Level and predictors of global cardiovascular risk among untreated newly diagnosed and treated black patients with arterial hypertension.

A cross sectional study

Lepira FB*,

Kayembe PK**,

M'Buyamba-Kabangu JR***.

Correspondence
François Lepira Bompeka, *MD, PhD*
Division of Nephrology; Department of Internal Medicine
University of Kinshasa Hospital
Po Box 123 Kinshasa XI
Phone: +243 99 99 16 466 ; E-mail: lepslepira@yahoo.fr
DR. Congo

Résumé

Objectif: évaluer le niveau et les déterminants du risque cardiovasculaire global chez les hypertendus nouvellement diagnostiqués et les patients noirs sous traitement antihypertenseur suivis en ambulatoire au Département de Médecine Interne des Cliniques Universitaires de Kinshasa.
Méthodes : analyse transversale des données cliniques et paracliniques de 100 patients hypertendus (47 femmes ; 47%) âgé de 20 ans ou plus. La table de stratification du risque cardiovasculaire de l'OMS/SIH de 2003 a été utilisée pour évaluer le niveau du risque cardiovasculaire global. La régression logistique multiple a été utilisée pour évaluer les déterminants indépendants du risque cardiovasculaire global en utilisant l'hypertrophie du ventricule gauche comme marqueur.
Résultats : Cinquante patients recevaient un traitement antihypertenseur ; ils étaient plus âgés (52 ± 8 vs 45 ± 9 ans; $p \leq 0.001$) et présentaient une hypertension (HTA) de plus longue durée (100 ± 77 vs 32 ± 48 mois, $p \leq 0.001$), une pression pulsée (PP) plus élevée (57 ± 15 vs 51 ± 14 mmHg; $p \leq 0.05$), un tour de taille plus grand (95 ± 12 vs 90 ± 11 cm; $p \leq 0.0001$) et une plus grande proportion d'hypertrophie ventriculaire gauche (68 vs 28%; $p \leq 0.05$) que ceux non encore traités. Dans le sous groupe de patients non encore traités, un risque cardiovasculaire (CV) global élevé a été observé chez 8 (16%), 30 (60%) et 12 (100%) patients présentant respectivement, une HTA grade 1, 2 et 3. Un risque CV global élevé a été observé chez 10 (83%), 17 (94%) et 12 (71%) patients sous traitement antihypertenseur ayant respectivement, une HTA grade 1, 2 et 3. En analyse multivariée, la durée d'HTA, le taux de HDL-c, la glycémie à jeun et le traitement antihypertenseur ont émergé comme les principaux déterminants du risque CV global. Une HTA de 2 ans ou plus était associée à un risque 7 fois plus élevé (OR ajusté 7.23; 95% CI 1.57-42.88) ; par contre, un taux élevé de HDL-c (OR ajusté 0.19 95% CI 0.05-0.65; p = 0.008) et le traitement antihypertenseur (OR ajusté 0.23 95% CI 0.08-0.64; p = 0.005) étaient des facteurs protecteurs.
Conclusion : quels que soient le stade et le statut thérapeutique, l'HTA dans la présente série est associée à un risque CV global élevé soulignant la nécessité d'une stratégie thérapeutique plus agressive.

Mots clés: risque cardiovasculaire global, niveau, déterminants, HTA, Noirs.

* Division of Nephrology, ***Hypertension unit, Department of Internal medicine, University of Kinshasa hospital and
Department of Epidemiology and Biostatistics, Kinshasa School of Public Health, University of Kinshasa

SUMMARY

Objective: to evaluate the level and determinants of global cardiovascular (CV) risk in untreated newly diagnosed and treated black patients with arterial hypertension.
Design: cross sectional study
Setting: Hypertension Outpatient Clinic, University of Kinshasa Hospital.
Methods: We obtained anthropometric, clinical, biological and electrocardiographic (ECG) measurements in 100 consecutive patients with arterial hypertension (47 females, 47%) aged 20 years or more. Risk stratification tables from WHO/ISH guidelines (2003) were used to stratify global CV risk. Multivariate logistic regression analysis was used to assess the independent predictors of hypertrophy of left ventricular based on ECG (ECG-LVH) as a marker of global CV risk.
Results: fifty patients (50%) were receiving antihypertensive therapy; they were older (52 ± 8 vs 45 ± 9 years; $p \leq 0.001$) and had hypertension for long time (100 ± 77 vs 32 ± 48 months, $p \leq 0.001$), a higher pulse pressure, PP (57 ± 15 vs 51 ± 14 mmHg; $p \leq 0.05$), waist circumference (95 ± 12 vs 90 ± 11 cm; $p \leq 0.0001$) and proportion of LVH (68 vs 28%; $p \leq 0.05$) in comparison to untreated patients for hypertension. In the group of untreated newly diagnosed patients, high CV risk was observed in 8 (16%), 30 (60%) and 12 (100%) patients in hypertension grade 1, 2 and 3, respectively. High CV risk was observed in 10 (83%), 17 (94%) and 12 (71%) treated patients in hypertension grade 1, 2 and 3, respectively. In multivariate adjusted analysis, the main determinants of CV risk were duration of hypertension (DHT), HDL-c, fasting plasma glucose and hypertension treatment. Patients with DHT > 2 years had a 7 times risk (adjusted OR 7.23; 95% CI 1.57-42.88) than those with DHT < 2 years. The risk was lower in patients with HDL-c > 1.03 mmol/l (adjusted OR 0.19 95% CI 0.05-0.65; p = 0.008) and those on hypertension treatment (adjusted OR 0.23 95% CI 0.08-0.64; p = 0.005).
Conclusion: Whatever the stage and the therapeutic status in these case series, hypertension is associated with high global CV risk highlighting the need for more aggressive strategy treatment.

Key words: global CV risk, predictors, hypertension, Blacks.

Introduction

Hypertension, notably untreated or uncontrolled, is a major risk factor for cardiovascular disease (CVD) morbidity and mortality (1). This high CV risk is thought to be partly explained by metabolic distur-bances, primarily linked to hypertension but also secondarily influenced by antihyper-tensive drugs themselves, target organ damage and associated clinical conditions (2-6). Thus, effective and rationale management of hypertension should be based on a comprehensive strategy integra-ting control of high blood pressure (BP) and associated risk factors (6). In this regard, most current hypertension guidelines emphasize the importance of assessing and managing global or total CV risk in an individual patient (3-7). Indeed, even in patients with controlled BP, the presence of additional risk factors is associated with increased risk of CV events (2-5). Accurate global CV risk evaluation appears as a prerequisite for devising cost-effective therapeutic strategies and setting the BP goal to be achieved and the intensity with it should be pursued in hypertensive patients (3, 8).

In Democratic Republic of Congo (DRC), the prevalence of hypertension has increased dramatically over the past decade reaching levels around 30% in the general population (9-12). Hypertension is associa-ted with multiple risk factors (13, 14). Despite the growing evidence of the importance of global CV risk on the care of hypertensive patients, antihypertensive therapy strategy remains still focused on the reduction of BP without a particular attention to other CV risk factors. The aim of the present study was to evaluate the level and determinants of global CV risk in untreated newly diagnosed and treated patients with arterial hypertension attending the Outpatient Hypertension Clinic at the Kinshasa University Hospital.

Material and methods

Cross sectional analysis for the presence of CKD and associated risk factors of data from 100 patients with essential hypertension enrolled consecutively in a case-control study of lipid and non lipid risk factors, described in details elsewhere (13). Hypertension was defined as essential only on the basis of medical history, physical examination and urinalysis; specific tests to rule out secondary causes of hypertension were not performed. Available lifestyle data included self reported physical activity and smoking habits. Data were also available for the duration of hypertension and current antihypertensive medication. Measures of adiposity included body mass index (BMI) and waist circumference. All patients had the following measurements made after 12 h fasting: total cholesterol (TC), high density lipoprotein-cholesterol (HDL-c), triglyce-rides, glucose, uric acid, fibrinogen, and creatinine. Low density lipoprotein-choles-terol (LDL-c) and creatinine clearance (CrCl) were calculated according to Friedewal (15) and Cockcroft and Gault (16) equations, respectively. Metabolic syndrome (MS) was defined according to NCEP-ATP III criteria (17). Hyperfibrinogenemia was defined as plasma fibrinogen levels > 3.5 g/l (18); hyperuricemia, as uric acid levels > 413 µmol/l (19). Electrocardiographic left ventricular hypertrophy (ECG-LVH) was defined according to Cornell voltage index as R wave in lead aVL ≥ 13 mm (20). Global CV risk defined as the likelihood of developing a major CV event (fatal or non fatal stroke or myocardial infarction) within the next 10 years was stratified in 3 categories (low, medium or moderate, high) according to 2003 WHO/ISH guidelines (21). All patients gave informed consent and research and ethic committee approved data collection.

Data are expressed as mean ± standard deviation (SD) or relative frequency in percent. The distribution of duration of hypertension and triglycerides being positively skewed, non parametric test

(Mann Whitney) was used for these variables. Chi square and Student t tests were used for comparing categorical and continuous variables normally distributed, respectively. Multiple logistic regression analysis was used to evaluate the independent contribution of selected variables in the global CV risk using LVH as a surrogate marker of CV risk. P value < 0.05 defined the level of statistical significance. All statistical analyses were performed with SPSS for Windows version 12.0.

Results

- General characteristics of the study population

Clinical and biological characteristics of the study population as a whole and stratified by treatment status are summarized in tables 1 and 2.

Table 1. Clinical characteristics of the study population as a whole and stratified by treatment status

Characteristic	Whole group (n = 100)	Untreated (n = 50)	Treated (n = 50)
Gender: M/F	53/47	31/19	28/22
Age, years	49 ± 10	45 ± 9	52 ± 8***
DHT, months	66 ± 72	32 ± 48	100 ± 77***
Drug regimen			
1 drug,%			54
2 drugs,%			40
3 drugs,%			6
BP control,%			6
Smoking,%	10	8	12
Alcohol,%	16	12	20
MS,%	33	30	36
LVH,%	49	28	68***
BMI, Kg/m^2	27 ± 5	27 ± 4	27 ± 5
WC, cm	94 ± 12	90 ± 11	95 ± 12***
SBP, mmHg	155 ± 19	152 ± 14	158 ± 22
DBP, mmHg	101 ± 10	101 ± 7	101 ± 10
PP, mmHg	54 ± 14	51 ± 16	57 ± 12*
Heart rate, b/min	79 ± 11	77 ± 14	80 ± 14

Data are expressed as mean ± SD or relative frequency in percent.
M: male, F: female, DHT: duration of hypertension, MS: metabolic syndrome LVH, left ventricular hypertrophy BMI: body mass index, WHR: waist circumference,
SBP: systolic blood pressure DBP, diastolic blood pressure PP, pulse pressure b, beat min, minute
*p ≤ 0.05 **p ≤ 0.01 ***p ≤ 0.001

Table 2. Biological characteristics of the study population as a whole and stratified by treatment status

Characteristic	Whole group (n = 100)	Untreated (n = 50)	Treated (n = 50)
TC, mmol/L	5.01 ± 1.49	4.88 ± 1.44	4.90 ± 1.49
LDL-c, mmol/L	3.36 ± 1.31	3.30 ± 1.29	3.42 ± 1.31
HDL-c, mmol/L	1.27 ± 0.38	1.24 ± 0.14	1.31 ± 0.41
TG, mmol/L	1.07 ± 0.67	1.08 ± 0.46	1.05 ± 0.49
Glucose, mmol/L	5.05 ± 0.77	4.94 ± 0.77	5.22 ± 0.77
Uric acid, mmol/L	393 ± 112	382 ± 97	411 ± 138
Fibrinogen, g/L	2.80 ± 0.80	2.79 ± 0.86	2.82 ± 0.73
Creatinine, µmol/L	85 ± 16	109 ± 34	113 ± 37
CrCl, mL/min	97 ± 16	78 ± 25	85 ± 40

Data are expressed as mean ± SD
TC: total cholesterol, LDL-c: low-density lipoprotein-cholesterol male, HDL-c: high-density lipoprotein-cholesterol, TG: triglycerides, CrCl: creatinine clearance min, minute
*p ≤ 0.05 **p ≤ 0.01 ***p ≤ 0.001

A total of 100 consecutive hypertensive patients (47 women) were examined. Their mean age was 49 ± 10 years and average levels of BMI and BP were 27 ± 5 Kg/m^2 and 155 ± 19/101 ± 10 mmHg, respectively. Fifty patients (50%) were receiving antihypertensive medication as monotherapy (n = 27) or combined therapy (two drugs, n = 20; three drugs, n = 3); treatment consisted of calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors, central acting drugs and beta blockers in 42%, 30%, 24%, 24% and 16% of patients, respectively.

Compared to untreated newly diagnosed patients, those receiving antihypertensive drugs were older (52 ± 8 vs 45 ± 9; p ≤ 0.001) and had hypertension with a longer duration (100 ± 77 vs 32 ± 48 months; p ≤ 0.001), a higher pulse pressure, PP (57 ± 15 vs 51 ± 14 mmHg; p ≤ 0.05), waist circumference (95 ± 12 vs 90 ± 11 cm; p ≤ 0.0001) and proportion of LVH (68 vs 28%; p ≤ 0.05) in comparison to those not yet on treatment. Differences observed between other biological variables of interest did not reach the level of statistical significance.

- Level of the global CV risk

According to 2003 WHO/ISH guidelines, hypertension grade 1, 2 and 3 was found in 8 (16%), 30 (60%) and 12 (24%) untreated newly diagnosed patients, respectively. High CV risk (> 20%) was observed in 6 (75%), 22 (73%) and 12 (100%) patients in hypertension grade 1, 2 and 3, respectively. Among treated patients, hypertension grade 1, 2 and 3 was observed in 12 (24%), 18 (36%) and 17 (34%) patients, respectively. High CV risk was present in 10 (83%), 17 (94%) and 12 (71%) patients, respectively.

Table 3. Multivariate predictors of the risk of left ventricular hypertrophy in hypertensive patients

Variable	β	SE	p value	OR 95% CI
DHT < 2 yrs	1			
DHT> 2 yrs	1.979	0.830	0.012	7.23 (1.57-42.88)
HDL-c < 1.03 mmol/l	1			
HDL-c > 1.03 mol/l	-1.647	0.621	0.008	0.19 (0.05-0.65)
FPG < 6.11 mmol/l	1			
FPG > 6.11 mmol/l	- 1.638	0.740	0.027	0.19 (0.04-0.82)
Antihypertensive treatment:				
No	1			
Yes	-1.467	0.525	0.005	0.23 (0.08-0.64)

B: regression coefficient, SE: standard error, aOR: adjusted odd ratio, CI: confidence interval, DHT: duration of hypertension, HDL-c: high density lipoprotein-cholesterol, FPG: fasting plasma glucose

Using LVH as a surrogate marker of global CV risk, duration of hypertension (DHT), HDL-c, fasting plasma glucose (FPG) and treatment status have emerged as the main independent predictors of global CV risk. Patients with hypertension of > 2 years had a 7 fold greater risk (adjusted OR 7.23; 95% CI 1.57-42.88) of having LVH in comparison to those with hypertension < 2 years. The risk was lower in patients with HDL-c > 1.03 mmol/l (adjusted OR 0.19 95% CI 0.05-0.65; p = 0.008), FPG > 6.11 mmol/l (adjusted OR 0.19; 95% CI 0.04-0.82) and those on antihypertensive therapy (adjusted OR 0.23 95% CI 0.08-0.64; p = 0.005).

Discussion

The main findings of the present cross-sectional analysis are as follows: first, treated hypertensives were older with hypertension of a longer duration and had increased PP levels, waist circumference and higher proportions of LVH; second, hypertension whatever the stage and treatment status was associated with increased global CV risk; third, duration of hypertension, HDL-c levels, FPG levels and treatment status have emerged as the main independent predictors of the risk of global CV risk.

Treated hypertensive patients were older with hypertension of longer duration and had increased PP. Age is a well-known powerful CV risk; absolute CV risk for any given level of BP has been reported to rise with age (22). Age-induced CV damage is thought to rely upon the process of CV remodelling (22-25) and the clustering of multiple risk factors (26). Vascular remodelling has been reported to be associated with arterial stiffness (25, 26) and subsequent increase in PP, a powerful CV risk factor (27, 28). In the present analysis, increased PP could be explained by the negative impact of the ageing process and associated risk factors on blood vessels. Another explanation could be the lack (29, 30) or differential control of systolic and diastolic BP with more focus put on the reduction of diastolic BP (31). Treated patients had also higher proportions of LVH. The negative impact of both ageing process and persistence of high BP with associated CV risk factors on CV system could explain the observed increase in LV mass (32). Increased waist circumference observed in treated patients may translate insulin resistance often associated with high BP that can be worsened by antihypertensive drugs (33).

According to current guidelines (2, 3), hypertension whatever the stage and treatment status was associated with high global CV risk. High global CV risk level has been reported to be the threshold

recommended for the initiation and the intensity of pharmacologic therapy (2, 3). BP control in patients with high global CV risk will often need the frequent use of three or more drugs (34). Many epidemiological and clinical studies have shown that an anti-hypertensive therapy based on angiotensin converting enzyme inhibitors (ACEIs), angiotensin II type 1 receptor blockers (ARBs) and calcium channel blockers (CCBs) in combination with HMG CoA reductase inhibitors (Statins) is effective and safe in reducing CV risk (35,36). Despite high residual global CV risk, the majority of treated patients in the present analysis were receiving monotherapy. The observed high global CV risk could also explain the poor BP control in treated patient (37). It has been reported than BP control declines with the increase of the number of risk factors (37).

Duration of hypertension, HDL-c levels, fasting PG and treatment status have emerged as the main predictors of CV risk. Global CV risk appears to increase with duration of hypertension. Duration of hyper-tension could translate as aforementioned the negative impact of ageing process on CV system. High HDL-c seems to be cardio-protective in the present analysis. Increased HDL-c levels have been reported to confer CV protection through inhibition of LDL-c oxidation (38). Elevated levels of FPG paradoxically conferred CV protection. This apparent paradoxical protective effect could be explained by the so-called phenomenon of reverse epidemiology of traditional risk factors seen in chronic diseases (39). Antihypertensive therapy was associated with low CV risk. This finding agrees with previous reports highlighting the role of antihypertensive therapy in the reduction of CV risk (37).

The interpretation of the results of the present study is confronted with some limitations. The cross sectional design of the present analysis precludes clear establish-ment of a causal relationship between LVH as a surrogate marker of CV risk and associated risk factors. Furthermore, the sample size could not allow sufficient power to detect additional associations. The relationship between variables of interest could be attenuated by a regression dilution bias since only a single measurement was performed. One wonders to what extent the conclusions of the present clinical based study could be extrapolated to the general population given the bias in the referral of patients.

Conclusion

The present cross-sectional analysis has shown that hypertension whatever the stage and treatment status is associated with high global CV risk highlighting the need for more aggressive therapeutic strategies. Anti-hypertensive therapy has emerged as one of the main independent predictors of CV risk and confers a CV protective effect. Due to methodological limitations, the results of the present analysis need to be confirmed and validated in a more elaborated study with a sample more representative of hypertensive population.

Author's contribution

LFB conceived of the study and participated in the study design, data acquisition and statistical analysis. MJR contributed in the study design and statistical analysis as well as in reviewing the manuscript. KKP conducted statistical analysis and reviewed the manuscript.

Acknowledgements

The authors gratefully thank Professor J Vandepitte of KU Leuven for kindly providing lipid and lipoprotein kits and KU Leuven Alumni for training opportunities offered to Prof Dr F Lepira to UZ Gathuisberg, Leuven. Warmful thanks to Professor Dr JJ Muyembe, head of the National Institute of Biomedical Research/Health Ministry and Professor Dr N Kayembe, head of the Division of Clinical Biology, University of Kinshasa Hospital for all the facilities obtained to carry out the present study. Finally, we would like to thank all participants who made by their consent the present study possible.

References

1. Abdulle AM, Nagelkerke NJ, Abouchacra S, Pathan JY, Adem A, Obineche EN. Under-treatment and under-diagnosis of hypertension: a serious problem in the United Emirates. *BMC Cardiovasc Disord* 2006; **6** (6): 24.
2. Ritz E. Total cardiovascular risk management. *Am J Cardiol* 2007; **100** (3A): 53J-60J.
3. Mancia G. Total cardiovascular risk: a new treatment concept. *J Hypertens* Suppl 2006; **24** (2): S17-24.
4. Basile J. Management of global cardiovascular risk across the continuum of hypertensive heart disease. *J Clin Hypertens* 2006; **8** (8 Suppl 2): 21-30.
5. Roccatagliata D, Avanzini F, Monesi L, Caimi V, Lauri D, Longoni P, Marchioli R, Tombesi M, Tognoni G, Roncaglioni MC. Is global cardiovascular risk considered in current practice? Treatment and control of hypertension, hyperlipidaemia, and diabetes according to patients risk level. *Vasc Health Risk Manag* 2006; **2**(4): 507-514.
6. Nilson P, Anderson DK, Anderson PE, Schawn A, Ostlind B, Malmborg R, Lithell H, Anderson OK. Cardiovascular risk factors in treated hypertensives- A nationwide, cross-sectional study in Sweden. *J Intern Med* 1993; **233** (3): 239-245.
7. Comisasca P, Avanzini F, Alli C, Colombo F, Tognoni G. Overall cardiovascular risk still ignored in general practice care of hypertension. *J Cardiovasc Risk* 2002; **9**(3): 147-152.
8. Pontremolli R, Leoncini G, Viazzi F, Parodi D, Vaccaro V, Falqui C, Parodi A, Vettoretti S, Ratto E, Deferrari G. Role of microalbuminuria in the assessment of cardiovascular risk in essential hypertension. *J Am Soc Nephrol* 2005; **16** Suppl 1: S39-41.
9. Tshiani K, Nseka M, Musuamba M, Lutete K. Epidemiology of Arterial Hypertension in Zaire. Results from a preliminary survey of 4,988 subjects. (Article in French). *Med Afr N* 1979; **26**: 67-75.
10. M'Buyamba-Kabangu JR, Fagard R, Staessen J, Lijnen P, Amery A. Correlates of blood pressure in rural and urban Zaire. *J Hypertens* 1987; **5**: 371-375.
11. Longo-Mbenza B, Vangu Ngoma D, Nahimana D, Ekwanzala F, Beya C, Mupepe Mayuku D, Mbungu S, M'Buyamba Kabangu JR, Bieleli E. The WHO Stepwise approach to assess prevalence and risk factors of non communicable diseases in Kinshasa, Democratic of the Congo. PASCAR conference abstracts. *Cardiovasc J S Afr* 2007; **15** (2): 111.
12. Sumaili EK, Krzesinski JM, Zinga CV, Cohen EP, Delanaye P, Munyanga SM et Nseka NM. Prevalence of chronic kidney disease in Kinshasa: results of a pilot study from the Democratic Republic of Congo. *Nephrol Dial Transplant* 2009; **24**(1): 117-122. Epub 2008, Aug 20.
13. Lepira FB, M'Buyamba-Kabangu JR, Kayembe PK, Nseka MN. Correlates of left ventricular hypertrophy in Black patients with arterial hypertension. *Cardiovasc J S Afr* 2006; **17** (1): 7-11.
14. Lepira FB, M'Buyamba-Kabangu JR, Kayembe PK, Ndeka MN. Correlates of serum lipids and lipoproteins in Congolese patients with arterial hypertension. *Cardiovasc J S Afr* 2005; **14** (5): 249-255.
15. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of LDL-cholesterol without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**: 499-508.
16. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31-41.
17. National Heart Lung and Blood Institute. Executive Summar of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment panel III). *JAMA* 2001; **285**: 2486-2497.
18. Fogari R, Annalia Z, Marasi G, Vanasia A, Villa A. Association of plasma fibrinogen levels and cardiovascular risk factors in hypertensive men. *Hypertension* 2006; **48**: 1043-1049.
19. Campo C, Ruilope LM, Segura J, Rodicio JL, Garcia-Robles L, Garcia-Puig J. Hyperuricemia, low urate excretion and target organ damage in essential hypertension. *Blood Press* 2003; **12** (5-6): 277-283.
20. De Kreutzenberg SV, Avogaro A, Tienno K, Del Prato S. Left ventricular mass in type 2 diabetes mellitus. A study employing a simple ECG index: the Cornell Voltage Index. *J Endocrinol Invest* 2000; **22** (3): 139-144.
21. 2003 WHO/ISH. Statement on management of hypetension. WHO/ISH writing group. *J Hypertens* 2003; **21**: 1983-1992.
22. Tuomilehto P. Impact of age on cardiovascular risk: implication for disease management. *Atherosclerosis* 2004; **5** (2 Suppl): 9-17.
23. Kenchaiah S, Pfeifer MA. Cardiac remodelling in systemic hypertension. *Med Clin North Am* 2004; **88** (1): 115-130.
24. Plante GE. Impact of ageing on the body vascular system. *Metabolism* 2003; **52** (10 Suppl 2): 31-35.
25. Smith SM, Mensah GA. Population aging and implications for epidemic cardiovascular

disease in sub-Saharan Africa. *Ethn Dis* 2003; **13** (2 Suppl 2): S77-80.
26. Ramos R, Marrugat J, Basagana X, Sala J, Masia R, Elosua R. REGICOR Investigators. The role of aging in cardiovascular risk factors clustering in non diabetic population free of coronary heart disease. *Eur J Clin Epidemiol* 2004; **109** (23 Suppl.: II-15-19.
27. Benetos. Influence of age, risk factors and cardiovascular and renal disease on arterial stiffness: clinical implications. *Am J Hypertens* 2002; **15**(12): 1201-1208.
28. Dart M, Kingwall BA. Pulse pressure – Review of mechanisms and clinical relevance. *J Am Coll Cardiol* 2004; **37** (4): 775-784.
29. Cushman WC. The burden of uncontrolled hypertension: morbidity and mortality associated with disease progression. *J Clin Hypertens* 2003; **5** (3 Suppl 2): 14-22.
30. Fagard RH, Van Den Enden M, Leeman M, Warling X. Survey on treatment of hypertension and the implementation of WHO/ISH risk stratification in primary care in Belgium. *J Hypertens* 2002; **20** (7):1297-1302.
31. Lloyd-Jones DM, Evans JC, Larsa MG, O'Donnell CJ, Roccella EJ, Levy D. Differential control of systolic and diastolic blood pressure. Factors associated with the lack of blood pressure control. *Hypertension* 2000; **36**: 594-599.
32. Varagic, Heart, aging and hypertension. *Curr Opin Cardiol* 2001; **16**: 336-341.
33. Schillaci G, Pirro M, Vaudo G, Gemelli F, Marchesi S, Porcellati C, Mannarino E. Prognostic value of the metabolic syndrome in essential hypertension. *J Am Coll Cardiol* 2004; **43** (10): 1817-1822.
34. Swift PA, Mc Gregor GA. The frequent need of three or more drugs to treat essential hypertension. What evidence for optimal combinations? *J Renin Angiotensin Aldosterone* 2002; **3** (2): 103-108.
35. Athyros VG, Mikhailidis DP, Papageorgiu AA, Boulokos VI, Pehlinadis AN, Symonidis AN, Elisaf M. Effects of statins and angiotensin converting enzyme inhibitors alone or in combination on clinical outcomes in patients with coronary heart disease. *J Hum Hypertens* 2004; **18** (11): 781-788.
36. FenvesA, Ram CV. Are angiotensins converting enzyme inhibitors and angiotensin II type 1 receptor blockers becoming the treatment of choice in African Americans? *Curr Hypertens Rep* 2002; **4** (4): 286-289.
37. Welch V, Tang SS. Treatment and control of blood pressure and lipids in patients with hypertension and additional risk factors. *Am J Cardiovasc Drugs* 2007; **7** (51): 381-389.
38. Zhang B, Bai H, Liu R, Kumagai K, Itabe H, Takama T, Saku K. Serum HDL-c levels modify the association between plasma levels of oxidatively modified LDL-c and cardiovascular disease in men. *Metabolism* 2004; **53** (4): 423-429.
39. Kalantar-Zadeh K, Kilpatrick RD, Wu DY. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 2004; **43** (8): 1439-1444.