The Treatment of Arterial Hypertension

ANDA-MARIANA BRAȘOVEANU[1,2], ROXANA CRUCE[3],
LAURENȚIU MOGOANTĂ[4], VALENTIN CÂRLIG[5]

[1]Department of Cardiology, Caracal Municipal Hospital, Olt County, Romania

[2]PhD Student, University of Medicine and Pharmacy of Craiova, Romania

[3]Department of Research Methodology, University of Medicine and Pharmacy of Craiova, Romania

[4]Department of Histology, University of Medicine and Pharmacy of Craiova, Romania

[5]Doctoral School, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT: Arterial hypertension is the leading cause of death worldwide and is one of the most important public health problems. Arterial hypertension is a major cardiovascular risk factor with an increasing incidence. In this paper we set out to analyze a group of 3050 patients hospitalized between January 2013 and December 2017 in terms of drug therapy. We found that the majority of patients received drug treatment with a converting-enzyme inhibitor as a monotherapy, and the most common drug association was the association between conversion enzyme inhibitor and calcium channel blocker.

KEYWORDS: Arterial hypertension, medical treatment, mortality

Introduction

Arterial hypertension (AHT) is the leading cause of death worldwide and is one of the most important public health problems. Arterial hypertension is a major cardiovascular risk factor with an increasing incidence [1].

Hypertension is defined by increasing blood pressure (BP) above 140/90mmHg.

The World Health Organization (WHO) [2] defined AHT as a persistent increase in systolic BP values above 140mmHg and/or diastolic≥90mmHg in persons not receiving antihypertensive therapy.

The 2018 ESH-ESC guidelines recommend that the first therapeutic goal should be to reduce values below 140/90mmHg for all patients.

If treatment is well tolerated, values should be lowered to 130/80mmHg or even below for most patients. In most patients below 65 years of age it is recommended to decrease the systolic blood pressure (SBP) in the range 120-129mmHg [3].

The prevalence of AHT increases with age, especially in over 30 years old patients.

The mechanisms involved in the occurrence of over 95% of cases of AHT are multiple. BP is determined by the product between cardiac output and peripheral resistance. AHT can result from the change of either factor. AHT has been called a "silent killer" because it is mostly undiagnosed and untreated, which leads to a silent impairment of blood vessels, heart, brain and kidneys. The BP reduction will lead to a decreased risk of stroke, chronic kidney disease, heart failure, aortic dissection, acute coronary events or even death.

In order to lower the BP we have several methods at hand, which range from changing the lifestyle to antihypertensive medication and even cardiovascular interventions such as renal denervation.

According to the new ESC/ESH guideline of 2018, it is recommended that antihypertensive treatment can be considered even at high normal BP values (130-139/85-89mmHG) if the cardiovascular risk is very high when associated with ischemic heart disease. Except for a few cases of secondary AHT, most cases cannot be cured [4].

The main classes of drugs used in the treatment of AHT are angiotensin II conversion enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium channel blockers and diuretics (thiazide and thiazide-like) [5,6].

Antihypertensive treatment can be started with a single drug or using two or three drugs given individually or in fixed dose tablets.

The current guideline recommends initiating antihypertensive treatment with a fixed-dose combination of two drugs that improves the efficiency and speed of BP control.

Aim

Our aim through this paper was to provide quantitative and qualitative data from a group of patients hospitalized that underwent various types of antihypertensive therapy.

Material and Methods

The studied group includes 3050 hypertensive patients admitted to the cardiology department of the Caracal Municipal Hospital between January 2013 and December 2017.

All patients over the age of 18 years were included regardless of gender, origin or AHT class. The value of systolic BP upon admission was considered as a reference value. The patients' consent was obtained for data processing, after obtaining the approval of the ethics commission from Caracal Municipal Hospital in order to process the data for scientific purposes.

Hypertensive patients received as antihypertensive treatment-mainly angiotensin converting enzyme inhibitors, followed by the association between angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers. Some received sartans, Ca-blockers and beta-blocker as monotherapy (Figure 1).

We prospectively collected data from the observation sheets and entered it into Microsoft Excel files for statistical analysis, in order to document any relationship between the clinical and paraclinical data of the patients.

To characterize the numerical data we used the common statistical indicators: the arithmetic mean and the standard deviation, as well as the scattering indicators-minimum, maximum, median and quartiles.

If the analysed data had a Gaussian distribution we compared the average values by using Student's t-test.

We recalled at six months intervals a subgroup of patients admitted between January and December 2017 for blood pressure measurement, in order to demonstrate if a certain class of antihypertensive medication can maintain lower BPs over a timeframe. We used the Chi square test to evaluate the difference in means.
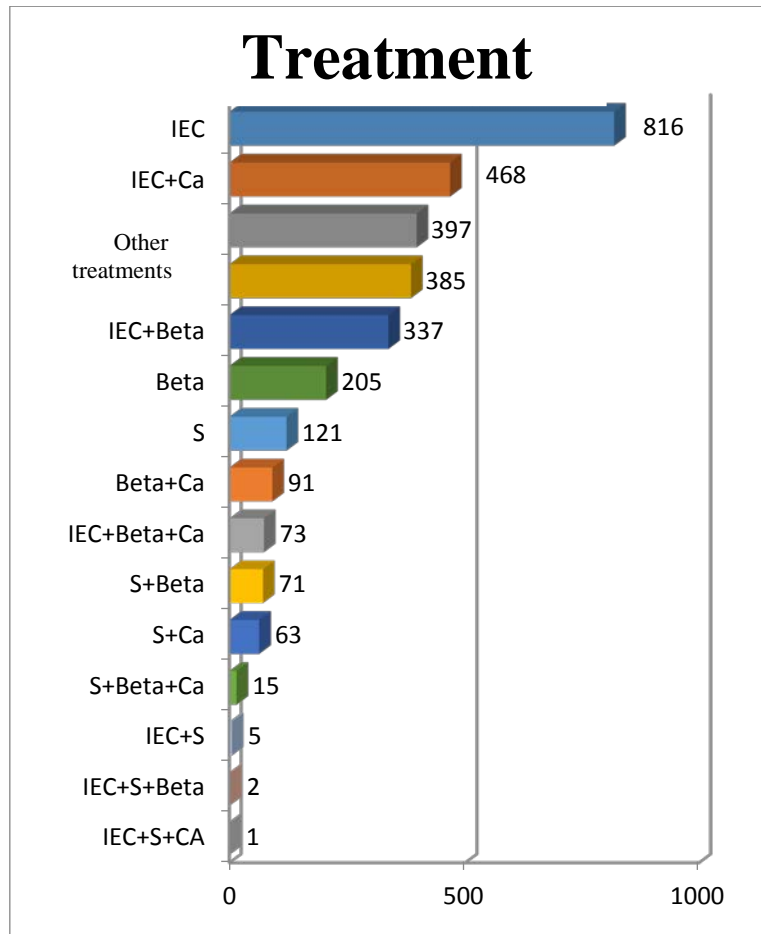

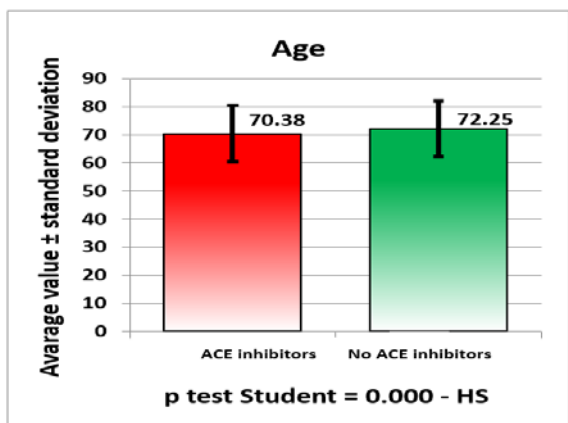*Figure 1. Distribution of patients according to drug therapy.*

Figure 2. Distribution of patients by age and administration of ACE inhibitors.

Results

Most of the 3050 patients admitted to the Caracal Municipal Hospital received IEC (26.75%). The most commonly used drug combination in our group was between IEC and Ca-blocker (15.34%). Ca-blockers were administered alone in 385 patients (12.62%). Sartans were administered alone in 121 patients (3.96%). Beta-blocking medication was used alone in 205 patients (6.72%).

The mean age of patients receiving ACE inhibitors was lower than that of patients without this medication, with a highly significant difference (p=0.00000028<0.001) (Figure 2).

In our group, we demonstrated using the Student's t-test, that there is a highly significant difference between the mean systolic blood pressure of those who received IEC treatment, respectively, those in the group who did not receive ACE inhibitors (p=0.000009<0.001) (Figure 3).
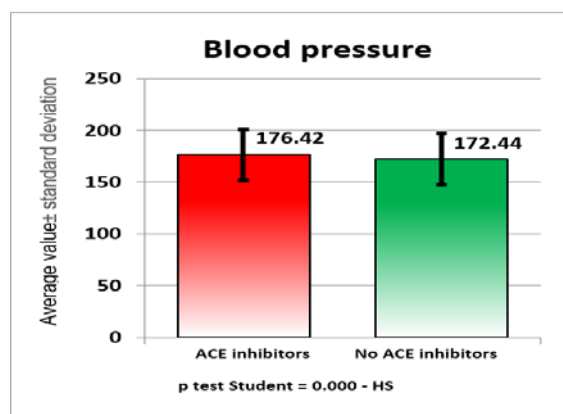

Figure 3. Distribution of patients by blood pressure value and administration of IEC.

By conducting the Student's t-test, we identified a highly significant difference between the systolic blood pressure of those who received Ca-blockers, respectively those who did not receive, with those in the group who received Ca-blockers having a mean blood pressure higher than the others (p=1.39x10^{-35} <0.001) (Figure 4).

We found no significant difference between the average ages of those who received treatment with Ca-blockers, compared to those who received other medications (p=0.074> 0.05) (Figure 5).
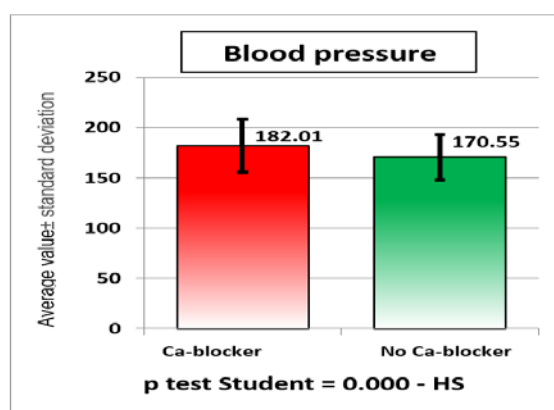

Figure 4. Distribution of patients by blood pressure value and administration of Ca-blocker.
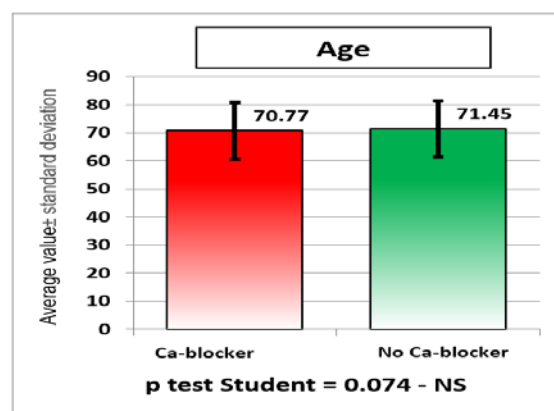

Figure 5. Distribution of patients by age and administration of Ca-blocker.

We found that the average ages of those who received treatment with sartans were higher than the others (p=0.031<0.05) (Figure 6).

By using the Student's t-test, we proved that those who received sartans had higher mean systolic blood pressure compared to those who did not receive this treatment (p=0.000017<0.001) (Figure 7).
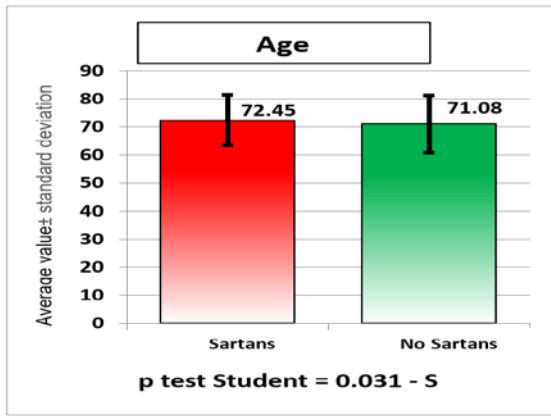
Figure 6. Distribution of patients by age and administration of sartans.
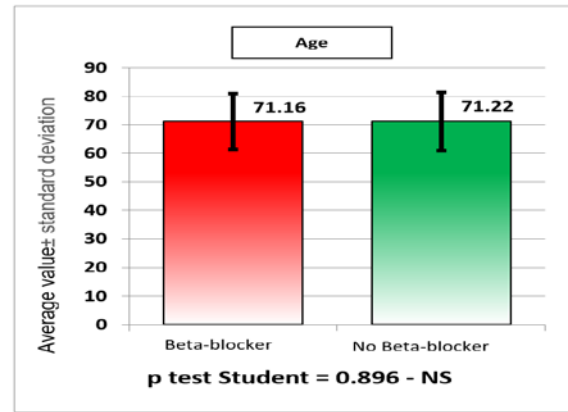

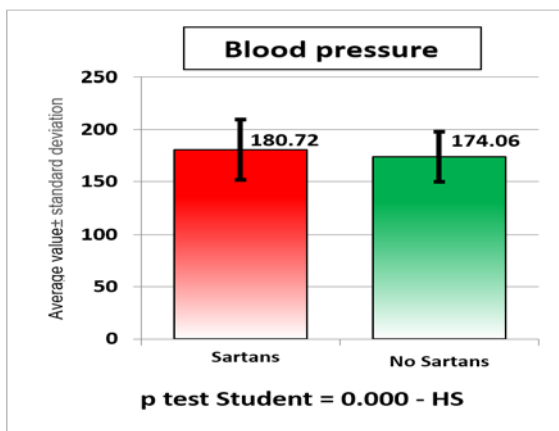*Figure 8. Distribution of patients by age and administration of beta-blocker.*

Figure 7. Distribution of patients by BP value and administration of sartans.
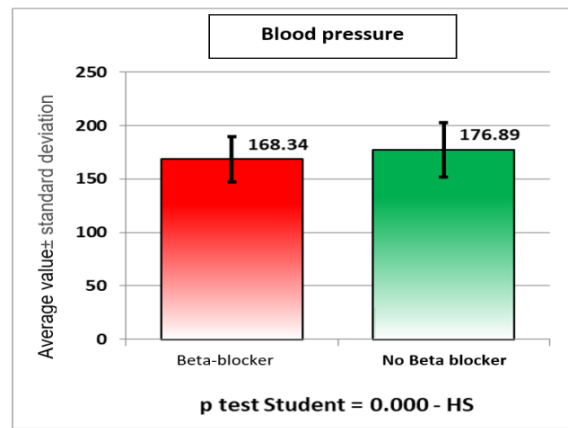

Figure 9. Distribution of patients by BP value and administration of beta-blocker.

In the group of 3050 patients we showed that there was no significant difference between the average ages of those who received treatment with beta-blockers, and those who did not receive, respectively (p=0.896>0.05) (Figure 8).

However, we identified a highly significant lower systolic blood pressure in those who received beta-blockers compared to those who did not receive this treatment (p=3.45×10^{-17}<0.001) (Figure 9).

We monitored a subgroup of 587 patients admitted between January and December 2017, recalling them at six months intervals for blood pressure measurement.

We identified a significantly higher percentage of cases of lowering BP in patients who had Ca-blockers prescribed compared to those who did not, with the result of the Chi square test being p=0.007<0.05 (Figure 10).

Although the percentage of those with low BP was higher among those who have undergone treatment with sartans too, the difference was not statistically significant (Chi square test p=0.475>0.05) (Figure 11).
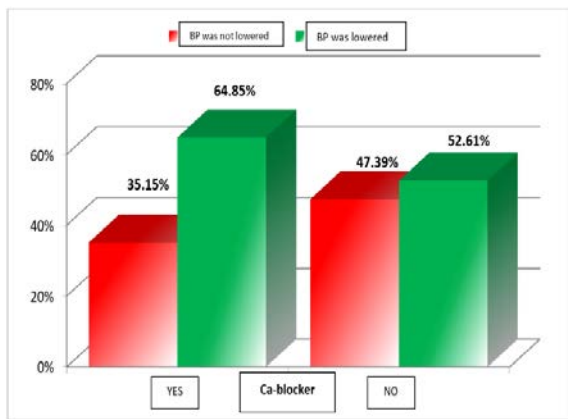
Figure 10. Distribution of patients by the administration of calcium-blocker.
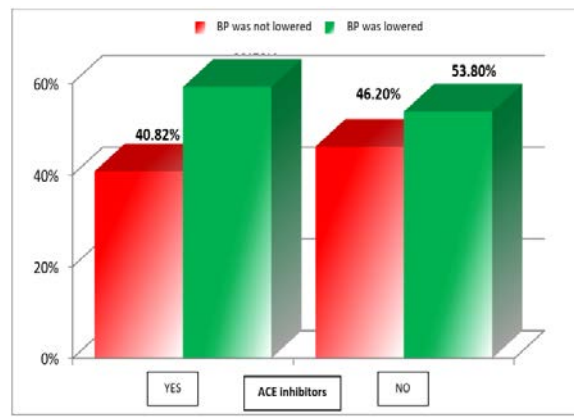

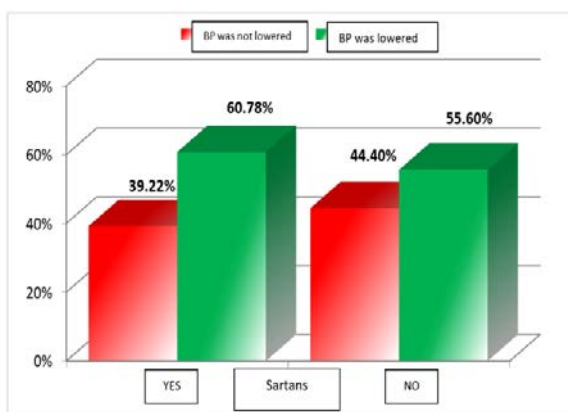**Figure 12. Distribution of patients by the administration of ACE inhibitors.**

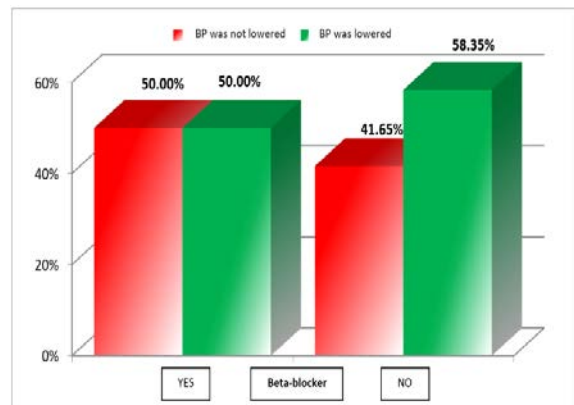**Figure 11. Distribution of patients by the administration of sartans.**

Figure 13. Distribution of patients by the administration of beta-blocker.

Also, although the percentage of those with low BP was higher among those who have undergone treatment with IEC, the difference was not statistically significant (p=0.195>0.05) (Figure 12).

Apparently, the percentage of patients with low BP was higher among those who did not have beta-blockers, alone or in combination with other drugs, but the difference was also not statistically significant, p=0.068>0.05 (Figure 13).

Discussions

Arterial Hypertension is a chronic condition defined as blood pressure above normal (120-139/80-89mm HG). According to the latest studies, AHT is an important public health problem affecting over one billion people, and by 2025 an estimate shows that AHT will affect 1.5 billion [7,8].

In addition to changing the lifestyle, the vast majority of hypertensive patients also need drug therapy to reach the therapeutic targets of blood pressure.

Blood pressure will decrease by a value that depends on several factors: age, presence of comorbidities and tolerability of treatment.

Angiotensin converting enzyme (ACE) inhibitors [9,10] but also angiotensin II receptor blockers belong to a class of drugs called and known as renin-angiotensin-aldosterone system inhibitors [11-13].

Aldosterone receptor antagonists and renin inhibitors also belong to this class.[14,15] Calcium channel blockers block the entry of calcium ions into the cells. At the myocardial level, calcium

ions generate impulses in the nodal tissue and drive these impulses to the myocardium [16-18].

Excitation and contraction of the myocardium occur with the involvement of calcium ions [19,20].

Due to the different chemical structure and the different way of binding to the calcium channel, these drugs are divided into two classes: dihydropyridines (nifedipine) with high vascular selectivity and non-dihydropyridines (diltiazem and verapamil) with anti-arrhythmic properties due to high nodal tissue selectivity [21-23].

Medication with beta-adrenergic receptor blockers is often used in cardiovascular pathology: angina pectoris, arterial hypertension, arrhythmias, heart failure, aortic dissection, CMHO, mitral valve prolapse, because catecholamines have an important role in the physiology of the cardiovascular system [24-36].

The studied group includes 3050 hypertensive patients admitted to the cardiology section of the Caracal Municipal Hospital between 2013 and 2017.

By analyzing the group from the viewpoint of the administered drug therapy, we found that the majority of patients received treatment with angiotensin converting enzyme inhibitors and from the viewpoint of the drug associations, the most frequent association was between the conversion enzyme inhibitors and the calcium channel blockers.

A peculiarity of our group is that the age of the patients who received inhibitors of the conversion enzyme is lower than that of the patients who did not receive this medication, which is a highly significant difference according to the Student's t-test.

Regarding the administration of calcium blockers, we did not find a highly significant difference between the ages of the patients who received, and those who did not receive this therapy, respectively.

According to the data from the literature and in our group the age of the patients who received medication with calcium channel blockers was higher compared to the age of the patients with IEC.

Comparing the average values of the BP with the administration of the drug therapy, we found that there are highly significant differences in the group that received IEC treatment, calcium blocker or sartans as a result of the Student's t-test.

Conclusions

Arterial hypertension is the most common diagnosis in patients on the lists of family doctors and represents the condition with the highest prescription of medication.

Most cases of arterial hypertension cannot be cured. In our group, administration of ACE inhibitors and Ca-blockers resulted in higher mean BP values compared to other medications.

Acknowledgement

Conflict of interests

None to declare.

References

1. Kaplan NM. Systemic hypertension: mechanisms and diagnosis in Braunwald 'S Heart Desease a textbook of Cardiovascular Medicine Elsevier Saunders, Seventh edition Philadelphia, Pensylvania, 2005, 28:959.
2. Guidelines Sub-Committee. 1999 World Health Organizations-International Society of Hypertension guidelines for the management of hypertension. J Hypertens, 1999, 17:151-183.
3. Bryan Williams, Giuseppe Mancia, Wilko Spiering, Enrico Agabiti Rosei, Michel Azizi ,Michel Burnier, Denis L. Clement, Antonio Coca, Giovanni de Simone, Anna Dominiczak, Thomas Kahan, Felix Mahfoud, Josep Redon, Luis Ruilope, Alberto Zanchetti, Mary Kerins, Sverre E. Kjeldsen, Reinhold Kreutz, Stephane Laurent. Ghidul ESC/ESH 2018 pentru managementul hipertensiunii arteriale. Romanian Journal of Cardiology, 2019, 29(1): 76.
4. Ronald G, Victor and Peter Libby. Systemic Hypertension: Management in Braunwald 'S Heart Desease a textbook of Cardiovascular Medicine Elsevier Saunders 2014, 44: 953.
5. Vinay Kumar, Abul Abbas, Nelson Fausto, Jon Aster. Pathologic Basis of Disease (8th ed). Saunders Elsevier, 2010, 11:450.
6. Giuseppe Mancia, Robert Fagard, Krzysztof Narkiewicz, Josep Redon, Alberto Zanchetti, Michael Böhm, Thierry Christiaens, Renata Cifkova, Guy De Backer, Anna Dominiczak, Maurizio Galderisi, Diederick E. Grobbee, Tiny Jaarsma, Paulus Kirchhof, Sverre E. Kjeldsen, Stéphane Laurent, Athanasios J. Manolis, Peter M. Nilsson, Luis Miguel Ruilope, Roland E. Schmieder, Per Anton Sirnes, Peter Sleight, Margus Viigimaa, Bernard Waeber, Faiez Zannad, ESH Scientific Council, Josep Redon, Anna Dominiczak, Krzysztof Narkiewicz, Peter M. Nilsson, Michel Burnier, Margus Viigimaa, Ettore Ambrosioni, Mark Caufield, Antonio Coca, Michael Hecht Olsen, Roland E. Schmieder, Costas Tsioufis, Philippe van de Borne. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Eur Heart J, 2013, 34:2159-2219.
7. Park JB, Kario K, Wang JG. Systolic hypertension: an increasing clinical challenge in Asia. Hypertens Res. 2015, 38(4):227-236.

8. Mubarik S, Malik SS, Mubarak R, Gilani M, Masood N. Hypertension associated risk factors in Pakistan: A multifactorial case-control study. J Pak Med Assoc. 2019, 69(8):1070-1073.

9. Simion R, Heller, DM, FRCP and on behalf of the ADVANCE Collaborative Group-A summary of the ADVANCE Trial. Diabetes Care, 2009, 32:s357-s361.

10. Connolly S, Yusuf S, Budaj A. Rationale and design of ACTIVE: the atrial fibrillation clopridogrel trial with irbesartan for prevention of vascular events. Am Heart J 2006, 151:1187-1193.

11. Atlas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic, J Manag Care Pharm. 2007, 13(8):9-20.

12. López-Sendón J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease, European Heart Journal, 2004, 25:1454-1470.

13. Vinay Kumar, Abul Abbas, Nelson Fausto, Jon Aster. Pathologic Basis of Disease (8th ed.). Saunders Elsevier, 2010, 11:493.

14. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting: pathophysiology, diagnosis, and treatment. Neurosurg Clin N Am, 2010, 21 (2): 339-52.

15. Amy Barreras, Cheryle Gurk-Turner. AngiotensinII receptor-blockers. Proc (Bayl Univ Med Cent), 2003, 16(1):123-126.

16. Opie LH, Coetzee WA.Fundamental Proprerties: Mechanisms, Classfication, Sites of Action. Clinical use of calcium channel antagonist drugs. Kluwer acaddemic publisher, 1989, 28:45.

17. Kiowski W, Bolli P, Erne P, Hulthén UL, Bühler FR. Mechanisms of action of calcium antagonists in hypertension. J Cardiovasc Pharmacol, 1987, 10(10):23.

18. Opie LH, Gersh BJ. Calcium Channel Blockers. Drugs for the Heart, 8th edition. Elsevier Saunders, Philadephia, 2013, 5:64-92.

19. Abernthy DR, Schwartz JB. Calcium-antagonist drugs. N Engl J Med 1999, 341:1447-1455.

20. Elliott WJ, Ram CVS. Calcium Channel Blockers. J Clean Hypertens 2011, 13:687-689.

21. Kusama Y, Kodani E, Nakagomi A, Otsuka T, Atarashi H, Kishida H, Mizuno K. Variant Angina and Coronary Artery Spasm: The Clinical Spectrum, Phatophysiology and Management. J Nippo N Med Sch, 2011, 78:4-12.

22. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH. 2013 ESC Guidelines on the Management of stable Coronary Artery Disease The task Force on the Management of stable Coronary Artery Disease of the European Society of Cardiology. Eur Heart J, 2013, 34:2949-3003.

23. Daniel Gherasim, Mircea Iurciuc, Cristina Voiculet, Alina Giuca, Virgil Petrescu, Florin Maghiar, Alexandra Gherghina, Adrian Tase, Carmen Ginghina. Investigation of patients' adherence to Angiotensin II Receptor Blockers drug treatment for hypertensive patients in primary medical care (I ADHERE). Romanian Journal of Cardiology, 2013, 23(4):324-330.

24. Opie LH, Gersh BJ. Calcium Channel Blockers. Drugs for the Heart, 8th edition. Elsevier Saunders, Philadephia, 2013, 5:30.

25. Andrea Barbuti, Biagio Gravante, Monica Riolfo, Raffaella Milanesi, Benedetta Terragni, Dario DiFrancesco. Localization of pacemaker channels in lipid rafts regulates channel kinetics. Circulation Research, 2004, 94(10):1325-1331.

26. Lionel H. Opie, Donald M. Bears. Mechanisms of Cardiac Contraction and Relaxation in Braunwald's heart disease: A textbook of cardiovascular medicine, 10th edition, Elsevier Saunders, Philadephia, 2015, 21:440-444.

27. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie 2013.ESC guidelines on the management of stable coronary artery disease. Eur Heart J, 2013, 34(38):2949-3003.

28. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-Segment elevation. Eur Heart J, 2016, 37(3):267-315.

29. Chatterjee S, Chaudhuri D, Vedanthan R, Fuster V, Ibanez B, Bangalore S, Mukherje L. Early intravenous beta blockers in patients with acute coronary syndrome-a meta-analysis of randomized trials. Int J Cardiol 2013, 168:915-921.

30. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P. ESC guidelines for the management of acute myocardial infarction în patients presenting with ST-Segment elevation: The Task Force on the management of ST-Segment elevation acute myocardial infarction of the European society of cardiology (ESC). Eur Heart J. 2012, 33(20):2569-2261.

31. Yano M, Yamamoto T, Ikemoto N, Matsuzaki M. Abnormal ryanodine receptor function in heart failure. Pharmacol Ther, 2005, 107(3):377-91.

32. Carmen G, Andreea C, Andreea R. Antagonitii de receptori beta adrenergici. Compendiu de terapie a bolilor cardiovasculare, 2016, 1:11-25.

33. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012:The Task Force For The Diagnosis And Treatment Of Acute And Cronich Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J, 2012, 33(14):1787-1847.

34. Giuseppe Mancia, Robert Fagard, Krzysztof Narkiewicz, Josep Redon, Alberto Zanchetti, Michael Böhm, Thierry Christiaens, Renata Cifkova, Guy De Backer, Anna Dominiczak, Maurizio Galderisi, Diederick E. Grobbee, Tiny Jaarsma, Paulus Kirchhof, Sverre E. Kjeldsen, Stéphane Laurent, Athanasios J. Manolis, Peter M. Nilsson, Luis Miguel Ruilope, Roland E. Schmieder, Per Anton Sirnes, Peter Sleight, Margus Viigimaa, Bernard Waeber, Faiez Zannad, ESH Scientific Council, Josep Redon, Anna Dominiczak, Krzysztof Narkiewicz, Peter M. Nilsson, Michel Burnier, Margus Viigimaa, Ettore Ambrosioni, Mark Caufield, Antonio Coca, Michael Hecht Olsen, Roland E. Schmieder, Costas Tsioufis, Philippe van de Borne. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Eur Heart J, 2013, 34:2178-2190.

35. Turnbull F1, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, Woodward M, MacMahon S. Blood Pressure Lowering Treatment Trialists'Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med, 2005, 165(12):1410-9.

36. Wiyonge CS, Bradley HA, Volmink J, Mayosi BM, Mbenin A, Opie LH. Beta-blockers for hypertension. Cochrane Database Syst Rev, 2012, 11:10.

37. The CAFE Investigators, and CAFE Steering Committee and Writing Committee, Bryan Williams, Peter S. Lacy, Simon M. Thom, Kennedy Cruickshank, Alice Stanton, David Collier, Alun D. Hughes, H. Thurston, Michael O'Rourke and for the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Investigators. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation, 2006, 113:1213-1225.

Corresponding Author: Anda-Mariana Braşoveanu, Department of Cardiology, Public Hospital of Caracal, Olt Count, 36 Plevnei Street, 235200 Caracal, Romania, e-mail: anda_serbann@yahoo.com