Cardiovascular continuum established more than 20 years ago proved to be extremely actual and the medical effort is focused on breaking this continuum in any of its part: risk factor control, control of comorbidities, slowing progression of the cardiac disease, developing strategies in order to reduce sudden cardiac death, cardiac failure or major adverse cardiac events (MACE). Chronic kidney disease with or without albuminuria represents a risk factor for cardiovascular mortality and morbidity being potential candidates for aggressive reduction of risk factors. Dialysate patients are exposed to higher risk of ischemic and arrhythmic events. Echocardiographic assessment of these patients is extremely important in risk stratification and treatment strategy in order to improve prognosis. Drugs proved to improve cardiac remodeling, reduce hypertrophy and LV mass and enhance ejection fraction, improved prognosis.

Keywords: chronic kidney disease, hemodialysis, cardiovascular risk

RAS Inhibition in Haemodialysis Patients
Impact on mortality

ADRIAN APOSTOL1#, LAZAR CHISAVU2#, NICOLAE ALBULESCU4, DANA STOIAN3, ADALBERT SCHILLER2

1 Victor Babes University of Medicine and Pharmacy, Cardiology Department, County Hospital Pius Brinzeu, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania
2 Victor Babes University of Medicine and Pharmacy, Nephrology Department, Emergency County Hospital Pius Brinzeu, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania
3 Victor Babes University of Medicine and Pharmacy, Endocrinology Department, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania.

Patients with chronic kidney disease (CKD) represent a special category of risk. As part of the renal and cardiovascular continuum from risk factors to end stage diseases, they develop clinical syndromes with potentially severe prognosis. Patients on dialysis have severe cardiac risk, have a peculiar hyperlipemic profile with intense atherogenic effect, phosphocalcic metabolic alterations and thus a higher rate of development of atheroma and degenerative valve diseases. They have higher cardiovascular mortality and morbidity being potential candidates for aggressive reduction of risk factors. Dialysate patients are exposed to higher risk of ischemic and arrhythmic events. Echocardiographic assessment of these patients is extremely important in risk stratification and treatment strategy in order to improve prognosis. Drugs proved to improve cardiac remodeling, reduce hypertrophy and LV mass and enhance ejection fraction, improved prognosis.

Keywords: chronic kidney disease, hemodialysis, cardiovascular risk

Experimental part
Material and methods
We studied 1200 dialysed patients with mean follow-up of 3 years. Mean age 57.8±2.3 years old, 52% men, being on dialyses treatment of the average duration of 6.5±2.3 years.

In all patients we performed clinical exam, standard electrocardiography (ECG), transthoracic echocardiography in M mode, 2D color and spectral flow Doppler parameters, to assess morphology and cardiac performance. The ECG and ECO evaluation were performed during hemodialysis procedure.

In a pilot group we evaluate eco parameters before and after dialysis and we noticed significant changes in left atrial dimensional, LV EDD - left ventricular end diastolic diameter and diastolic filling according to mitral flow pattern. These parameters are highly influenced by fluid retention and varies in different moments of dialysis, being then of low interest in long term prognostic assessment and mimicking other clinical situation of fluid retention [8,9]. In order to keep the evaluation simple we assess left ventricular dimensions and hypertrophy, left ventricular mass, left ventricular ejection fraction (EF), endomyocardial calcification, valvular changes, presence of pericardial effusion table 1.

Statistical analysis
Two-group comparisons were performed using t-test and Fisher test, correlation has been evaluated with Pearson test. Statistical significance was considered if p<0.05.
Results and discussions

In our studied population we find only 11% of patients with normal eco parameters, the rest have left ventricular hypertrophy in 74%, dilatation 43%, degenerative valvular changes 41%, valvular incompetence associated with ischemia 18%. Regarding the efficacy of dialyses we assess pericardial effusion, endomyocardial calcification 19% and pulmonary hypertension - assessed on tricuspid flow. We measured LV morphologic parameters: EDD - end diastolic diameter, ESD - end systolic diameter, IVS-interventricular septum, LV mass calculated with Devereux formula, and functional parameters and their dynamic: ejection fraction EF, diastolic filling through Appleton pattern. At the same time we assess endomyocardial calcification and degenerative valvular involvement. All data assimilate EF as the most powerful prognostic parameter. But ones have to discriminate between real improvement in EF because positive remodeling and changes in EF due to hemodynamic changes in pressure or, most frequently, volume overload in valvular involvement. We compare all parameters at the beginning of the study and after 3 years on dialysis for the survival and deceased patients. There are significant differences between the two groups (p=0.00034) in all morphologic parameters and also EF as shown in figure1.

Patients who survive have rather normal LV dimensions, EF in normal range and varying in years also in normal range over 50%. On the other hand, deceased patients have significant higher EDD and ESD, thicker hearts with IVS 15±2.8 and impaired EF 41±3.7%.

We assessed the impact of different medications on survival. Those which had the most important impact were also those which proved to induce positive remodeling [13]. Blood pressure control with RAS inhibitors – ACE inhibitors or sartans (in case of cough), had the best prognosis. In figure 2 the difference after 3 years of treatment in patients with and without RAS inhibitors is shown, taking into account that we compare patients with the same characteristics (etiology, age, comorbidities, duration of dialysis treatment), and in whom we achieved blood pressure control.

| echocardiographic changes | Changes prevalence% |
|--------------------------|---------------------|
| Normal                   | 11                  |
| Left ventricular hypertrophy | 74              |
| Dilatation               | 43                  |
| Degenerative valvular changes | 41             |
| Ischemic valvular changes | 18                 |
| EF                       | Attention associated valvulopathy |
| Pericardial effusion     | 28                  |
| Endomyocardial calcification | 19            |
| Pulmonary hypertension   | 28                  |

Table 1

ECHOCARDIOGRAPHIC DATA

Fig. 1. Eco parameters in surviving and deceased patients

Fig. 2. Changes in eco parameters in patients treated with ACEi or sartans
Heart rate was another strong factor that influenced prognosis. It is common knowledge now (after Beautiful and Shift trials) that target heart rate is 62 b/min in patients without anemia. Survival curves showed that best prognosis was achieved in patients treated with RAS inhibition with near normal morphologic parameters and with heart rate below 70 b/min as showed in figure 3.

The principal causes of death in dialysis patients are cardiovascular events and infections. We have to control blood pressure, ischemia but also factors that can precipitate MACE such as diselectrolitemia and anemia.

Conclusions

Efficient hemodialysis procedure is an important step in order to control high blood pressure but LV hypertrophy of hypertensive dialysed patient (DP) has some peculiarities like higher risk of ischemic and arrhythmic events.

ACE inhibitors and betablockers at the highest tolerated dose decreased cardiovascular morbidity and mortality and improved quality of life. Small doses of these drugs proved to be effective even in patients where hemodialysis alone was enough to control blood pressure. ACE inhibitors reduced hypertension and improved diastolic filling.

Antiischemic treatment, active surveillance of arrhythmias, control of blood pressure and electrolytes are of paramount importance. Changes in treatment according to guidelines improved blood pressure control, echo parameters and dialysis flow. All of these are main contributors for better prognosis.

References

1. *** CHRONIC KIDNEY DISEASE PROGNOSIS CONSORTIUM, The Lancet, Volume 375, Issue 9731, Pages 2073 - 2081, 12 June 2010
2. REICH, J. Am.Soc.Nephrol.(2007) 18:3177
3. AMANN K ET AL. Nephrol Dial Transplant (2000) 15: 1493-1503
4. GADALEAN F, SIMU M, PARV F, VOROVENCI R, TUDOR R, SCHILLER A, TIMAR R, PETRICA L, VELCIOV S, GLUHOVSCHI C, BOB F, MIHAESCU A, TIMAR B, SPASOVSKI G, IVAN V (2017). The impact of acute kidney injury on in-hospital mortality in acute ischemic stroke patients undergoing intravenous thrombolysis. PLOS ONE Volume:12 Issue:10 Article number:0185589 Published:OCT 17 2017
5. LIGHEZAN R, STURZA A, DUICU OM, CEASUSU RA, VADUVA A, GASPAR M, FEIER H, VAIDA M, IVAN V, LIGHEZAN D, MUNTEANU DM, MORNOS C. - Monoamine oxidase inhibition improves vascular function in mammary arteries from non diabetic and diabetic patients with coronary heart disease. Can J Physiol Pharmacol.2016, Oct; 94(10):1040-1047
6. ROGOBETE AF, SANDESC D, BEDREAG OH, PAPURICA M, POPOVICI SE, BRATU T, POPOIU CM, NITU R, DRAGOMIR T, AABED HIM, IVAN MV. MicroRNA Expression is Associated with Sepsis Disorders in Critically Ill Polytrauma Patients. Cells. 2018;7(12):271. Published 2018 Dec 13. doi:10.3390/cells7120271
7. I.VAN, M.V., ROGOBETE, A., BEDREAG, O., et. al., New Molecular and Epigenic Expression as Novel Biomarkers in Critically Ill Polytrauma Patients with Acute Kidney Injury (AKI) -Clinical Laboratory, volume:64 Issue:5, pg 663-668
8. IVAN, M., V., PETRE, I., VLAICU, B., APOSTOL, A., TESLOIANU, D., MUNTEANU, M., COSTACHESCU, R., MOLERIU, L.V., LAZAR, F., The Use of Pulse Wave Velocity in Predicting Pre-Eclampsia in High-Risk Women, Rev. Chim., (Bucharest), 69, no 5, 2018, p. 1260
9. PETRE I, CRAINA M, CHIRIA M V D, STELEA L, MOLERIU L C, POP E, IURCUIC M, STOIAN D, IVAN M V - Evaluation of Hemodynamic and Arterial Stiffness Parameters in Women with HTN/Preeclampsia, The 17thNational Congress of the Romanian Society of Obstetrics and Gynecology, 20-22 September 2018, Iasi, Romania, pag 639-643, Ed. Filioprint Editore Proceedings, ISBN 978-88-886313-3-5
10. MUNTEANU, M., APOSTOL, A., IVAN, M.V., New Consideration Regarding Chronic Kidney Disease, Cardiovascular Disease and Dislipidemia in Diabetic Patients. Rev. Chim.(Bucharest), 69, no 8, 2018, p. 2064
11. HAGARUCHI ET AL.:Diabetes Res and Clin. Pract 83 (2009): 295-299
12. WEINER D.E ET AL. J Am Soc Nephrol 15:1307-1315, 2004
13. VAN VARK L.C, BERTRAND M, AKKERHUIS M, BRUGTS JJ, FOX K, MOURAD J AND BOERSMA E - Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158998 patients. Eur Heart J . 2012 Apr 17. Epub ahead of print. doi:10.1093/eurheartj/ehs075
Manuscript received: 23.10.2018