# Hyperkalemia and Cardiovascular Diseases: New Molecules for the Treatment

**CAMELIA CRISTINA DIACONU[1,2]*, ANA MARIA ALEXANDRA STANESCU[1], ANCA PANTEA STOIAN[1], RADU CIPRIAN TINCU[1,2], CRISTIAN COBILINSCHI[1,2], RAZVAN ION FLORIN DRAGOMIRESCU[3,4], BOGDAN SOCEA[1,5], DAN ARSENIE SPINU[1,6], DRAGOS MARCU[1,6], LAURA ILEANA SOCEA[7], OVIDIU GABRIEL BRATU[1,6,8]**

[1]University of Medicine and Pharmacy Carol Davila, 8 Eroii Sanitari Str, Bucharest, 050474, Bucharest, Romania

[2]Clinical Emergency Hospital of Bucharest, 8 Calea Floreasca, 014461, Bucharest, Romania

[3]St. John Emergency Clinical Hospital,Department of Nephrology and Dialysis, 13 Vitan Barzesti Road., 042122, Bucharest, Romania

[4]Carol Davila University of Medicine and Pharmacy Bucharest, Clinical Department No. 3, 37 Dionisie Lupu Str., 020021, Bucharest, Romania

[5]Clinical Emergency Hospital Sfantul Pantelimon, 340-342 Pantelimon Str, 021659, Bucharest, Romania

[6]Carol Davila University, Emergency Central Military Hospital, 88 Mircea Vulcanescu Str, 010825, Bucharest, Romania

[7]Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Organic Chemistry Department, 6 Traian Vuia Str., 020956, Bucharest, Romania

[8]Associated member of the Academy of Romanian Scientists, 54 Splailu Independentei, 030167, Bucharest, Romania

*Potassium is a key electrolyte for the maintenance of cardiovascular system health, being involved in a broad array of vital physiological processes. Hyperkalemia is a common clinical problem and potentially life-threatening condition predominantly seen in patients with cardiac and kidney disease, especially if receiving treatment with inhibitors of the renin-angiotensin-aldosterone axis. Several studies have demonstrated the short and long-term morbidity and mortality that hyperkalemia induces in patients with cardiovascular diseases. Plenty of data is currently emerging on this topic. This paper aims to review the new strategies and molecules for improving the management of hyperkalemia.*

*Key words: potassium, kyperkalemia, cardiovascular disease, potassium binders*

Potassium is a key electrolyte for the maintenance of cardiovascular system health, being involved in a broad array of vital physiological processes [1-4]. The potassium stores in an adult individual are about 3500 mEq [5]. Potassium is the most abundant electrolyte in the human body, the majority of potassium cations being intracellular (98%) and only 2% extracellular. The intracellular-extracellular gradient of $K^+$ is maintained by the activity of the $Na^+$-$K^+$ adenosine triphosphatase (ATPase) pump; this pump transports 3 $Na^+$ cations out of the cell, in exchange of 2 $K^+$ cations inside the cell [6]. The potassium stores of the body are maintained by the balance between the dietary intake of potassium and the kidney excretion [7-10]. The majority of potassium filtered by the kidney is reabsorbed in the proximal tubules [11]. The secretion of potassium is controlled by the renin-angiotensin-aldosterone system (RAAS). Hyperkalemia is relatively frequently encountered in the clinical practice, either due to increased potassium intake or impaired kidney excretion, more rare due to altered movement of potassium from extracellular to intracellular space [12-18]. Patients with cardiovascular diseases frequently receive treatment with drugs that affect the renin-angiotensin-aldosterone system, drugs that have proven benefits for the evolution of cardiovascular diseases [19-20]. This is the reason why cardiovascular patients have increased risk of hyperkalemia, which may cause fatal arrhythmias, such as ventricular fibrillation, asystole, cardiac conduction disturbances and eventually cardiac arrest. All the muscular cells from the body depend on extracellular potassium in order to repolarize. The cells of the cardiac conduction system heavily rely on extracellular potassium and calcium for depolarization and repolarization. When serum potassium is higher than normal, the transcellular gradient is altered and the symptoms of hyperkalemia appear.

## Experimental part

Usually, hyperkalemia is defined as a serum potassium higher than 5.5 mEq/L [21]. The prevalence of hyperkalemia in the general population is between 2-3% [22]. Cardiovascular diseases increase the risk of hyperkalemia. One retrospective study on over 15,000 patients with arterial hypertension and heart failure has found that 24.5% had hyperkalemia [23]. The predictors of hyperkalemia in these patients were age, the presence of chronic kidney disease [24], diabetes [25], coronary heart disease [26], and use of medication such as angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) [23]. The CHARM trial (Candesartan in Heart Failure - Assessment of Reduction in Mortality and Morbidity) has demonstrated a prevalence of hyperkalemia of 5.2% in patients treated with candesartan (an angiotensin receptor blocker), as compared to 1.8% in patients who received placebo.

The cardiovascular medications associated with increased risk of hyperkalemia are ACEI, ARBs, potassium–sparing diuretics (spironolactone, amiloride, triamterene, eplerenone, and finerenone), direct renin inhibitors, and also beta-blockers and nonsteroidal anti-inflammatory drugs (NSAIDs). In some cases, heparin may be responsible for hyperkalemia. The risk of hyperkalemia is increased in patients with associated risk factors, such as chronic kidney disease, diabetes mellitus, decompensated heart

* email: drcameliadiaconu@gmail.com

All authors had equal contribution and share the first authorship

failure, dehydration, concomitant use of herbal or other dietary supplements rich in potassium [27-31]. One review has found an incidence of hyperkalemia between 1.9-38.4% in clinical trials of ACEI, ARBs, aldosterone antagonists and direct renin inhibitors [22]. It is possible that these reported rates of hyperkalemia underestimate the real prevalence of this electrolyte disorder in the clinical practice.

Betablockers reduce the cellular uptake of $K^+$ and may induce only a mild increase of serum potassium, if the renal function is normal [32]. In patients with chronic kidney disease or those taking other drugs, such as RAAS blockers, the risk of hyperkalemia is higher. ACEI or ARBs induce an increase of serum $K^+$ by 0.3-0.4 mEq/L in the presence of a normal renal function [33]; the risk is higher in case of co-administration of aldosterone antagonists, potassium supplements or in the presence of chronic kidney disease [34-36]. Aldosterone antagonists impair the capacity of the distal nephron to excrete potassium and rise the risk of hyperkalemia [35]. One retrospective study of patients with heart failure evaluated the rate of hyperkalemia in patients who received an ACEI compared with those who received both an ACEI and an aldosterone antagonist; from 100 patients, 16 patients who received combined treatment developped hyperkalemia, in comparison with only one hyperkalemic patient who received only an ACEI [37]. Heparin impairs the renal excretion of potassium in patients with chronic kidney disease, being an inhibitor of aldosterone secretion [38]. NSAIDs, especially when administered in patients with heart failure and chronic kidney disease, may lead to hyperkalemia, by decreasing the renin secretion [39]. Digoxin, another drug used for the treatment of cardiovascular diseases, especially heart failure, inhibits the activity of the $Na^+$-$K^+$ ATP-ase pump, the risk of hyperkalemia increasing in parallel with the dose of digoxin [40]. Medical prescription of these drugs should be followed by a careful monitoring of serum potassium in all patients, and even more attentive if the patients associate other risk factors for hyperkalemia.

Any disorder that leads to renal impaired function can determine the appearance of hyperkalemia including here all types of nephritis [41], transplant rejection and obstructive diseases of the urinary tract [42]. Another condition, like trauma, burns, surgery, hemolysis, massive tumor lysis and especially rhabdomyolysis, can produce hyperkalemia through tissue destruction, due to the fact that dying cells release potassium into blood flow [43-47]. Along with hyperkalemia, many patients with chronic kidney disease presents lots of complications, such as anemia, vascular calcifications [48], abnormalities in mineral and bone metabolism leading to bone fractures which needs minimal-invasive bone osteosynthesis with minimal tissue destruction in order to avoid further complications [49-51].

The clinical manifestations of hyperkalemia depend on the level of serum potassium, the main consequences being muscle weakness and cardiac arrhythmias, with high risk of death. Sometimes, in mild kyperkalemia, the patients are asymptomatic, the electrolyte disorder being diagnosed incidentally on laboratory tests. The clinical manifestations might be muscle weakness or cramps, tetany, dyspnea, palpitations, paresthesias, confusion, altered mental status, which needs a careful differential diagnosis with diseases that have similar manifestations that should be treated accordingly [52-55].

## Results and discussions

Management of hyperkalemia requires potassium monitoring in all cardiovascular patients at risk. Acute or severe metabolic acidosis should be corrected with sodium bicarbonate intravenously, that can promote the shift of potassium from the extracellular to the intracellular space. If the acidosis is chronic, it may be corrected with oral sodium bicarbonate. Sodium bicarbonate does not decrease the serum potassium level in the absence of metabolic acidosis.

The acute management of hyperkalemia includes administration of calcium gluconate, insulin or beta2 adrenergic agonists. Calcium antagonizes the effects of $K^+$ at the level of the cell membrane. Insulin increases the cellular potassium intake, by increasing the $Na^+$-$K^+$-ATPase activity. Inhaled beta2-adrenergic agonists (albuterol, salbutamol) also increase the cellular potassium intake, by activating the $Na^+$-$K^+$-ATPase activity.

The chronic management of hyperkalemia uses diuretics, to enhance excretion of potassium in proximal and distal tubules, by increasing the delivery of sodium to the collecting duct.

Potassium-binding resins increase the colonic excretion of potassium, by decreasing the luminal potassium. The potassium secretion in the colon has two mechanisms: passive and active secretion. The passive secretion is a major component of colonic $K^+$ secretion and is highest in the distal colon. The active secretion occurs in the proximal and distal colon and is similar to active $K^+$ secretion in the renal distal nephron.

Sodium polystyrene sulfonate and calcium polystyrene sulfonate are used for severe hyperkalemia. Sodium polystyrene sulfonate is an enteral potassium-sodium exchange resin, that binds potassium, and may be given in sorbitol or mixed with water or syrup. Sorbitol induces diarrhea, as a side effect, with additional lowering of potassium. Because diarrhea may not be well tolerated by patients, sodium polystyrene sulfonate is administered preferably mixed with water or syrup. Other side effects of the drug are acute bowel necrosis, retention enema, hypernatremia. Sodium polystyrene sulfonate was approved by FDA (Food and Drug Administration) in 1958, but in 2009 a warning has appeared, regarding the risks of colonic necrosis and the potential harm of suspensions in sorbitol [56].

Patiromer calcium is a newer potassium exchange resin, insoluble in typical solvents, passing undegradated through the gastrointestinal tract. Patiromer binds potassium in the gastrointestinal lumen, increasing fecal potassium excretion and decreasing the absorption of potassium in the serum. In AMETHYST-DN trial (RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropahty), that included hyperkalemic patients with diabetic nephropathy, treatment with patiromer was associated with significant decreases of serum potassium after one month of treatment [57]. Another trial, OPAL-HK (Evaluating the Efficacy and Safety of Patiromer on the Treatment of Hyperkalemia) demonstrated that, in patients with chronic kidney disease receiving RAAS inhibitors, patiromer induced a sustained reduction of serum potassium level as compared with placebo [58]. The patients included in this trial had the diagnosis of chronic kidney disease stage 3 or 4, received a RAAS inhibitor and were hyperkalemic, with a potassium level between 5.1-6.5 mEq/L. They received a dose of 4.2 g or 8.4 g twice daily for 4 weeks. At the end of the 4 weeks, 76% of patients included reached the target value of serum potassium [59]. Because patiromer binds also to magnesium in the gastrointestinal tract, it may reduce the magnesium absorption, hypomagnesiemia being reported in 5.3% of patients treated with patiromer in clinical trials [57]. However, hypomagnesiemia was only mild and did

not lead to the necessity of patiromer treatment discontinuation.

Sodium zirconium cyclosilicate (ZS-9) is another novel potassium binder, used in the treatment of acute or chronic hyperkalemia. ZS-9 is not absorbed and has a structure that entrap potassium cations throughout the gastrointestinal tract [59]. It uses sodium and hydrogen as the exchange ions for potassium. ZS-9 was studied in two trials that included hyperkalemic patients. One study selected patients with hyperkalemia (5.0-6.5 mEq/L) who received ZS-9 in doses of 1.25, 2.5, 5 or 10 g, three times/day, for 48 h [33]. ZS-9 was effective in all the patients, leading to a significant decrease of potassium levels [60]. The study continued for 12 days, with the same beneficial effects, especially in patients receiving higher doses of ZS-9 (5 g or 10 g). The drug was well tolerated, the most frequent side effect being diarrhea (however, the rate of diarrhea was similar with placebo) [58]. The HARMONIZE trial (Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance) studied the effects of ZS-9 (5 g, 10 g or 15 g daily) in 258 hyperkalemic patients, with a serum potassium $\geq$ 5.1 mEq/L [61]. The percentage of patients with normalized potassium was significantly higher among patients who received ZS-9 versus placebo. The early onset of action of ZS-9 was noticed during the trial. Serum potassium normalized in 98% of patients after 48 h of treatment with ZS-9 [61]. Regarding the adverse effects, no treatment-related serious adverse effects were reported, the adverse effects being comparable with placebo.

An important aspect of the hyperkalemia management is the use of renal replacement therapy in refractory cases of drug therapy and to avoid the usage of antidiuretic drugs or drugs that leads to potassium release and accumulation [62-64].

## Conclusions

Hyperkalemia is a relatively frequent electrolytic disorder in patients with cardiovascular diseases, especially heart failure, and it is associated with increased risk of death, because of ventricular arrhythmias or conduction disturbances. Current medications with proven cardioprotective and renoprotective effects, such as antialdosterone diuretics, ACEI or ARBs, play a role in the etiology of hyperkalemia. The appearance of hyperkalemia, or the fear of it, may lead to the insufficient use of these beneficial drugs in patients with cardiovascular diseases. However, hyperkalemia treatment is more appropriate than avoidance of these drugs in patients with cardiovascular diseases.

Current traditional agents for the chronic treatment of hyperkalemia are relatively inconsistent. Potassium-binding agents may be a better and novel option for the management of chronic hyperkalemia. These resins are relatively slow acting and are usually indicated to control the potassium level on long term. Two new drugs, patiromer and ZS-9, may offer a safer alternative, with more reliable outcomes, for the treatment of chronic hyperkalemia. In cases of severe hyperkalemia, life-threatening, emergency hemodialysis is indicated. Optimizing the treatment with RAAS inhibitors in cardiovascular patients to achieve their cardiorenal benefits is an important objective for the physicians involved in the healthcare of these patients.

## References


1.DIACONU, C., NASTASA, A., ZAKI, A.R., ARSALAN, M., The 2nd International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications - INTERDIAB 2016 Proceedings, pp 201-210. Niculescu Publishing House. Editors SERAFINCEANU, C., NEGOITA, O., ELIAN, V

2.DIACONU, C., BALACEANU, A., COSTACHE, C., J. Hepatol., **60**, Supplement 1, 2014, S515. The International Liver Congress, 49th annual meeting of the European Association for the Study of Liver, April 9-13, 2014, London, UK.

3.YAKIMOV, I., GRUEV, I., TSANOVA-SAVOVA, S., Arch. Balk. Med. Union., **51**, no. 3, 2016, p. 358

4.DRĂGOI, C.M., NICOLAE, A.C., GRIGORE, C., DINU-PIRVU, C.E., ARSENE, A.L., The 2nd International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications- Diabetes Mellitus as Cardiovascular Disease, INTERDIAB 2016 Proceedings, Niculescu Publishing House, Bucharest, 221-229. Editors SERAFINCEANU, C., NEGOITĂ, O., ELIAN, V

5.PUTCHA, N., ALLON, M., Semin. Dial., **20**, 2007, p. 431

6. SWEADNER, K.J., GOLDIN, S.M., N. Engl. J. Med., **302**, 1980, p. 777

7.PARASCHIV, B., DEDIU, G., IANCU, A., BRATU, O., DIACONU, C., Arch. Balk. Med. Union, **52**, no. 1, 2017, p. 39

8.DRAGHICI, T., NEGREANU, L., BRATU, O., TINCU, R., SOCEA, B., IANCU, M.A., STANESCU, A.M., DIACONU, C., Arch. Balk. Med. Union, **53**, no. 1, 2018, p. 76

9.SOCEA, B., NICA, A., BRATU, O., DIACONU, C., SMARANDA, A., SOCEA, L., BERTESTEANU, S., DIMITRIU, M., CARAP, A., CONSTANTIN, V., Arch. Balk. Med. Union, **53**, no. 1, 2018, p. 143

10.SOCEA, B., NICA, A.A., SMARANDA, C.A., CARAP, A.C., SOCEA, L.I., DIMITRIU, M., BRATU, O.G., MOCULESCU, C.E., BERTE'TEANU, S.V.G., CONSTANTIN, V.D. Arch. Balk. Med. Union, **52**, no. 4, 2017, p. 467

11.MITITELU, R., BRATU, O., Modern Medicine, **24**, no. 4, 2017, p. 199

12.LASLO, C., IOAN, B., BRATU, O., SOCEA, B., DIACONU, C., Arch. Balk. Med. Union, **53**, no. 1, 2018, p. 96

13. DIACONU, C., NASTASA, A., ZAKI, A.R., ISTRATIE, B., RAHIMUDDIN, N., IANCU, M.A., BALACEANU, A., J. Hypertens., **34**, 2016, e-Suppl 1:e320

14.CIPU, D.S., CIPU, D., BUCUR, A., MATUSZ, A.A., DUMITRAS&CU, V., Arch. Balk. Med. Union., **52**, no. 3, 2017, p. 306

15. BALACEANU, A., DIACONU, C., ARON, G., Med. Ultrason., **16**, no. 2, 2014, p.172

16.ISVORANU, I., PERIDE, I., RADULESCU, D., NICULAE, A., SINESCU, R.D., CHECHERITA, I.A., Rev. Chim. (Bucharest), **66**, nr. 9, 2015, p. 1316

17.DIACONU, C., Arch. Balk. Med. Union., **51**, no. 3, 2016, p. 307

18.DIACONU, C., BALACEANU, A., BARTOS, D., Arch. Balk. Med. Union., **49**, no. 3, 2014, p. 247

19.PAREPA, R.I., SUCEVEANU, A.I., MAZILU, L., MOHAMED, A., NITA, D., TUTA L.A., Farmacia, **65**, 2017, p. 120

20.NITA, D., GURZUN, M., CHIRIAC, L., CIRSTEA, A.I., PAREPA, R.I., BARBILIAN, A.G., Romanian Biotechnological Letters, **22**, no. 2, 2017, p. 12347

21.*** UK Renal Association. www.renal.org/guidelines/joint-guidelines/treatment-of-acute-hyperkalaemia-in-adults#sthash.GI1GDFeb.dpbs. March 1, 2014. Accessed March 17, 2018

22. KOVESDY, C.P., Nat. Rev. Nephrol., **10**, no. 11, 2014, p. 653

23. JAIN, N., KOTLA, S., LITTLE, B.B., WEIDEMAN, R.A., BRILAKIS, E.S., REILLY, R.F., BANERJEE, S., Am. J. Cardiol., **109**, no. 10, 2012, p. 1510

24. NECHITA, A.M., PITURU, S., RADULESCU, D., PERIDE, I., NEGREANU, L., NICULAE, A., FERECHIDE, D., CHECHERITA, I.A., SINESCU, R.D. Farmacia, **64**, nr. 3, 2016, p. 348

25. POIANA C, CAPATINA C. Journal of Clinical Densitometry, **20**, nr. 3, 2017, p. 432.

26. DAVID, C., BOVER, J., VOICULET, C., PERIDE, I., PETCU, L.C., NICULAE, A., COVIC, A., CHECHERITA, I.A., Int. Urol. Nephrol., **49**, nr. 4, 2017, p. 689
27. RAEBEL, M.A., Cardiovasc Ther., **30**, no. 3, 2012, e156
28. MANDA, G., CHECHERITA, A.I., COMANESCU, M.V., HINESCU, M.E. Mediators Inflamm., **2015**, 2015, p. 604208
29. PALMER, B.F., N. Engl. J. Med., **351**, no. 6, 2004, p. 585
30. CHECHERITA, I.A., SMARANDACHE, D., RADULESCU, D., PERIDE, I., BRATU, O., CIOCALTEU, A., SEBE, I., LASCAR, I. **108**, nr. 5, 2013, p. 736
31. CAPATINA, C., GHINEA, A., DUMITRASCU, A., POIANA, C., Int. J. Diabetes Dev. Ctries., **36**, nr. 4, 2016, p. 393
32. ROSE, B.D., POST, T.W., In: Rose BD, Post TW, eds. Clinical Physiology of Acid-base and Electrolyte Disorders, 5th ed. New York, NY: McGraw-Hill, 2001, p. 888
33. TEXTOR, S.C., BRAVO, E.L., FOUAD, F.M., TARAZI, R.C., Am. J. Med., **73**, 1982, p.
34. SHIER, D.N., KUSANO, E., STONER, G.D., FRANCO-SAENZ, R., MULROW, P.J., Endocrinology., **125**, 1989, p. 486
35. BURGESS, E., Expert Opin. Pharmacother., **5**, 2004, p. 2573
36. CHECHERITA, I.A., DAVID, C., CIOCALTEU, A., LASCAR, I. Chirurgia (Bucur.), **104**, nr. 5, 2009, p. 525
37. CRUZ, C.S., CRUZ, A.A., DESOUZA, M.C.A., Nephrol. Dial. Transplant., **18,** 2003, p.1814
38. OSTER, J.R., SINGER, I., FISHMAN, L.M., Am. J. Med., **98**, 1995, p. 575
39. DERAY, G., Presse Med., **33**, 2004, p. 483
40. APERIA, A., J. Intern. Med., **261**, 2007, p. 44
41. NICULAE, A., PERIDE, I., VINEREANU, V., RADULESCU, D., BRATU, O.G., GEAVLETE, B.F., CHECHERITA, I.A., Rom. J. Morphol. Embryol., **58**, nr. 3, 2017, p. 1065
42. GEAVLETE, B.F., BRINZEA, A., CHECHERITA, I.A., ZURAC, S.A., GEORGESCU, D.A., BASTIAN, A.E., ENE, C.V., BULAI, C.A., GEAVLETE, D.O., ZAHARIA, M.R., GEAVLETE, P.A., Rom. J. Morphol. Embryol., **56**, nr. 3, 2015, p. 1069
43. NEAGU, T.P., SINESCU, R.D., ENACHE, V., ACHIM, S.C., TIGLIS, M.I., MIREA, L.E., Rom. J. Morphol. Embryol., **58**, nr. 2, 2017, p. 603
44. POIANA, C.A., NEAMTU, M.C., AVRAMESCU, E.T., CARSOTE, M., TRIFANESCU, R., TERZEA, D., NEAMTU, O.M., FERECHIDE, D., DANCIULESCU MIULESCU, R., Rom. J. Morphol. Embryol., **54**, Suppl 3, 2013, p. 717
45. SINESCU, R.D., NICULAE, A.N., PERIDE, I.L., VASILESCU, F.L., BRATU, O.G., MISCHIANU, D.L., JINGA, M.A., CHECHERITA, I.A., Rom. J. Morphol. Embryol., **56**, nr. 2, 2015, p. 601
46. NEAGU, T.P., TIGLIS, M., BOTEZATU, D., ENACHE, V., COBILINSCHI, C.O., VALCEA-PRECUP, M.S., GRINTESCU, I.M., Rom. J. Morphol. Embryol., **58**, nr. 1, 2017, p. 33
47. PAUN, D.L., POIANA, C., PETRIS, R., RADIAN, S., MIULESCU, R.D., CONSTANTINESCU, G., ORBAN, C. Chirurgia (Bucur.), **108**, nr. 6, 2013, p. 900
48. PERIDE, I., CHECHERITA, I.A., SMARANDACHE, D.R., RADULESCU, D., SINESCU, R.D., NICULAE, A., PRICOP, C., Rom. J. Morphol. Embryol., **56**, nr. 2, 2015, p. 777
49. NEAGU, T.P., TIGLIS, M., COCOLOS, I., JECAN, C.R., Rom. J. Morphol. Embryol., **57**, nr. 4, 2016, p. 1215
50. NEAGU, T.P., ENACHE, V., COCOLOS, I., TIGLIS, M., COBILINSCHI, C., TINCU, R., Rom. J. Morphol. Embryol., **57**, nr. 2, 2016, p. 437
51. NEAGU, T.P., TIGLIS, M., POPP, C.G., JECAN, C.R., Rom. J. Morphol. Embryol., **57**, nr. 3, 2016, p. 1051
52. CAPATINA, C., CARAGHEORGHEOPOL, A., BERTEANU, M., POIANA, C., Exp. Clin. Endocrinol. Diabetes, **124**, nr. 8, 2016, p. 461
53. BADILA, E., WEISS, A.E., BARTOª, D., DUMITRACHE, E.L., TATARANU, L.G., CIUBOTARU, G.V., NEAGU, T.P., ENACHE, V., POPA, V.B., JAPIE, C., Rom. J. Morphol. Embryol., **58**, nr. 3, 2017, p. 983
54. CAPATINA, C.,CAPATINA, C.O., CHIRICA, V.I., POIANA, C., Rom. J. Leg. Med., **24**, 2016, p. 199
55. NEAGU, T.P., COCOLOS, I., COBILINSCHI, C., TIGLIS, M., FLORESCU, I.P., BADILA, E., SINESCU, R.D., Rev. Chim.(Bucharest), **68**, no. 12, 2017 p. 2978
56. STERNS, H., ROJAS, M., BERNSTEIN, P., CHENNUPATI, S., J. Am. Soc. Nephrol., **21**, no. 5, 2010, p. 733
57. BAKRIS, G.L., PITT, B., WEIR, M.R., FREEMAN, M.W., MAYO, M.R., GARZA, D., STASIV, Y., ZAWADAKI, R., BERMAN, L., BUSHINSKY, D.A., JAMA., **314**, no. 2, 2015, p.151
58. WEIR, M.R., BAKRIS, G.L., BUSHINSKY, D.A., MAYO, M.R., GARZA, D., STASIV, Y., WITTES, J., CHRIST-SCHMIDT, H., BERMAN, L., PITT, B., N. Engl. J. Med., **372**, no. 3, 2015, p. 211
59. ASH, S.R., SINGH, B., LAVIN, P.T., STAVROS, F., RASMUSSEN, H.S., Kidney (Int., **88**, no. 2, 2015, p. 404
60. PACKHAM, D.K., RASMUSSEN, H.S., LAVIN, P.T., EL-SHAHAWY, M.A., ROGER, S.D., BLOCK, G., QUNIBI, W., PERGOLA, P., SINGH, B., N. Engl. J. Med., **372**, no. 3, 2015, p. 222
61. KOSIBOROD, M., RASMUSSEN, H.S., LAVIN, P., QUNIBI, W., SPINOWITZ, B., PACKHAM, D., ROGER, S.D., YANG, A., LERMA, E., SINGH, B., JAMA., **312**, no. 21, 2014, p. 2223
62. CHECHERITA, I.A., DAVID, C.R., DIACONU, V., CIOCALTEU, A., LASCAR, I., Rom. J. Morphol. Embryol., **52**, Suppl 3, 2011, p. 1047
63. TIGLIS, M., GRINETESCU, I.C., NEAGU, T.P., TURCU, F.L., COCOLOS, A.M., GRINTESCU, I.M., Rev. Chim.(Bucharest), **69**, no. 2, 2018, p. 391
64. PRICOP, C., BRANISTEANU, D.D., ORSOLYA, M., PUIA, D., MATEI, A., CHECHERITA, I.A. Int. Urol. Nephrol., **48**, nr. 2, 2016, p. 183

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