New Cardiovascular Risk Factors and Their Use for an Accurate Cardiovascular Risk Assessment in Hypertensive Patients

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ABSTRACT

Objectives: To analyze the predictive value of new cardiovascular (CV) risk factors for CV risk assessment in the adult Romanian hypertensive (HT) population.

Methods: Hypertensive adults aged between 40-65 years of age, identified in national representative SEPHAR II survey were evaluated by anthropometric, BP and arterial stiffness measurements: aortic pulse wave velocity (PWVao), aortic augmentation index (AIXao), revers time (RT) and central systolic blood pressure (SBPao), 12 lead ECGs and laboratory workup. Values above the 4th quartile of mean SBP standard deviation (s.d.) defined increased BP variability. Log(TG/HDL-cholesterol) defined atherogenic index of plasma (AIP). Serum uric acid levels above 5.70 mg/dl for women and 7.0 mg/dl for males defined hyperuricemia (HUA). CV risk was assessed based on SCORE chart for high CV risk countries. Binary logistic regression using a stepwise likelihood ratio method (adjustments for major confounders and colliniarity analysis) was used in order to validate predictors of high and very high CV risk class.

Results: The mean SBP value of the study group was 148.46±19.61 mmHg. Over forty percent of hypertensives had a high and very high CV risk. Predictors of high/very high CV risk category validated by regression analysis were: increased visit-to-visit BP variability (OR: 2.49; 95%CI: 1.67-3.73), PWVao (OR: 1.12; 95%CI: 1.02-1.22), RT (OR: 0.95; 95% CI: 0.93-0.98), SBPao (OR: 1.01; 95%CI: 1.01-1.03) and AIP (OR: 7.08; 95%CI: 3.91-12.82).

Conclusion: The results of our study suggests that the new CV risk factors such as increased BP variability, arterial stiffness indices and AIP are useful tools for a more accurate identification of hypertensives patients at high and very high CV risk.

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INTRODUCTION

Romania is currently a high CV risk country where unfortunately cardiovascular disease (CVD) prevention still represents a major challenge for the whole population, politicians, and public health workers (1-5).

Identification of persons at high risk of developing CVD, but who are currently asymptomatic is one of the main objectives of prevention.

At present, cardiovascular risk assessment in daily clinical practice is based on risk algorithms such as Framingham (6) and SCORE (7), in their majority based on traditional CV risk factors and without taking into account markers of subclinical target organ damage, which are proved to have an additive value for CV risk assessment (8,9).

Thus, in the absence of an accurate assessment of CV risk, therapeutic strategies based on risk levels, recommended by current guidelines for the management of arterial hypertension (10), may be initiated later, leaving an individual with a real high CV risk unprotected due to its inadequate classification as belonging to a lower CV risk class.

At present over 100 new risk factors are listed in the literature that can improve the CV risk assessment.

Unlike Framingham and SCORE, risk assessment algorithm recommended 2013 ESH-ESC guidelines includes markers of target organ damage: pulse pressure (PP) over 60 mmHg, left ventricular hypertrophy (LVH) on ECG or on echocardiography, intima-media thickness (IMT) >0.9 mm, ankle-brachial index (ABI) <0.9, carotid-femoral pulse wave velocity (PWVcf) >10 m/s, estimated glomerular filtration rate (eGFR) 30-60 ml/min/1.73 m², and the presence of microalbuminuria (10).

Arterial stiffness markers, such as pulse wave velocity, augmentation index and central aortic blood pressure has proved their additive value over traditional scores - Framingham and SCORE, to identify patients at high CV risk (11-17).

With the appearance on the market of oscillometric devices for arterial stiffness measurement, which allow a much faster and easier acquisition of these data, has opened up the perspective arterial stiffness assessment in daily practice and at populational level, this kind of devices being adequate for use in epidemiologic studies (18-23).

Moreover, by extending the use of ambulatory blood pressure monitoring and home blood pressure monitoring, hypertensive patients may benefit from the evaluation of blood pressure variability that in condition of very high values may represent a CV risk factor per se, independent of the blood pressure values (24-28).

Last but not least, increased levels of serum uric acid (SUA) and atherogenic index of plasma (AIP) represent two new CV risk factors that can be readily assessed in practice and which are proven in the scientific literature as predictors of major cardiovascular events (29-33).

Up to now, there are a limited number of studies that have addressed the improvement in CV risk assessment by adding markers of subclinical target organ damage to conventional risk algorithms at population level.

The main objectives of this study are to analyze the CV risk of the Romanian adult hypertensive population, based on traditional risk algorithms, to evaluate the predictive power of new cardiovascular risk factors to correctly classify hypertensive patients into high CV risk categories.

METHODS

From the total number of 798 adult hypertensive subjects identified in the national representative SEPHAR II (Study for the Evaluation of Prevalence of Hypertension and Cardiovascular Risk in Romania II) survey we selected those satisfying the age criterion 40-65 years of age (this being the age interval for which SCORE charts are applied for CV risk assessment). Thus are study sample included a total number of 424 hypertensive adults.

The detailed methodology of SEPHAR II has been previously published and will not be presented further (1-5).

Studied parameters and their assessment

Blood pressure (BP) values were defined by the arithmetic mean of the second and third measurements from each of the 2 study visits, without taking into consideration the first measurement from each study visit. BP measurements were made using an automatic oscillometric BP measuring device – model A&D UA 95 Plus (A&D Company Limited, Tokyo, Japan)
certified by the Association for the Advancement of Medical Instrumentation. Measurements were separated by 1 minute at least, according to ESH/ESC recommendations (10).

Visit-to-visit blood pressure variability (BPV) was assessed by standard deviation (s.d.) of the mean systolic blood pressure (SBP). Values above the 75th percentile of mean SBP's d. distribution defined increased SBP variability.

Arterial stiffness parameters were measured during the second study visit - aortic pulse wave velocity (PWVao), reversion time (RT), central (aortic) systolic blood pressure (SBPao) and aortic augmentation index (AIxao), using an oscillometric device - Arteriograph IrDA (Medexpert, Budapest, Hungary) according to a specific methodology (18).

Smoking was defined as current smoking of at least one cigarette per day.

Hypercholesterolemia was assessed by NCEP ATPIII recommendations as total serum cholesterol (TC) level ≥ 200 mg/dl (34). Log (TG/HDL-cholesterol) defined atherogenic index of plasma (AIP) (33).

Normal serum uric acid (SUA) levels were 2.40 mg/dl - 5.70 mg/dl for women and 3.4 mg/dl - 7.0 mg/dl for men, according to the reference values of the central laboratory, values above these limits defining hyperuricemia (HUA).

Cardiovascular risk was assessed using SCORE chart for high risk countries (7). CV risk categories were defined as follows: low risk - SCORE <1%, medium risk - SCORE 1-4%; high risk - SCORE 5-9%; very high risk - SCORE ≥10% or the presence of at least one of the following, regardless of SCORE values: manifest CV disease (ischemic heart disease, peripheral artery disease, stroke), diabetes mellitus, moderate-severe renal failure (eGFRMDRD <60 ml/min/1.73 m²).

Statistical analysis

A descriptive analysis (means, medians, standard deviations, and range for continuous data and frequency analysis for categorical data) was performed for all the target variables in the whole study groups. The 25th, 50th and 75th percentiles were calculated in order to determine the 4 quartiles of the SBP's d. distribution.

Kolmogorov-Smirnov test was used to analyze continuous data distribution, according to which ANOVA or Kruskal-Wallis test were further used in analysis for differences between means of 4 independent study subgroups. Chi-square test was used to analyze differences between categorical data.

Binary logistic regression using a stepwise Likelihood ratio method including multicollinearity testing (tolerance less than 0.1 and VIF value greater than 10) and adjustments for confounders was used for validation of predictors of high and very high total CV risk (as dependent variable).

Statistical analysis was performed with IBM SPSS Statistics 20.0 software at a significance level of p <0.05.

RESULTS

General characteristics of the study group

Gender distribution in the study group was similar (204 female hypertensives, 48.1% vs. 220 males hypertensive, 51.9%, p = 0.437), even after adjustments for area of residence: rural area – F: 78 subjects; 45.9% vs. M: 92 subjects; 54.1; urban area: F- 126 subjects; 49.6% vs. M – 128 subjects; 50.4%; p = 0.452.

Mean age of the study group was 51.46±5.82 years, the most frequently encountered age being 52 years. In urban areas female hypertensives were significantly older than male hypertensives (F- 53.75 years vs, M – 51.48years; p = 0.002) while in rural areas mean age was similar in both genders (F- 50.22 years vs, M – 49.33 years; p = 0.249).

Active smoking was recorded in 115 subjects, representing 27.13% from the sample. Both in urban and rural areas, smoking was more prevalent among male hypertensives (rural area – F: 13 subjects; 16.7% vs. M: 32 subjects; 37.4; p = 0.003 urban area: F- 22 subjects; 17.5% vs. M – 46 subjects; 36.5%; p = 0.001).

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Mean total serum cholesterol level was 218.39±45.91mg/dl, ranging from 101.08 mg/dl (minimum value) up to 355.53 mg/dl (maximum value), the most frequently encountered value being 176mg/dl. There were no significant differences in mean total serum cholesterol levels between the two genders, even after adjustment for area of residence (rural area: F- 224.99 mg/dl vs. M – 230.54 mg/dl; p = 0.457; urban area: F- 212.10 mg/dl vs. M – 211.76 mg/dl; p = 0.951).
Hypercholesterolemia was recorded in 279 subjects, representing 65.81% from the sample, without significant difference among genders, even after adjustment for area of residence (rural area: F- 53 subjects; 67.9% vs. M – 68 subjects; 73.9%; p = 0.392; urban area: F- 81 subjects; 64.3% vs. M – 77 subjects; 60.6%; p = 0.548).

Systolic blood pressure values (SBP) in the studied sample ranged between 107 mmHg (minimum value) and 222.75 mmHg (maximum value) with a mean value of 148.46±19.61 mmHg, the most frequently recorded SBP value being 145.5 mmHg. There were no significant gender differences in mean SBP (rural area: F-153.66 mmHg vs. M– 155.58 mmHg; p = 0.520; urban area: F- 143.51 mmHg vs. M– 145.04 mmHg; p = 0.521).

10-year risk of fatal CV events of the study group

According to SCORE chart for high CV risk countries, median value of 10-year risk of fatal CV events of the study group was 1%, ranging from 0% - 17%. Male hypertensives had a significantly higher risk compared with female hypertensives, difference that remained significant after adjustment for area of residence (rural area: F- 0.88% vs. M – 3.13%; p <0.0001; urban area: F- 1.33% vs. M – 3.37%; p <0.0001).

The majority of the hypertensive patients from the study sample had a high and very high 10-year risk of fatal CV events (SCORE ≥5%) (Figure 1).

Both in rural and urban areas, hypertensive male had more frequently a high and very high CV risk according to SCORE, than hypertensive females (Table 1).

New CV risk factors’ distribution across CV risk categories

SBP’s.d. values increased significantly from the mean value of 2.83 mmHg recorded in the low risk category up to the mean value of 6.01 mmHg recorded in the very high risk category. More, the proportion of hypertensive patients with increased visit-to-visit SBP variability (values above the 75th percentile of the SBP’s.d. distribution) increased significantly from 10.2% in the low risk category up to 49% in the very high risk category (Table 2).

**TABLE 1.** Cardiovascular risk of study sample based on SCORE. Values are presented as absolute number (percent); *chi square test; CV: cardiovascular; F: female gender; M: male gender.

<table>
<thead>
<tr>
<th>Low CV risk</th>
<th>Moderate CV risk</th>
<th>High CV risk</th>
<th>Very high CV risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural</td>
<td>25 (32.1)</td>
<td>4.1 (0-39.8)</td>
<td>12 (11.2)</td>
</tr>
<tr>
<td>Urban</td>
<td>37 (29.4)</td>
<td>3 (3.1)</td>
<td>7 (6.8)</td>
</tr>
</tbody>
</table>

**TABLE 2.** New CV risk factors’ distribution across SCORE CV risk categories. Values are presented as mean±s.d. for continuos parametric variables and median (range) for continuos nonparametric variable and absolute number (percent) for categorical variables; *Kruskal-Wallis test, ** ANOVA; *** chi-square test; NS: nonstatistical significant (p > 0.05); SBP’s.d.: systolic blood pressure’ standard deviation; PWVao: aortic pulse wave velocity; AIXao: aortic augmentation index; RT: return time; SBPao: central (aortic) systolic blood pressure; AIP: atherogenic index of plasma; SUA: serum uric acid; HUA: hyperuricemia.
Central systolic blood pressure (SBPao) had a significantly increased from the mean value of 142.20 mmHg in the low risk category up to the mean value of 152.23 mmHg in the very high-risk category (Table 2).

Aortic augmentation index (AIXao) also significantly increased from the mean value of 36.13% in the low risk category up to the mean value of 38.10% in the high risk category and to the mean value of 38.60% in the very high risk category, the former two being statistically similar (Table 2).

Mean aortic pulse wave velocity (PWVao) recorded in high and very high risk categories was similar and significantly higher than the mean value recorded in medium and low risk categories. Also, the proportion of hypertensive subjects with PWVao values >10 m/s significantly increased from 11% in the low risk category up to 44.1% in the very high-risk category (Table 2).

Mean return time (RT) recorded in very high-risk category was significantly shorter than mean RT recorded in the other three risk categories (Table 2).

Atherogenic index of plasma (AIP) had a significant increase across the four risk categories, from the mean value of 0.24 recorded in the low risk category up to the mean value of 0.54 recorded in the very high-risk category (Table 2).

Mean serum uric acid levels (SUA) recorded in very high risk category was similar to those recorded in high and medium risk categories, but significantly higher that mean SUA levels recorded in low risk category. There were no significant differences between the 4 risk categories regarding the proportion of hypertensive subjects with hyperuricemia (HUA) (Table 2).

**Contribution of new CV risk factors in cardiovascular risk assessment**

Bivariate logistic regression analysis, having „high and very high CV risk category” as dependent variable and SBP’s.d. quartiles (Q_s.d.TAS), aortic pulse wave velocity (PWVao), aortic augmentation index (AIXao), return time (RT), central systolic blood pressure (SBPao), atherogenic index of plasma (AIP) and serum uric acid (AUS), as independent variable, using a “forward LR“ method, confirmed as predictors of membership to high and very high risk category the following (Table 2):

- **Q4_sd_SBP:** the probability of belonging to the high and very high risk category of a hypertensive subject with SBP’s.d. values >10.69 mmHg (above the 75th percentile) is 2.49 times higher that the one of a hypertensive subjects whose SBP’s.d. values are ≤10.69 mmHg.
- **SBPao:** for every unit increase in SBPao above the mean value of 147.79 mmHg there is a 1.01 fold increase in the probability of belonging to the high and very high risk category.
- **PWVao:** for every unit increase in PWVao above the mean value of 10.27 m/s, there is a 1.11 fold increase in the probability of belonging to the high and very high risk category.
- **RT:** for every unit decrease in RT below the mean value of 108.56 ms there is a 0.95 fold increase in the probability of belonging to the high and very high risk category.
- **AIP:** for every unit increase in AIP above the mean value of 0.42 m/s, there is a 7.08 fold increase in the probability of belonging to the high and very high risk category.

Aortic augmentation index and serum uric acid were not validated as predictors of CV risk categories according to SCORE.

The prediction model that includes all the above mentioned 5 predictors has 84.7% power of correctly predicting the membership of hypertensive subjects to high and very high risk category (Figure 2).

Applying this model to the study sample, 70 subjects, representing 16.51% were reclassified as predictors of CV risk categories according to SCORE.

The prediction model that includes all the above mentioned 5 predictors has 84.7% power of correctly predicting the membership of hypertensive subjects to high and very high risk category (Figure 2).

Applying this model to the study sample, 70 subjects, representing 16.51% were reclassified as follows: 51 subjects from the total number of 231 initially classified in low and medium risk categories were reclassified in high and very high risk category, 19 subjects from
the total number of 193 initially classified in high and very high risk category were reclassified in low and moderate risk category (Figure 3).

Based on this prediction model the reclassified structure of the study sample is: 199 hypertensive subjects representing 46.93% of total in low/moderate risk category and 512 hypertensive subjects representing 53.07% of total in high/very high risk category (Figure 3).

**DISCUSSIONS**

The results of our study confirms that adult Romanian hypertensive patients are at a high and very high 10-year risk of fatal CV events, requiring prompt and adequate therapeutic intervention in order to decrease their CV morbi-mortality, stressing the need for an accurate CV risk assessment in this group of patients.

More, our results confirm increased SBP variability, arterial stiffness parameters and atherogenic index of plasma as predictors of CV risk categories according to SCORE.

Both increased visit-to-visit SBP variability and arterial stiffness parameters were proved by several trials as independent predictors of CV risk in hypertensive patients, together with the lack of BP control (11-17, 24-28). Increased visit-to-visit SBP variability and arterial stiffness contribute to total CV risk by specific mechanisms, the most probable hypothesis assuming that increased arterial stiffness induces increased SBP variability. In hypertensive patients, this interaction can have a negative effect on BP control (35).

One important limit of the BPV analysis is using a limited number of BP measurements performed only on two different occasions. However, having six measurements per subject in total, from which four measurements were used to define BPV, we could presume an acceptable reproducibility for this parameter. On the other hand, our study evaluates the interindividual variability, a surrogate of intra-individual BPV, an approach questioned by some researchers, but which was also successfully used in other population-based studies for analyzing BP variability and also has been found to correlate with incident stroke in large outcome trials (26, 36).

Based on the results of this study, for every 10 mmHg increase in SBP the probability of belonging in the high/very high risk category of a hypertensive increases with 10%, increase that is similar to that evidence by Roman and co-workers analyzing the data from The Strong Heart study, where for every 10 mmHg increase in SBP there was a 15% increase in risk of fatal and non-fatal CV events in patients without evidence of CV disease, followed-up for a mean period of 4.8 years (37).

The first recommendation of aortic pulse wave velocity use in CV risk assessment of hypertensive subjects was in 2007, when the
CONCLUSIONS

Adult Romanian hypertensive patients are at a high and very high 10-year risk of fatal CV events, requiring prompt and adequate therapeutic intervention in order to decrease their CV morbi-mortality, stressing the need for an accurate CV risk assessment.

Based on the results of this study, increased SBP variability, aortic pulse wave velocity, reverse time, central (aortic) systolic blood pressure, and atherogenic index of plasma have an additive value for CV risk assessment above SCORE.

The prediction model including above mentioned 5 predictors has an 84.7% power of correctly predicting the membership of hypertensive subjects to high and very high risk category and requires validation in prospective fashion.

Conflict of interest: none declared.

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