (flunarisine) and calcium channel chelators[5].

Other neuroprotection measures mentioned by Isenman and Schultz, affecting processes which take place in cerebral tissues, are:

a) measures which combine with processes in the nervous system and in other tissues, and which belong to multi-organ protection;
b) protection measures specific to the nervous system, belonging to neuroprotection.

b) Neuroprotection has a component that addresses strictly the nervous system, in neurodegenerative processes. The main diseases with neurodegenerative components are multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer disease. These diseases will benefit from specific neuroprotection measures. An important role is played by multiglial activity control[15].

To sum up there are:

– Neuroprotection measures with an effect on other organs too, and which belong to multi-organ protection.
– Specific neuroprotection measures which act on the nervous system.

If protection measures targeted against cardiovascular diseases have proved their efficacy in cerebral lesions as well, clinical trials in neuroprotection could not demonstrate a positive effect in neurodegenerative conditions including surgery, epilepsy, traumatic brain and spinal cord injury, Alzheimer disease, Parkinson's disease, amyotrophic lateral sclerosis and some psychiatric diseases[16].

THE ROLE PLAYED BY NEPHROPROTECTION IN MULTI-ORGAN PROTECTION

Nephroprotection is composed of measures which block the progressive evolution of renal diseases.

Table III. Specific neuroprotection measures

Drug	Action	Authors
Specific GABA receptor antagonists Serotonin antagonists Opioid antagonists	Decrease the glutamate flux which refers to neurotransmiters	Isenman and Schultz[5]
Growth factors FGFbeta and GDNF	Compensate the lack of neurotrophins	Isenman and Schultz[5]
Vascular endothelial factor (VEGF)	Promotes neurogenesis and cerebral angiogenesis. Therapeutical potential in ischaemic disorders	Sun y cols.[14]

Therefore the knowledge of progression mechanisms of renal diseases and the evaluation of the main therapies is necessary. These are presented in the article «Renoprotection: one or many therapies», published in Kidney Int 2001, 59 p: 1211-1226 by Hebert et al. In the following we will briefly present the measures shown in the afore mentioned paper, by maintaining the large frame of multi-organ protection- renal, cardiac and neural, respectively[17].

As mentioned before, nephroprotection measures are targeted against progression mechanisms of renal diseases. Some of these mechanisms act not only against the kidney, but also in other systems, such as the vascular one. This complex protection is included in the multi-organ protection.

Table IV presents the main mechanisms of the progression of renal diseases, which need measures of nephroprotection.

Progression mechanisms of chronic kidney diseases require cellular and molecular mediators. They follow a common pathway, a fact which needs treatment strategies addressed to it, in order to stop the evolution of the disease. The most commonly utilized treatments are: ACEIs, NSAIDs, mycophenolate mofetil[44, 45]. Fishbane y cols. have demonstrated the cytoprotective effect of darbepoetin/ epoetin alfa using pig tubular and mouse mesangial cell cultures[3].

CARDIOPROTECTION AND ITS RELATION TO NEPHROPROTECTION AND NEUROPROTECTION

The heart is subjected to a large number of aggressions with the participation of multiple risk factors. Protection against them is referred to as cardioprotection. It may refer to acute events, being referred to as acute cardioprotection, or to chronic diseases, a fact which defines chronic cardioprotection.

We shall first have a look at chronic cardioprotection, as it addresses through the measures taken, other organs too, such as the kidney and the brain. They are also nephroprotection and cardioprotection measures. This is due to some common factors acting upon the three organs, which implies taking common protective measures.

The measures of acute cardioprotection are much more specific to the heart, the other organs, such as kidney and the brain, benefiting indirectly from the cardiac protective effect.

According to Kannel, based on the Framingham study, the most important risk factors in coronary disease are:

- Hypertension, dislipidaemia by increase of LDL cholesterol and a low level of HDL cholesterol, smoking, diabetes, advanced age. Other high risk factors for cardiovascular disease are represented by: physical inactivity, obesity, premature cardiac disease, family history, hypertriglyceridaemia, lipidic profile including low and dense LDL, increase in homocysteine level, abnormal coagulation factors[46].
- The metabolic syndrome is a high risk factor for heart disease, irrespective of the cholesterol leve[47, 48].

Other risk factors for the development of coronary disease are represented by left ventricular hypertrophy on electrocardiography[49].

According to Wilson, emerging risk factors for chronic heart disease are: C reactive protein, microalbuminuria, vitamins and homocysteine, plasma fibrinogen, and coronary artery calcification[49].

The main affection related to the cardiovascular apparatus is represented by atherosclerosis, a diffuse process which affects the heart, the kidneys, the brain and the limbs. The presence of an atherosclerotic lesion in an area raises the suspicion of its existence in other vascular areas, too. Thus, the Framingham study has revealed the fact that those who had an initial myocardial attack had history of stroke in 5-10% of the cases.

Analyzing the risk factors involved in cardiac lesions, we see that they are mostly risk factors for the entire cardiovascular system, being able to produce lesions in other organs too, such as the brain, the kidneys, and the limbs.

Therefore, the cardioprotection factors addressing the heart are, to a certain extent, common to the other organs such as the kidney, the brain, and to the entire vascular system.

Ranking first is hypotensive medication, primarily ACEIs or ATII receptor blockers, followed by lipid lowering medication, correction of carbohydrate metabolism disturbances, cessation of smoking, etc.

Cardioprotection means not only prevention of lesions to coronary vessels, but it is also prevention of myocyte affection.

The myocardium subjected to chronic activity undergoes processes of reshaping, a phenomenon referred to as myocardial remodelling. It includes myocitary hypertrophy, contractile dysfunction, myocyte apoptosis and matrix remodelling. If the process is not stopped, the lesions will evolve towards myocardial failure[50].

Left ventricular hypertrophy is mainly under the influence of angiotensin[11] which acts as a vasoconstrictor as well as a growth factor promoter: ACEIs

Table IV. Mechanisms of renal diseases and measures of nephroprotection

Factors	Mode of action	Consequences	Affected org. K	H	B	Protection measures	Studies
AHT	Impact on renal circulation Increase of filtration pressure	– Increse in albuminuria (proteinuria) – Benign or malignant nephrosclerosis	+	+	+	BP lowering medication	Taal MV y cols.[18] Brenner BM[19], Remuzzi G and Bertani T[20]
AII Excess	– Direct action on mesangial cells and tubules – Direct action on vessels or through RAS	Influences the vascular system directly and also through aldosterone Local activation of RAS	+	+	+	ACEIs ARBs ACEIs + ARBs ACEIs + ARBs (interfere with the local RAS)	Taal y cols.[18], Brenner[19], Kuczera y cols.[21], Taylor AA[22]
Aldosterone excess	Aldosterone-independent mediator of renal remodelling	– Myocardial fibrosis – Renal fibrosis – Progression of hypertensive renal vascular disease and diabetic nephropathy	+	+		Anti-aldosterone drugs +/- RAS blockage through ACEIs	Brown y cols.[23] Hollenberg y cols.[24]
Excess of NaCl	Takes part in pathogenic mechanisms of hypertension	AHT	+	+	+	Diuretics Natrium restriction	Heeg y cols.[25], Bakris and Smith[26]
Water overload	Increased urinary volume determines an accelerated renal disease progression through increase of intratubular pressure	Associated to NaCl excess influences BP	+	+	+	Appropriate water intake control	Hebert y cols.[17], Ozkaya y cols.[27]
Lipid metabolism disorders	Contribute to atherosclerosis	Primary vascular lesions on renal, coronary and cerebral circulation	+	+	+	Diet, Lipid lowering drugs: statins and fibrates with antiproteinuric effect	Wanner C and Quaschning T[28], Vogt[29], Kasiske y cols.[30]
Proteinuria	– Hypoproteinaemia – Increased serum lipid production with secondary dislipidaemia – Overload of proximal tubular epithelial cells with complement, inflammaroty lipoproteins, iron species	Atherosclerosis High risk of progressive renal function loss Cardiovascular morbidity and mortality	+	+	+	RAS blockers Statins Selective NSAIDs Sulodexide	Hebert[17], Vogt[29], Gluhovschi y cols.[60], Gambaro y cols.[59]
Anaemia		Leads to progression of renal disease	+	+	+	Iron, folic acid, erythropoietin (reduces left ventricular mass, ameliorates cardiac ischaemia, improves outcomes in CRF)	Bagnis y cols.[31], Fine y cols.[32], Bahlmann y cols.[33]
Sympathetic overactivity	Renal damage-chemo- and baroreceptors are activated	Increase in cathecolamine turnover in hypothalamus and increase in efferent sympathetic nerve traffic	+	+		Alfa-beta blockers (carvedilol) improved the efferent sympathetic nerve traffic survival and ejection fraction in dialysis patients with congestive heart failure	Dikow y cols.[34], Cice y cols.[35], Converse y cols.[36]

➤ ➤ ➤

Table IV. Mechanisms of renal diseases and measures of nephroprotection *(cont.)*

Factors	Mode of action	Consequences	Affected org. K	H	B	Protection measures	Studies
Hyperglucaemia in diabetes mellitus	Metabolic disorders lead to lesions of kidney heart and brain Lipid metabolism will participate in atherosclerosis which affects blood vessels	Disturbance of matrix due to protein glycosilation Microangiopathy Macroangiopathy Fibrosis and sclerosis glomerulosclerosis	+	+	+	Correction of hyperglycaemia Correction of associated metabolic disorders	Parving y cols.[37]
Phosphorus and Calcium balance disorders	Hyperphosphataemia with secondary hyperparathyroidism Increased levels of parathormone which is considered uraemic toxin	Calcium deposits in vessels Parathormone leads to cardiac fibroblasts activation	+	+		Diet, phosphorus and calcium balance disorders correction: vitamin D, sevelamer, low protein diet	Aman y cols.[38]
Smoking	Vascular risk factor	In diabetic nephropathy, IgA nephropathy, Polycystic kidney- is an independent risk factor	+	+	+		Orth y cols.[39]
Plasma homocyteine			+	+		Folic acid	Samuelson y cols.[40] Benett-Richards y cols.[41]
Increase of procoagulants	Vascular risk factor		+	+	+		Hebert y cols.[17]
Decrease of oestrogens	Vascular risk factor		+	+	+		
Insulin resistance	Cardiovascular risk factor Increase of C peptide Increase of plasmatic insulin	In overweight patients focal segmental glomerulosclerosis	+	+		Weight loss	Hebert y cols.[17]
Hypokalaemia		Renal lesions: progressive renal fibrosis Negative effect on heart: arrhythmias	+	+		Administration of potassium	
NSAIDs	Utilized in order to reduce proteinuria in renal diseases, have an effect on the prostaglandin system	Can produce glomerular and interstitial lesions	+	+		Cessation of treatment	Cramer and Bock[42], Mukherjef y cols.[43]

can inhibit the All action and slow the progression of vascular and myocardial remodelling. A cardioprotective measure is performed through this.

The hypertrophy process is also under the influence of other factors, such as cathecolamines, neurohormones, endothelin, aldosterone, TNF alpha, specific oxygen species. These factors, in their turn, require cardioprotective measures.

Besides activation of the renin- angiotensin- aldosterone system, neurohormonal stimulation is also achieved by the activation of the sympathetic nervous system. The activation of the sympathetic nervous system determines functional and structural changes which will influence the cardiovascular disease. Complex studies have demonstrated that beta-blockers significantly lower morbidity and the death rate of patients with cardiovascular diseases.

Beta-blockers and statins have additive anti-atherosclerotic effect, acting in various ways. Also, RAS blockade associated with statins has the same effect[29].

The Heart Protection Study conducted on 20,000 persons with cardiovascular event risk has revealed, in a group of persons, that after 5 years simvastatin reduced heart attacks, the first stroke and the need for revascularization by 24%[51].

In patients having undergone beta-blockers and statins therapy simultaneously, it has been shown that the favourable effect of these associations is more significant. Coronary heart protection needs therapeutic measures addressing hypertension, lipid metabolism disturbances, arterial thrombosis, arrhythmias etc.

Schwartzkopf y cols. underline in essential AHT patients the regression of left ventricle hypertrophy and of myocardial fibrosis, the latter being attributed to the direct and long-term effects of perindopril upon the collagen metabolism at myocardial level[52].

Endothelial injury in situations that affect the cardiovascular system determine important changes

Endothelial injuries are produced during the affection of the cardiovascular system, due to numerous factors, such as AHT, angiotensin II, endothelin, lipids, smoking, increase of procoagulants etc.

H von Bayer y cols. mention the Virchow triad, that contains the following: arterial wall anomalies, blood components changes and haemodynamic alterations[53].

These phenomena are associated with micro inflammatory processes, especially in the atheromatous plaque.

Endothelin receptors and AT I receptors participate in this process as well[54, 55].

Endothelial dysfunction with NO and CGMP deficiency play an important role in the pathogenesis of essential AHT and of AHT secondary to CRF, even in the first stages[56].

CRF is regarded as a vasculopathic state[57].

Microalbuminuria can occur, according to Schiffrin, in parallel with the development of endothelial dysfunction, as hypertension progresses[58].

Among drugs which act on glycosaminoglycans, with a role in reduction of their alteration, Sulodexide has been evidenced, its role being proved in the decline of proteinuria in diabetic nephropathy[59], but also other nephropathies[60], thus developing a nephroprotective activity.

Acute cardioprotection relates primarily to myocardic acute ischaemia, cardiac surgery, and cardiac arrest.

A metabolic and pharmacological endogene cardioprotection; is described within endogene cardioprotection, the main role is played by the stimulation of the adenosinic receptor which activates C phospholipase with endogene protector release, favouring nitric oxid synthesis.

Metabolic cardioprotection is based on insulin and glucose infusion. Pharmacological cardioprotection benefits from beta-blockers, calcium channel blockers, angiotensin- conversion enzyme inhibitors, trimetazidine as cellular anti-ischaemic agenel.

Acute cardioprotection measures can also act during acute multi-organ suffering, the kidney obviously benefiting from such measures.

Thus, acute cardioprotection measures can also have nephroprotective effect. For example, their application in acute myocardial infarction, ensuring an adequate blood pressure for renal perfusion, can prevent the onset of renal ischaernic lesions and of ARF At the same time, in a patient with ischaemic atherosclerotic lesions, including cerebral ones, they can prevent a cerebral vascular event.

Cardioprotection and chronic renal diseases

Patients with chronic kidney diseases with cardiovascular involvement benefit from cardioprotective measures as well.

The chance of a patient with CKD to develop ,end stage renal failure is lower then the chance to die from a cardiovascular complication[62]. Data from the Hypertension Detection and Follow-up Program (HDFP) involving nearly 11,000 individuals show that 58 percent of deaths in participants with baseline serum creatinine greater than or equal to 1.7 mg/dL were secondary to cardiovascular causes[63].

As the great majority of renal diseases show the affection of cardiovascular system especially in the renal insufficiency stage, cardioprotection measures are necessary, as well as nephroprotection measures. Partly these measures overlap. Many of the risk factors for kidney disease and cardiovascular disease are similar[64]. Dikov has analysed the cardiovascular risk factors in renal failure and found that there are not only classical risk factors: hypertension, hypervolaemia, dislipidaemia, sympathetic hyperreactivity, hyperhomocysteinaemia, but also nonclassical risk factors such as anaemia, hyperphosphataemia, hyperparathyroidism and microinflammation. Most of the risk factors superpose on the cardiovascular ones, cardioprotection measures being similar to those utilized in nephroprotection[34].

London y cols. have demonstrated by treatment with perindopril administered to a group of CRF patients of various etiologies, an improvement of diastolic performance of the left ventricle concomitantly with a significant reduction of the left ventricle and

decrease in septal hypertrophy. These results have been obtained independently of the AHT control[6] London attributes the above- mentioned results to the blocking of the circulating angiotensin renin system and to that of the local or cardiac one, respectively. The blocking of the local system would prevent the action of ATII from stimulating myocytary hypertrophy at myocardial level and that of aldosterone from initiating myocardial fibrosis[6].

Blockers, thrombolysis, aspirin and statins can be considered as cardioprotective drugs[65]. Anaemia is a factor implied in cardiac hypertrophy, frequently encountered in uraemic patients[66].

Rabelink considers that cardiovascular mortality in patients with end stage renal failure is probably among the highest in medicine[67]. The atherosclerosis begins in early stages of chronic renal disease and worsens in haemodialysis patients[68]. According to Jungers y cols. cardioprotection is an essential component of the treatment of chronic renal failure in the predialytic stage[69]. The prevention of left ventricular hypertension by an appropriate control of BP by utilizing ACEIs, anaemia control and volaemic control, reduce the risk for cardiovascular disease before and after renal transplantation[68]. Chronic inflammation as evidenced by increased levels of C-reactive protein (CRP), predicts all causes of cardiovascular mortality in short-term studies[70].

Locatelli y cols. showed that cardiovascular diseases have a main role in the morbidity and mortality of patients with renal replacement therapy- 50% of the causes of death[66].

Cardioprotection has more recently emerged as another fundamental goal in the treatment of CRF patients in the predialysis phase[71]. It should be performed in patients with renal replacement therapies as well.

Cardioprotection and cerebral diseases

Many studies are targeted against concomitant cardiac and cerebral lesions with common protection measures.

The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial has evaluated the protective role of Norvasc in the progression of coronary and carotid lesions[72].

Losartan International for End Point Reduction in Hypertension Study (LIFE) reports a substantial decrease of cardiac events and stroke in patients treated with losartan[73].

Mannami y cols. presented in the Suita Study (a populational study performed on 1,896 males and 2,102 females) a strong and significant relationship between aggregation of major coronary risk factors and the acceleration of carotid atherosclerosis in the general population of a Japonese City[74].

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) performed on 33,357 participants has highlighted the role of chronic heart disease, stroke, angina treated in out-patients, cardiac failure and peripheric vascular disease[75].

Sever y cols., reported in a randomized multicentric study the prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower than average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial (Lipid Lowering Arm ASCOTLLA)[76].

It can be seen that the cardioprotection measures addressing the vascular system in general, ensure, besides the protection of the heart (cardioprotection), that one of the kidney (nephroprotection) and of the nervous system (neuroprotection), practically achieving multi-organ protection measures.

SOME DATA CONCERNING THE CONCOMITANT RENAL, CARDIAC AND CEREBRAL INJURY

As we mentioned earlier in a brief presentation of nephroprotection, neuroprotection and cardioprotection, the fact that the affection of one organ in general is not an isolated phenomenon, but it also is associated with the affection of other organs and systems as well. We want to re-discuss the main factors through which the kidney intervenes in the production of cardiac and cerebral lesions. Renal affection often determines the subsequent onset of cardiac and of neurological involvement.

In patients with normal renal function cardiac and cerebral lesions are due to vascular injuries of the heart and the brain, lesions that follow hypertension and/or metabolic disturbances. A great majority of patients with glomerular disease show hypertension, often severe and associated with cardiac and/or cerebral lesions.

Renal vascular lesions could reach obstruction of over 75% with an aggravation of initial hypertension, due to renal artery stenosis, which can lead to cerebral and cardiac lesions, as well as renal lesions on the non-stenosed kidney benign or malignant nephroangiosclerosis.

Lipid metabolism disturbances and coagulation disorders that occur in the nephrotic syndrome could lead to atherosclerotic lesions, to vessel injuries, such as coronary and cerebral ones. Renal vascular thrombosis is not an exception.

At the same time patients with renal failure show lipid metabolism disturbances, which together with

those of phosphorus and calcium balance could produce vascular lesions, both cardiac and cerebral. The renal vessels are not protected against these disturbances. Albuminuria is considered by Jones as a potential indicator of renal dysfunction, being associated with a risk of renal and cardiovascular morbidity in patients with hypertension[77].

After the presentation of data concerning nephroprotection, cardioprotection and neuroprotection we consider to review data concerning multiple organ affection, with reference to concomitant lesions of kidney, heart and brain, with some examples from the literature and studies performed by us.

Organ injury- renal, cardiac or cerebral- together with the therapeutic measures used to treat them, have been the target of numerous studies, some of them multicentric trials. Generally, they refer to the incidence of organ affection and the effect of treatment. Others, however, highlight the affection of two or, rarely, three organs, most frequently related to cardiovascular injury.

The HOPE study (Heart Outcomes Prevention Evaluation study) has demonstrated the effect of ramipril (angiotensin-converting enzyme inhibitor) compared to placebo in patients at high risk of cardiovascular events. Ramipril reduced the rates of MI, stroke and cardiovascular death[78].

The MICRO-HOPE study (Microalbuminuria, Cardiovascular and Renal Outcomes in Heart Outcomes Prevention Evaluation) evaluates the renal and cardiovascular effects of an ACE inhibitor and microvascular outcomes in patients with diabetes mellitus.

Ramipril reduced the risk of a combined microvascular outcome (overt nephropathy, dialysis or retinal laser therapy)[79].

The concomitant injury of more than one organ related to renal affections has been signaled in two of our studies.

The first of them was performed on a group of 547 patients with chronic renal failure in the predialytic phase, admitted to the Nephrology Department, Timisoara, during the period 1991-2002; 191 of them have been followed up for a mean period of 19.38 ± 23.55 months.

We observed that 458 patients (83.72%) had hypertension, 288 of them had hypertensive cardiopathy (56.65%) and 8 cases stroke. This study highlighted in a group of patients with chronic renal failure, the concomitant affection of three important organs: heart, kidney and brain.

The implication of the vascular factor through hypertension has been demonstrated by the follow up of patients with CRF with hypertension compared to those without hypertension. Despite the antihypertensive treatment, the decline of renal function could not be stopped.

Hypertension is a proved risk factor. Patients with CRF and hypertension have a degradation rate of renal function (delta creatinine clearance) higher than patients without hypertension: 21.97 ± 18.68 ml/min as compared to 15.6 ± 10.5 ml/min ($P < 0,05$). The association of risk factors (proteinuria, hypercholesterolemia) for CRF progression generated degradation of the renal function significantly higher than the isolated risk factors[80].

Our study has underlined the fact that, in order to prevent renal, cardiac and cerebral lesions, some measures of nephroprotection, cardioprotection and neuroprotection are necessary. The common protection of the three organs is defined as multi-organ protection. These measures could influence proteinuria.

In a prospective study, we followed up the reno-, cardio- and cerebrovascular protective effects of perindopril in patients with primary chronic glomerulonephritis.

A 12 month-study with ACEI perindopril was conducted on a group of 21 patients with primary chronic glomerulonephritis with normal renal function or mild renal impairment admitted to the Dept. of Nephrology, Timisoara.

Cardiovascular and cerebrovascular effects of perindopril were monitored by ultrasound (left ventricular hypertrophy, left ventricular mass, E/A ratio, ejection fraction, isovolumic relaxation time), Doppler ultrasonography (pulsatility index- internal carotid artery), transcranial Doppler (PI - middle cerebral artery).

The effect on renal function was monitored through the following parameters: creatinine clearance, serum creatinine, serum Na, serum K, proteinuria.

Perindopril proved to be efficient in lowering blood pressure, correcting left ventricular hypertrophy and mass. The ejection fraction showed little change.

The cerebroprotective effect was proved by the decrease in the pulsatility index (a measure of vascular distensibility and compliance through the ratio systolic velocity- diastolic velocity/ mean velocity).

Although proteinuria declined from 5.57 ± 1.0 to 1.02 ± 0.36 g/24 h, the nephroprotective effect of this drug is less in terms of creatinine clearance, the latter decreasing after 12 months from 81.85 ± 11.27 to 76.42 ± 9.56 ml/min[81].

This study showed that hypertension and proteinuria are not the sole determiners of progression of chronic glomerular diseases. Their correction does

not stop the course of the disease. Multi-organ protection measures have to parallel attempts addressed to the etiology of the disease. Therefore, they should complement and not substitute the specific therapy.

The concomitant renal, cardiac and cerebral affection has been signaled in the literature in both experimental studies and in renal patients.

Richer y cols., using trandolapril, and Vacher et al. using quinapril, have highlighted, in spontaneously hypertensive rats, after ACEI treatment, the regression of fibrinoid necrosis lesions in small intracerebral vessels, an effect noticed in cardiac and renal vessels, too[7,8].

Jungers y cols., have signaled an increased incidence of cardiovascular accidents of atherosclerotic nature as well as of cerebrovascular ones in renal patients in the predialytic stage[69].

General measures of protection could have different effects on different organs

The use of ACEIs or of AII receptor blockers, which have a favorable influence on renal, cerebral and coronary circulation, as well as on the left heart hypertrophy, can have sometimes a negative effect on renal circulation, losing their nephroprotective role.

Sometimes this treatment could have a negative influence on local circulation in chronic renal failure, where vasodilatation produced by ACEIs or AII receptor blockers is predominant in the efferent arteriole, a fact which will lead to the loss of an important regulating mechanism of intrarenal circulation, a factor that maintains the filtration pressure. These mechanisms lead to the occurrence or aggravation of progressive renal failure.

From nephroprotection, cardioprotection, neuroprotection to multi-organ protection means the way from organ protection therapy to a complex multi-organ protection

A lot of risk factors act against an organ, and therefore, the protection is not possible with a single drug. It is preferable to use a drug which acts against several risk factors. ACEIs and ARBs have a general hypotensive effect that has a renal, cardiac and cerebral protective effect. At the same time they have an antiproteinuric effect, through their action on renal circulation.

The effect on one or more risk factors that act simultaneously against more organs makes the use of drugs with concomitant actions against them necessary. Lipid-lowering drugs will have similar actions against coronary and renal sectors.

Because it is not yet possible to have a drug that offers protection against the main risk factors, an association of them has been proposed, such as the concomitant administration of several drugs which will lead to a complex protection therapy.

Law y cols., have proposed a pill that contains aspirin, a statin, three anti- hypertensive drugs (half a dose) and folic acid in order to obtain a cardioprotective effect on cardiovascular diseases[82].

Schieppati and Remuzzi have defined this pill as «superpill» and they have proposed the utilization of several drugs in patients with chronic renal diseases and proteinuria > I g/24 hours[83].

They recommend the initiation of therapy with low doses of ACEIs that could be increased, if necessary, to maximal doses. If target BP of 120/80 mmHg and proteinuria below 0.3 g/24 h have not been achieved it is necessary to add ARBs, at the beginning half the dose, which can be increased gradually.

In order to obtain the control of BP, and to correct hyperkalaemia, it is necessary to add a diuretic. If target BP and proteinuria is still not achieved, it is necessary to add another hypotensive antiproteinuric drug, such as a nondihidropyridine calcium channel blocker.

In patients with low-density lipoprotein (LDL) cholesterol over 100 mg/dI a statin is added, and in patients with diabetes mellitus an appropriate glycaemia control is necessary in order to obtain a target glycosilated Hb of 7.5%.

Brenner has proposed a pill that contains a combination of the following: aspirin, lovastatin and lisinopril. He named it ASTACE (aspirin, statin and ACE inhibitor). According to Brenner, it should have a low cost and universal approach to vital target organ protection[19].

The question is raised: when do we speak about neuroprotection, cardioprotection, nephroprotection and when about multi-organ protection?

We consider that we speak about multi-organ protection when vascular injuries occur which, in hypertension, affect the circulatory system, including the vascularization of the kidney, brain and heart; or on the other hand, in diabetes mellitus, when the three organs are affected through vascular and metabolic mechanisms.

Therefore, if the pathologic process affects only one organ, such as in the degenerative diseases of the nervous system, the measures will be defined by neuroprotection, or nephroprotection, if they act on the kidney, and cardioprotection if the heart is the target organ.

The use of the terms cardioprotection, nephroprotection and neuroprotection is necessary when the

disease of a single organ is evident, while the presence of a common pathological factor can not be found. This is the case of glomerulonephritis, myocarditis or a degenerative disease of the nervous system.

The term multi-organ protection does not exclude that of organ protection: a patient is often treated by means of multi-organ protection and specific organ (kidney, heart, brain) protection, as well.

Multi-organ protection is composed of:

- Firstly, circulation, because through it a multiple-organ protection is obtained, by means of nephroprotection, cardioprotection and neuroprotection, the measures used being identical.
- Secondly, metabolic changes, also common to different organs, the most relevant example being the oxidative stress.

Together with multi-organ protection, every patient needs specific protective measures, according to the localization of the disease.

A great attention is being given to the development of organ protection at the molecular level and to cytoprotection, which represents a perspective in multi-organ protection, as well as in single organ protection.

Multi-organ protection primary deals with common measures addressed to nephroprotection, cardioprotection and neuroprotection, because the kidneys, heart and brain are injured concomitantly. We believe that the term multi-organ protection does not exclude general measures that are targeted against other organs too, besides the above mentioned organs.

The advantages offered are represented by the approach to organ protection according to the facts discussed in this paper:

- The organism is approached as a whole with a specific approach for the affected organ;
- At the same time, the measures are individualized by the approach to the main disease.
- Multicentric studies are recommended to approach the kidney, heart and brain concomitantly and interrelatedly.
- Preferential use of drugs with complex action. Example: ACEIs, ARBs (hypotensive effect, on the intrarenal circulation, on the local RAS, antiproteinuric effect). These drugs combine the effects of multi-organ protection with those of single organ protection (nephroprotection).
- Use of some tablets, that contain many drugs, which address many factors that need protection.

REFERENCES

1. Schömig M, Eisenhardt A, Ritz E: The microinflammatory state of uremia. Blood Purif 18: 327-332, 2000.
2. Zimmermann J, Herrlinger S, Pruy A y cols.: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 55: 648-658, 1999.
3. Fishbane S, Ragolia L, Palaia T, Johnson B, Elzein H, Maesaka JK: Cytoprotection by darbepoetin/ epoetin alfa in pig tubular and mouse mesangial cells. Kidney Int 65: 452-458, 2004.
4. Jain Pharma Biotech-reports. Neuroprotection-drugs, markets and companies. p: 1-28, 2003.
5. Isenmann S, Schulz JB: Neuroprotection. In Brandt T, Dichgans J, Diener HC. (ed). Therapie und Verlauf neurologischer Erkrankungen, Verlag W. Kohlhammer Stuttgart, 2003.
6. London GM, Pannier B, Guerin AP y cols.: Hypertrophy, Aortic Compliance Peripheral Resistance and wave Reflection in End-Stage renal Disease. Comparative effects of ACE Inhibition and Calcium Channel Blockade. Circulation 90: 2786 - 2796, 1994.
7. Richer C, Fornes P, Vacher E, Bruneval P, Giudicelli JP: Trandolapril's Protective Effects in Stroke-Prone spontaneously Hypertensive Rats Persists Long After Treatment Withdrawal. Am J Cardiol 73: 26c-35c, 1994.
8. Vacher E, Fornes P, Domergue V y cols.: Quinapril Prevents Stroke Both During and After the Treatment Period in Stroke from Spontaneously Hypertensive Rats. Am J Hypertens 3: 951-959, 1993.
9. Corvol JC, Bouzamondo A, Sirol M, Hulot JS, Sánchez P, Lechar P: Differential Effects of Lipid-Lowering Therapies on Stroke Prevention: A Meta-analysis of Randomized Trials. Arch Intern Med 163 (6): 669-676, 2003.
10. Crouse JT 3rd, Byington RP, Hien HM, Furberg GD: Reductase inhibitor monotherapy and stroke prevention. Arch Intern Med 157; (12): 1305-1310, 1997.
11. Vesey D, Cheung C, Pat B, Endre Z, Gobe G, Johnson DW: Erythropoetin protects against ischaemic acute renal injury. Nephrol Dial Transplant 19 (2): 348-355, 2004.
12. Digicaylioglu M, Lipton SA: Erythropoetin-mediated neuroprotection involves cross-talk between Jak2 and NF-KB signaling cascades. Nature 412: 641-647, 2001.
13. Robertson GS, Crocker SJ, Nicholson W, Schulz JB: Neuroprotection by the inhibitor of apoptosis Brain pathology 10: 283-292, 2000.
14. Sun Y, Jin K, Me L, Child SJ, Mao XO, Logvinova A, Greenberg DA: VEGF-induced neuroprotection, neurogenesis and angiogenesis after focal cerebral ischernia. J Clin Invest 111 (12): 1843-1851, 2003.
15. Bieber K, Luiten PGM: Mechanism of neurodegeneration and neuroprotection. BCN Annual report 1999, 2000, 2001.
16. Pitkanen A: Clinical trials in neuroprotection. Drugs 6: 200-2002, 2003.
17. Hebert L, Wilmer WA, Falkenhain ME, Ladson-Wofford SE, Nahman Jr NS, Rovin BH: Renoprotection: one or many therapy. Kidney Int 59: 1211-1226, 2001.
18. Taal MW, Brenner RM: Combination ACEI and ARB therapy: additional benefit in renoprotection. Current Opin Nephrol Hypert 11: 377-381, 2002.
19. Brenner BM: The history and future of nephroprotection. Kidney Int 64 (4): 1163, 2003.
20. Remuzzi G, Bertani T: Pathophysiology of progressive nephropathies. N Engl J Med 339 (20: 1448-1456, 1998.
21. Kuczera M, Hilgers KF, Lisson C y cols.: Local angiotensin formation in siblings of uraemic hypertensive and renovascular hypertensive rats. J Hypertens 9: 41-48, 1991.

22. Taylor AA: Is there a place for combining angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists in the treatment of hypertension, renal disease or congestive heart failure. Current Opin Nephrol Hypert 10: 643-648, 2001.
23. Brown NJ, Nakamura A, Ma L y cols.: Aldosterone modulates plasminogen activator inhibitor-I and glomerulosclerosis in vivo. Kidney Int 58: 1219-1227, 2000.
24. Hollenberg NK: Aldosterone in the development and progression of renal injury. Kidney Int 66 (1): 1-10, 2004.
25. Heeg J, Dejong P, Van der Hem GK y cols.: Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. Kidney Int 36: 272-279, 1989.
26. Bakris G, Smith A: Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. Ann Intern Med 125: 201-204, 1996.
27. Ozkaya M, OK E, Cirit M y cols.: Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. Nephrol Dial Transplant 13: 1489-1493, 1998.
28. Wanner C, Quaschning T: Dyslipidaemia and renal disease: pathogenesis and clinical consequences. Current Opin Nephrol Hypert 10: 195, 2001.
29. Vogt L, Laverman GD, Dullaart RPF, Navis G: Lipid management in proteinuric patients: do not overlook the importance of proteinuria reduction. Nephrol Dial Transplant 19 (1): 5-8, 2004.
30. Kasiske BL, O'Donnel MP, Cleary MP, Keane WF: Treatment of hyperlipidemia reduces glomerular injury in obese Zucker rats. Kidney Int 33: 667-672, 1988.
31. Bagnis C, Beaufils H, Jacquiand C y cols.: Erythropoetin enhances recovery after cisplatin-induced acute renal failure in the rat. Nephrol Dial Transplant 16: 932-938, 2001.
32. Fine L, Orphanides C, Norman J: Progressive renal disease The chronic hypoxia hypothesis. Kidney Int 53: s74-s78, 1998.
33. Bahlmann FH, De Groot K, Haller H, Fliser D: Erythropoetin is it more than correcting anemia? Nephrol Dial Transplant 19 (1): 20-22, 2004.
34. Dikow R, Adamczak M, Henríquez DE, Ritz E: Strategies to decrease cardiovascular mortality in patients with endstage renal disease. Kidney Int 2002, 61 (Supl. 80): s5-slO
35. Cice G, Ferrara L, Di Benedetto A y cols.: Dilated cardiomyopathy in dialysis patients-beneficial effects of carvedilol: A double-blind placebo-controlled trial. J Am Coll Cardiol 37: 407-411, 2001.
36. Converse RL, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, Victor RG: Sympathetic overactivity in patients with chronic renal failure. N Engl J Med 327 (27): 1912-1918, 1992.
37. Parving HH, Hovind P, Rossing K, Andersen S: Evolving strategies for renoprotection: diabetic nephropathy. Current Opin Nephrol Hypert 10: 515-522, 2001.
38. Amann K, Ritz E, Wiest G y cols.: A role of parathyroid hormone for the activation of cardiac fibroblasts in uremia. J Am Soc Nephrol 4: 1814-1819, 1994.
39. Orth S, Stockmann A, Conradt C y cols.: Smoking as a risk factor for end-stage renal failure in men with primary renal disease. Kidney Int 54: 926-931, 1998.
40. Samuelsson O, Lee D, Attman PO y cols.: The plasma levels of homocysteine are elevated in moderate renal insufficiency but do not predict the fate of progression. Nephrol Dial Transplant 82: 306-311, 1999.
41. Bennett-Richards K, Kattenhorn M, Donald A y cols.: Does oral folic acid lower total homocysteine levels and improve endothelial function in children with chronic renal failure. Circulation 105: 1810-1815, 2002.
42. Cramer W, Bock K: Symptoms and causes of chronic hipokalaemia nephropathy in man. Clin Nephrol 7: 112, 1077.
43. Mukherjef D, Nissen SE, Topol EJ: Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 286: 954-959, 2001.
44. Taal MW, Brenner BM: Evolving strategies for nephroprotection: non-diabetic chronic renal disease. Current Opin Nephrol Hypert 10: 523-531, 2001.
45. Taal MW, Omer SA, Nadim MK, Mackenizie HS: Cellular and molecular mediators in common pathway mechanisms of chronic renal disease progression. Current Opin Nephrol Hypert 9: 323-331, 2000.
46. Kannel W, arson M: Long-term epidemiologic prediction of coronary disease. The Framingham experience. Cardiology 82: 137-152, 1993.
47. Kannel WB: Cardioprotection: What is it? Who needs it? Am J Manag Care 8 (Supl. 9): 5-12, 2002.
48. Kannel WB: Blood pressure as a cardiovascular risk factor. JAMA 275: 1571-1576, 1996.
49. Wilson PW: Established risk factors and coronary artery disease. The Framingham Study. Am J Hypertens 7, et 2 p: 7s-12s, 1994.
50. Maytin M, Colucci WS: Molecular and cellular mechanisms of myocardial remodeling. J Nucl Cardiol 9: 319-327, 2002.
51. Heart protection study collaborative group MRC/bhf: Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: A randomised placebo-controlled trial. Lancet 360: 7-22, 2002.
52. Schwartzkopff B, Boerriger G, Brehm MU, Koestering M, Mundhenke M: Regression of Interstitial fibrosis by Chronic Treatment with ACE-Inhibitors in Patients with Hypertensive Heart Disease. Circulation 98: 4154, 1998.
53. Von Bayer H, Hopfenmuller W, Riedel E, Affeld K: Atherosclerosis: current concepts of pathophysiology and pharmacological intervention based on trial outcomes. Clinical. Nephrol 60 (Supl.): S31-S48, 2003.
54. Amann K, Tenberger GM, Tenyi M, Simonoviciene A, Koch A, Orth S, Ritz E. Remodeling of resistance arteries in renal failure: effect of endothelin receptor blockade. J Am Soc Nephrol 12: 2040-2050, 2001.
55. Rossi GP, Saccheto A, Rizzoni D, Bova S, Porteri E, Mazzocchi G, Belloni AS, Bahcelioglu M, Nussdorfer GG, Pessina AC: Blockade of angiotensin II type I receptor and not of endothelial receptor prevents hypertension and cardiovascular disease in transgenic (mREN2)27 rats via adrenocortical steroid-independent mechanisms. Arteriosclerosis, thrombosis and vascular 20: 949-964, 2000.
56. Angelini D, Parrini M, Carlini A, Fiorin I, Antonelli A: Endothelin and nitric oxid balance: comparison between essential hypertensive and chronic renal failure patients. Am J Hypert 44 (Supl. 4): A62, 2001.
57. W Luke RG: Chronic renal failure- a vasculopathic state. N Engl J Med 339 (12): 841-843, 1998.
58. Schiffrin EL: Effects of anti hypertensive drugs on vascular remodeling: do they predict outcome in response to antihypertensive therapy. Current Opin Nephrol Hypert 10: 617-624, 2001.
59. Gambaro G, Kinalska I, Pont'uch P, Hertlova M, Olsolsky J, Manitius J, Fedele D, Czekalski S, Perusikova J, Skrka J, Taton J, Grzeszczak W, Crepaldi G: Oral sulodexide reduces albuminuria in microalbuminuric and macroalbuminuric diabetic patients: the Di.N.A.S. randomized trial. J Am Soc Nephrol 13: 1615-1625, 2002.
60. Gluhovschi Gh, Schiller A, Raica M, Petrica L, Trandafirescu V, Velciov S, Bozdog Gh, Patrascu C, Gluhovschi C: The effects of the therapy with natural glycosaminoglycans (Sulodexide) on proteinuria in different types of glomerulonephri-

tis. Facta Univ. Series Medicine and Biology 8, 1, 26-30 Nis, Yugoslavia, 2001.
61. Raja IC: Cardioproteccion: un triunfo de la biomedicina del siglo XX. Rev Cubana Invest Biomed 18 (2): 146-150, 1999.
62. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classfication and Stratification, National Kidney Foundation Inc., 2002.
63. Shulman NB, Ford CE, Hall WD y cols.: Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-Up Program Cooperative Group. Hypertension 13: 180, 1989.
64. Levin A: Anemia and left ventricular hypertrophy in chronic kidney disease populations: A review of the current state of knowledge. Kidney Int 61 (Supl. 80): 535-538, 2002.
65. Adonakoudis G, Youras CS: A pentagon of prevention against coronary heart disease cardioprotection. Hellenic J Cardiol (Athens) 41: 35-50, 2000.
66. Locatelli F, Bommer J, London GM, Martin-Malo A, Wanner C, Yaqoob M, Zoccali C: Cardiovascular disease determinants in chronic renal failure: clinic approach and treatment. Nephrol Dial Transplant 16 (1): 459-468, 2001.
67. Rabelink TJ: Cardiovascular risk in patients with renal disease treating the risk or treating the risk factor? Nephrol Dial Transplant 19 (1): 23-26, 2004.
68. Demeny E: Cardiovascular disease after renal transplantation. Kidney Int 61 (Supl. 80): s78-s84, 2002.
69. Jungers P: Late referral: loss of chance for the patient, loss of money for society. Nephrol Dial Transplant 17: 371-375, 2002.
70. Warmer C, Zimmermann J, Schwedler S, Metyger T: Inflammation and cardiovascular risk in dialysis patients. Kidney Int 61 (Supl. 80): s99-s102, 2002.
71. Jungers P, Oualim Z, Nguyen-Khoa T, Massy Z,London G: La cardioprotection: un composante essentielle du tretment de insuffisance renale chronique au stade predialytique. Nephrologie 24 (2): 79-89, 2003.
72. Byington RP, Miller MF, Herrington D, Riley W, Pitt B, Furberg CD, Hunninghake DB, Mancini GBJ: Rational design and baseline characteristics of the prospective randomized evaluation of the vascular effects of Norvasc trial (PREVENT). Am J Cardiol 80: 1087-1090, 1997.
73. Dalhof B, Devereux RR, Kjeldsen SE, Julius S, Beevers G, Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 359: 995-1003, 2002.
74. Mannami T, Baba S, Ogata J: Strong and significant relationship between aggregation of major coronary risk factors and the acceleration of carotid atherosclerosis in the general population of a Japanese city: the Suita study. Arch Intern Med 160 (15): 2297-2303, 2000.
75. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. The Antihypertensive and Lipid-Lowering Treatment to renal Prevent Heart Attack Trial (ALLHAT). JAMA 288: 2981-2997, 2002.
76. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, Mc Innes GT, Mehisen J, Nieminen M, O'Brien E, Ostergren J: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower than average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes. Trial Lipid Lowering Arm (ASCOT LLP) a multicentric randomised controlled Trial. Lancet 361 (9364): 1149-1158, 2003.
77. Jones CA: Hypertension and renal dysfunction: NHANES III. J Am Soc Nephrol 14: s71-s75, 2003.
78. The Hope (Heart Outcomes Prevention Evaluation). Lancet 355: 253-259, 2000.
79. Effect of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE sub-study. Lancet 355: 253-259, 2000.
80. Gluhovschi G, Bozdog G, Schiller A, Trandafirescu V, Petrica L, Velciov S, Gluhovschi C, Bob F, Cràiniceanu M: Arterial hypertension in patients with chronic renal failure in the predialytic phase. Its role as risk factor beside proteinuria and lipid metabolism perturbation. XIIIth European meeting on hypertension. Milan (Italy) June 13/17. Abstract 300 k, s: 293, 2003.
81. Petrica L, Petrica M, Bob F, Gluhovschi Gh, Turcan M, Ivan V, Brdnzan L, Schiller A, Velciov S, Trandafirescu V, Bozdog G, Gluhovschi C, Popescu A, Stanciu A, Sdndesc D: Renal-, cardiac- and cerebroprotective effects of perindopril in patients with primary chronic glomerulonephritis. Nefrología 2003, 8, Nr. 20-21: 71, 2003.
82. Law MR, Wald NJ, Morris JK, Jordan RE: Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ 326: 1427-1435, 2003.
83. Schieppati A, Remuzzi G: The future of renoprotection: Frustration and promises. Kidney Int 64 (6): 1947-1955, 2003.