The Impact of hs-CRP on Cardiovascular Risk Stratification in Pilots and Air Traffic Controllers

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INTRODUCTION: We assessed determinants of serum hs-CRP level in pilots and air traffic controllers (ATCs) and its impact on their atherosclerotic cardiovascular disease (ASCVD) risk.

METHODS: We obtained serum hs-CRP measurements, evaluated traditional cardiovascular risk factors and assessed global ASCVD risk based on 2018 ESH/ESC guidelines. Elevated hs-CRP was hs-CRP values > 3 mg $\cdot$ L^{-1}. Determinants of elevated hs-CRP were assessed using stepwise logistic regression analysis. We used the net reclassification method to evaluate the impact of hs-CRP levels on global ASCVD risk.

RESULTS: Of the 335 subjects (mean age 45.4 $\pm$ 11.6 yr, 70% pilots, 99% men, 37% Caucasians), 127 individuals (39.5%) presented with elevated hs-CRP levels. Compared to those with normal hs-CRP, individuals with elevated hs-CRP were older with faster heart rate and higher blood pressure, BMI, and P wave amplitude. The proportion of individuals with elevated hs-CRP was greater among those with smoking habits, physical inactivity, MetS, tachycardia, altered P wave axis, LVH, and HT-TOD. Aging (aOR 2.15 [1.67–6.98]), hypertension (aOR 3.88 [2.29–6.58]), type 2 diabetes (aOR 6.71 [1.77–10.49]), tachycardia (aOR 2.03 [1.91–4.53]), and LVH (aOR 2.13 [1.64–7.11]) were the main factors associated with elevated hs-CRP levels. Low, moderate, high, and very high risk were observed in 24 (15%), 68 (41%), 62 (37%), and 12 (7%) subjects, respectively. Including hs-CRP resulted in the net reclassification of 25% of subjects, mostly from moderate to high risk.

CONCLUSION: The integration of hs-CRP improved the estimation of global ASCVD risk stratification. However, a survey with a comprehensive population assessing the cost/benefit impact of such a referral is needed.

KEYWORDS: hs-CRP, cardiovascular risk factors, pilots, air traffic controllers.

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Arterial hypertension clusters in most cases with additional risk factors, highlighting the need for comprehensive and integrated management, in view of effective prevention and control of atherosclerotic cardiovascular disease (ASCVD).[2] To implement such an approach, several risk prediction models in the general population, as well as in specific groups such as hypertensive patients, were launched to estimate 10-yr global ASCVD risk.[5] These comprise among others the Framingham ASCVD risk score, Systematic Coronary Risk Evaluation (SCORE), and European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines. Unfortunately, all these models failed to accurately and fully estimate ASCVD risk since some patients with low risk developed clinical ASCVD, highlighting the need for the improvement of these prediction models by integrating new biomarkers to the different models.[3] Among new biomarkers carotid intima-media thickness (cIMT) and high-specific C-reactive protein (hs-CRP) have been reported to improve risk prediction ability of classical prediction models.[10,19] In this regard, Lepira et al., in a cross-sectional study on the impact of cIMT on global CV risk based on 2007 ESH/ESC guidelines in 60 hypertensive patients at least 40 yr of age, found that the inclusion of cIMT may enhance risk stratification mainly in

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hypertensive patients with moderate or intermediate risk.[12] It has been reported that hs-CRP, a marker of inflammation, endothelial dysfunction, and subsequent atherosclerosis, could be more easily used to estimate ASCVD risk than cIMT that requires sophisticated equipment and particular operator skills, especially in developing countries.[13] However, the relationship between elevated hs-CRP and ASCVD risk remains a matter of controversy. Studies showing a robust association between hs-CRP and risk factors for coronary heart diseases such as obesity, diabetes, physical inactivity, smoking, and alcohol use have been published together with surveys that only highlight a modest relationship with CVD.[7] The role of age, gender, and ethnicity on hs-CRP variability has been recognized.[7] Although aircrew are considered a high ASCVD group,[4] few studies have assessed global ASCVD risk as well as improvement of its prediction by integrating new biomarkers such as hs-CRP to classical models. In a matched case-control study, a New Zealand Guidelines Group (NZGG) found that the adjusted Framingham score applied to Oceania-based airline pilots had low sensitivity and failed to predict 47% of the CV events, thus underscoring the need for the improvement of the performance of this score.[22]

In the Democratic Republic of the Congo (DRC), where hypertension is highly prevalent with increased ASCVD morbid-mortality,[14] hs-CRP was found to be elevated among untreated hypertensive patients and those with nondipping ambulatory blood pressure (BP) patterns.[17] Global ASCVD risk in hypertensive patients and its improvement by integration of new biomarkers to classical prediction models has already been assessed.[12] The present study aims to extend such assessment to other high risk groups, namely pilots and air traffic controllers (ATCs), by integrating hs-CRP to classical ASCVD risk prediction models.

METHODS

Subjects

As per International Civil Aviation Organization (ICAO) and Civilian Aviation Authority (CAA)/DRC regulations, pilots and ATCs hold class 1 and 3 licenses, respectively. Pilots and ATCs attending medical centers appointed by the CAA/DRC for aeronautical medical examination from January to December 2017 were invited to volunteer in a cross-sectional study on contribution of hs-CRP to global ASCVD risk. Their medical history, aeronautical license class, sociodemographic data, and lifestyle habits were obtained by ad hoc questionnaire.

Based on the recommendations by the local ethical committee of the University of Kinshasa School of Public Health the subjects verbally expressed their informed consent before enrollment in conformity with the declaration of Helsinki.

Procedures

Seated BP was measured using a validated OMRON M6 HEM 7001 monitor with a cuff size suitable for the arm perimeter secured on the dominant arm. Three records were taken after a 5-min rest in a quiet room with a 2-min interval between them; their average was used for analysis. Pulse pressure (PP) was systolic minus diastolic BP. BP $\geq$ 140/90 mmHg or use of BP lowering medications defined hypertension. PP $>$ 60 mmHg defined subclinical atherosclerosis. Hypertensive subjects with BP not at recommended goals of $<$ 140/90 mmHg (or $<$ 130/80 mmHg in those with diabetes or CKD) were labeled uncontrolled. Physical examination also included measurements of body height, weight, and waist circumference (WC) obtained in upright position with the individuals lightly dressed without shoes. Body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters) and values $\geq 25\ kg \cdot m^{-2}$ defined overweight/obesity. WC $>$ 94 cm in men and $>$ 80 cm in women (for Africans) or $>$ 102 cm in men and $>$ 88 cm in women (for Caucasians) defined abdominal obesity. A standard 12-lead electrocardiogram (ECG) was recorded to assess heart rate (HR), P wave duration, PR and QTc intervals, P wave axis, and QRS duration. To correct QT interval for heart rate, we used the $QT_C = QT + 1.75$ (HR-60) formula. We combined the Sokolow-Lyon and the Gender-specific Cornell voltage criteria to define ECG-based LVH. Tachycardia was HR $>$ 90 bpm.

Fasting blood sample and morning spot urine were obtained for measurements of glucose, cholesterol (total and fractions), triglycerides (TG), creatinine, and hs-CRP (using immunoturbidimetric method), and proteinuria. Simplified Modification of Diet in Renal Disease (MDRD) study equation, taking into account gender and ethnicity, was used to estimate glomerular filtration rate (eGFR). White blood cells (WBCs) and platelets were measured with EDTA whole blood methods (Systmex XN-1000, 6 parts). Glycemia $> 126\ mg \cdot dl^{-1}$ or self-reported diagnosis, and/or use of glycemic lowering medications was considered as having type 2 diabetes. Abdominal obesity associated with at least two of the following characteristics: BP $>$ 130/85 mmHg and/or use of high BP lowering drugs, fasting blood glucose $> 100\ mg \cdot dl^{-1}$ and/or diagnosed type 2 diabetes, serum triglycerides $> 150\ mg \cdot dl^{-1}$ or use of lipid lowering drugs, high density lipoprotein cholesterol (HDL-c) $< 50\ mg \cdot dl^{-1}$ in women or $< 40\ mg \cdot dl^{-1}$ in men represented metabolic syndrome (MetS). Low HDL-c and/or increased TG levels defined atherogenic dyslipidemia. Hs-CRP $> 3\ mg \cdot L^{-1}$ represented higher serum hs-CRP levels. Reduced kidney function (RKF) was defined by eGFR $< 60\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$. Altered P wave axis (aPWA) was any metrics outer of 0 through 75°. Proteinuria was considered present if dipstick was 2+ or more in the absence of urinary infection or hematuria.

According to 2018 ESH/ESC guidelines, 10-yr global ASCVD risk estimate was stratified as low ($<$ 10%), moderate (between 10% and 20%), high (between 20% and 30%), or very high ($\geq$ 30%). Individuals with RKF and MetS were automatically considered to be at high ASCVD risk. Hypertension-associated target organ damage (TOD) was defined as the presence of at least one of the followings: PP $>$ 60 mmHg, ECG- or echo-based LVH, RKF, and/or established CV or renal disease.

Statistical Analyses

Data were presented as frequencies or mean ± SD as applicable. The Student's *t*-test was used to assess the differences between means, whereas the Pearson's Chi-squared or Fisher's exact test were used as appropriate to compare proportions. Logistic regression was used to assess the independent relationship between level of Hs-CRP and ASCVD risk in a stepwise logistic regression modeling the high ASCVD risk. The adjusted odd ratio (aOR) values and 95% of confidence intervals (CI) were calculated. P values < 0.05 were considered to be statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 17.0) software.

RESULTS

Sociodemographic and clinical characteristics of the study population as a whole and according to hs-CRP levels are depicted in **Table I**. There were 335 individuals (mean age 45 ± 11 yr, 94% men, 70% pilots, 67% black Africans, Caucasians 33%) included in the present study. Hs-CRP level was elevated in 127 (37.9%) individuals who were older (49 ± 11 vs. 43 ± 11 yr, $P < 0.001$) with faster HR (70 ± 12 vs. 60 ± 11 bpm) and higher ($P = 0.01$ or less) SBP (150 ± 22 vs. 128 ± 17 mmHg), DBP (90 ± 15 vs. 78 ± 12 mmHg), BMI (28.6 ± 4.3 vs. 26.4 ± 4.2 $kg \cdot m^{-2}$), and P wave amplitude (114 ± 17 vs. 107 ± 19 ms) compared to individuals with normal hs-CRP levels. There was no significant difference in hs-CRP levels according to gender, professional class, or ethnic status.

Table II shows a higher ($P = 0.001$) blood glucose level (108 ± 42 vs. 94 ± 13 $mg \cdot dl^{-1}$) and a greater ($P = 0.002$) number of risk factors (2.4 ± 1.0 vs. 1.7 ± 1.0) among subjects with elevated hs-CRP in comparison to those with normal hs-CRP levels. WBCs, platelets, eGFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), and cholesterol variables were similar in the two hs-CRP level categories.

The rate of increased hs-CRP level predominated among individuals with components of MetS such as hypertension (75 vs. 35%; $P < 0.001$), type 2 diabetes (15.2 vs. 1.4%; $P < 0.001$), overweight/obesity (85 vs. 66%; $P < 0.001$), abdominal obesity (62 vs. 39%; $P < 0.001$), tachycardia (19 vs. 7%; $P = 0.001$), and those with aPWA (7 vs. 1%; $P = 0.006$) and LVH (8 vs. 2%; $P = 0.02$). Individuals with elevated hs-CRP tended to be smokers (34 vs. 24%; $P = 0.028$), physically inactive (79 vs. 61%; $P < 0.001$) with a high frequency of hypertension-TOD (14 vs. 7%, $P = 0.031$).

The associations of elevated hs-CRP levels with risk factors in pilots and ATCs appear in **Table III**. In univariate analysis, age ≥ 55 yr, drinking, smoking, physical activity, hypertension, overweight/obesity, abdominal obesity, type 2 diabetes, tachycardia, and LVH were the factors significantly associated with elevated hs-CRP levels. In multivariate analysis, the strength of the association observed in univariate analysis persisted only for aging, drinking, hypertension, types 2 diabetes, and LVH. The odds of having increased hs-CRP levels were 2, 2, 2, 3, 4, and 7 times greater in individuals with aging, tachycardia, LVH, drinking, hypertension, and type 2 diabetes compared to their counterparts, respectively.

The rate of low, intermediate moderate, high, and very high global ASCVD risk estimation based on 2018 ESH/ESSC guidelines without inclusion of hs-CRP level is illustrated in **Fig. 1**. With the inclusion of hs-CRP in the estimation no modification occurred among those with very high ASCVD risk. However, 38 subjects (56%) switched from moderate to high ASCVD risk categories while 5 individuals (20%) moved from the low ASCVD risk to the moderate one. Thus, the net reclassification enhancement concerned 43 individuals (25%). With this rearrangement, the final number of individuals in each category appears in Fig. 1.

Table I. Sociodemographic and Clinical Characteristics of the Study Population, Stratified by hs-CRP Levels.

	OVERALL	ELEVATED hs-CRP	NORMAL hs-CRP	
CHARACTERISTICS	N = 335	N = 127	N = 208	P
Age, years	45 ± 11	49 ± 11	43 ± 11	<0.001
Gender				0.567
Men, N(%)	314(94)	119(94)	195(94)	
Women, N(%)	21(6)	8(6)	13(6)	
Professional class				0.055
Pilots	236(70)	82(74)	154(64)	
ATCs	99(30)	45(26)	54(35)	
Race				0.522
African	224(67)	84(66)	140(67)	
Caucasian	111(33)	43(34)	68(33)	
SBP, mmHg	136 ± 22	150 ± 22	128 ± 17	<0.001
DBP, mmHg	83 ± 14	90 ± 15	78 ± 12	<0.001
Weight, kg	84 ± 14	88 ± 13	81 ± 14	<0.001
Height, m	175 ± 8	176 ± 8	175 ± 8	0.906
BMI, $kg \cdot m^{-2}$	27.2 ± 4.4	28.6 ± 4.3	26.4 ± 4.2	<0.001
PP, mmHg	54 ± 14	60 ± 15	49 ± 13	<0.001
ECG features				
HR, bpm	67 ± 12	70 ± 12	66 ± 11	0.001
P wave, ms	110 ± 19	114 ± 17	107 ± 19	0.002
PR Interval, ms	163 ± 26	167 ± 23	161 ± 28	0.055
QRS, ms	89 ± 11	89 ± 9	89 ± 12	0.879
QTc Interval, ms	451 ± 398	435 ± 292	460 ± 451	0.589

Values are mean ± SD, or absolute (N) and relative (in percent) frequency; ECG = electrocardiogram; QTc = QT corrected.

DISCUSSION

Regardless of their African or Caucasian origin, nearly half of individuals with MetS had an elevated hs-CRP level that was associated with aging, tachycardia, LVH, and various components of the syndrome. The integration of hs-CRP levels to 2018 ESH/ESC risk guidelines

Table II. Paraclinic Characteristics of the Study Population, Stratified by hs-CRP Levels.

CHARACTERISTICS	OVERALL *N* = 335	ELEVATED hs-CRP *N* = 127	NORMAL hs-CRP *N* = 208	*P*
White blood cells, x10^3	6 ± 2	6 ± 2	6 ± 2	0.105
Platelets, x10^3	229 ± 56	223 ± 47	233 ± 60	0.134
Creatinine, mg · dl^{-1}	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.489
eGFR (ml · min^{-1} · 1.73 m^{-2})	101 ± 17	100 ± 16	102 ± 17	0.188
Serum Glucose, mg · dl^{-1}	99 ± 29	108 ± 42	94 ± 13	0.001
TC, mg · dl^{-1}	196 ± 43	200 ± 43	194 ± 43	0.18
HDL-C, mg · dl^{-1}	52 ± 18	52 ± 21	52 ± 15	0.96
LDL-C, mg · dl^{-1}	128 ± 40	133 ± 40	125 ± 40	0.055
TC/HDL-C	4.1 ± 1.6	4.3 ± 1.6	4.0 ± 1.6	0.201
VLDL-C, mg · dl^{-1}	26 ± 19	26 ± 17	26 ± 20	0.879
TG, mg · dl^{-1}	124 ± 99	123 ± 76	125 ± 111	0.847
Risk factors, *N*	2.0 ± 1.0	2.4 ± 1.0	1.7 ± 1.0	<0.002

Values are mean ± SD, or absolute (N) and relative (in percent) frequency.
eGFR = estimated glomerular filtration Ratio; hs-CRP = high sensitivity C-Reactive Protein; Log = logarithm; TG = triglycerides; HDL-c = high-density lipoprotein-cholesterol; Vldl = Very light lipoprotein-cholesterol; ECG = electrocardiogram; QTc = QT corrected.

substantially improved risk stratification mostly in those with moderate ASCVD risk.

In our study, the rate of elevated hs-CRP among individuals with MetS clearly exceeds the 28.5% reported by Alonso-Rodríguez et al. in a cross sectional survey of 1009 healthy Caucasian male airline pilots.[1] Variances in the definition of MetS (IDF vs. ATPIII) could partially explain the observed disparities. The association of hs-CRP with aging concurs with the literature. In the analysis of 8874 patients from the National Health and Nutrition Examination Survey (NHANES), the mean hs-CRP levels increased with age.[25] Similarly, hs-CRP was reported to significantly increase with age in male pilots with MetS when compared to those without such a syndrome.[1] The association we found between high level of hs-CRP and various CV risk factors such as hypertension, uncontrolled hypertension, type 2 diabetes, overweight/obesity, and abdominal obesity that are components of MetS and its link to other inflammatory markers such as white blood cells count are not unexpected. Similar results have been previously reported in prehypertensive and hypertensive subjects.[23] The plausible mechanisms might rely on vascular inflammation (soluble intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and monocyte chemoattractant protein-1) and reactive oxygen species (ROS) promoted by high BP.[8] Likewise, the positive relationship between hs-CRP and type 2 diabetes could be accounted for by obesity indices and insulin levels as shown in the ARIC study and the Multi-Ethnic Study of Atherosclerosis (MESA study).[3] In line with other surveys, abdominal obesity was associated with higher hs-CRP. In the Dallas Heart study, obesity modified the association between hs-CRP and atherosclerosis.[9] IL-6 produced by cells in atherosclerotic plaques as well as adipose tissue may elucidate the solid association between hs-CRP and obesity. According to the JUPITER survey, the association between hs-CRP and subclinical atherosclerosis is largely accounted for by obesity.[20] High levels of hs-CRP were also linked to smoking, tachycardia, LVH, altered P wave axis, and higher ASCVD risk, which are phenotypes that herald accelerated atherosclerosis. In the present work, hs-CRP was associated with tachycardia with no difference in the two ethnic groups enrolled. Our results concur with data from the MESA study, a cohort of four racial groups, through which the authors speculated that increased HR was associated with inflammation assessed by hs-CRP, interleukin-6, and fibrinogen.[15] Like in the SABPA study, one could invoke the fact that inflammation acts with BP to promote factors that induce structural wall abnormalities in African men leading to development of LVH.[18] Such a relationship seems to be mediated by comorbid conditions. Finally, the slightly but nonsignificant higher hs-CRP levels among women and Caucasians as compared with men and African blacks, respectively, appear at variance with the NHANES findings. Most literature posits the mean serum hs-CRP of American blacks to be higher than that of Caucasians and Asians.[21] However, to the best of our knowledge, no study had compared mean serum hs-CRP of African blacks of both sexes with that of any other ethnicity.

Table III. Univariate and Multivariate-Adjusted Odds Ratios of High hs-CRP in Pilots and Air Traffic Controllers.

CHARACTERISTICS	UNIVARIATE ANALYSIS OR (CI 95%)	*P*	MULTIVARIATE ANALYSIS aOR (CI 95%)	*P*
Age ≥ 55 yr (Yes vs. No)	2.04 (1.25-3.32)	0.004	2.15 (1.67-6.98)	0.02
Drinking (Yes vs. No)	4.98 (1.96-12.65)	0.001	2.76 (1.85-8.93)	0.019
Smoking (Yes vs. No)	2.08 (1.18-3.68)	0.012	1.90 (0.99-3.63)	0.052
Physical activity (Yes vs. No)	2.28 (1.09-5.26)	0.045	1.57 (0.59-4.11)	0.362
Hypertension (Yes vs. No)	5.59 (3.42-9.14)	<0.001	3.88 (2.29-6.58)	<0.001
Overweight/obesity (Yes vs. No)	2.84 (1.61-4.99)	<0.001	1.60 (0.83-3.12)	0.163
Abdominal obesity (Yes vs. No)	2.66 (1.68-4.19)	<0.001	1.56 (0.90-2.70)	0.110
Tachycardia (Yes vs. No)	3.28 (1.63-6.61)	0.001	2.03 (1.91-4.53)	0.013
Type 2 diabetes (Yes vs. No)	12.96 (3.77-16.59)	<0.001	6.71 (1.77-10.49)	0.005
LVH (Yes vs. No)	3.52 (1.17-10.54)	0.025	2.13 (1.64-7.11)	0.019

OR = odds ratio; ORa = adjusted odds ratio; CI = confidence intervals; hs-CRP = high sensitivity C-Reactive Protein; LVH = left ventricular hypertrophy.

When hs-CRP was incorporated for ASCVD risk assessment, reclassification occurred in a quarter of individuals mainly from moderate (22.9%) risk category that shifted toward higher risk levels. This is higher than the 1.52% from the Emerging Risk Factor Collaboration (ERFC) study[9] and the 16% from the Swedish Malmö Diet and Cancer Study.[16] Including coronary artery calcium in the Framingham Risk Score, the Rotterdam Study[24] and the MESA cohort,[11]

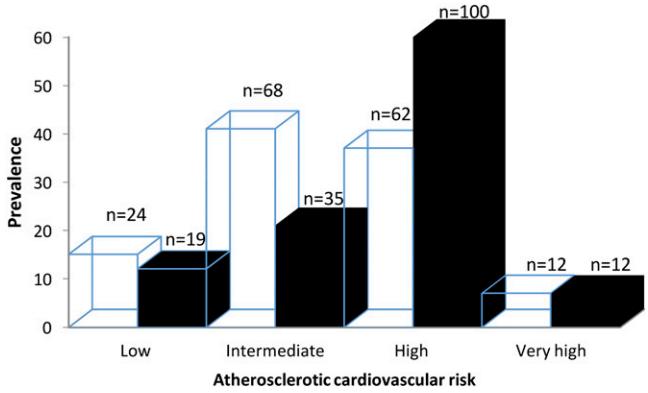

Fig. 1. Global ASCVD risk without (white bars) and with (black bars) hs-CRP in hypertensive ($N = 166$) pilots and ATCs based on 2018 ESH/ESSC guidelines. Abbreviation: hs-CRP: high sensitivity C-reactive protein.

respectively, reclassified 19.3% and 65.9% initially intermediate-risk individuals to a higher risk level. Both hs-CRP level and family history taken into account in the Reynolds Risk Score (RRS) reclassified 8% of moderate-risk men to a higher-level risk category.[6] It should be pointed out that the hs-CRP level yields high correlation with risk factors already in the ASCVD model. This could account for its impact on the observed reclassification.

Our study has some limitations and strengths. Various comorbidities, from infection to cancer, which could, in tandem with aging, enhance hs-CRP levels were not investigated. Moreover, the cross-sectional nature of our study does not allot plausible causality between ASCVD risk and hs-CRP. Furthermore, the small sample of pilots and ATCs with a very limited proportion of female personnel included in the survey, all of them operating in a single country (DRC), precludes safe generalizability of our findings to other settings. Nevertheless, this study has the merit of highlighting the impact of hs-CRP on ASCVD risk assessment in pilots and ATCs operating in a sub-Sahara African environment. As current recommendations for ASCVD risk estimate do not include hs-CRP, our data reinforce the need for larger surveys designed to evaluate these variances as well as both the economic consequences of such a referral.

In the present case series, elevated hs-CRP levels, prevalent among individuals with MetS, was associated with aging, hypertension, type 2 diabetes, abdominal obesity, tachycardia, and LVH in pilots and ATCs. Integrating hs-CRP in global ASCVD risk based on 2018 ESC/ESH guidelines enhances risk estimate chiefly in intermediate risk hypertensive individuals.

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