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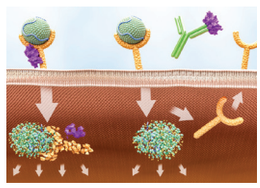
Prime Time News



Indian Scenario

Eighty percent of global burden of hypertension is in low-income and middle-income areas. The authors aimed to assess the point prevalence of hypertension, pre-hypertension, associated risk factors, and awareness about high blood pressure in a subsistent farmer community in India.

Therapeutic Updates

The use of unattended automated office blood pressure (uAutoOBP) versus attended automated (aAutoOBP) and manual auscultatory office blood pressure (AuscOBP) measurements is a topic of current controversy.

Views and Reviews

Atrial fibrillation (AF) is the most common cardiac arrhythmia and it is frequently encountered in chronic kidney disease (CKD) subjects. CKD patients are already at high risk for cardiovascular (CV) complications and the addition of AF further aggravates the prognosis.

Top Stories

Clinical Update

There is compelling data showing that the proportion of visits with blood pressure control below 140/90 is a graded predictor of hypertension-related outcomes.

Practical Case Study in Hypertension

The definition of resistant hypertension is based on office blood pressure (BP) measurements. ABPM is mandatory in resistant hypertensive patients to define true and white-coat resistant hypertension, as the latter group has a better prognosis.

LOOK INSIDE for Rhythm Puzzle

Practice Guide

In this review, the main differences between American and European recommendations are highlighted, along with the arguments exposed by both groups of experts and their possible impact affecting clinical practice in hypertension management.

Images that Teach

LGE-imaging for the quantification of irreversible myocardial injury has been extensively validated in coronary heart disease. However, dynamic changes of LGE have been described following an acute coronary syndrome, which may impair the analysis of myocardial viability.

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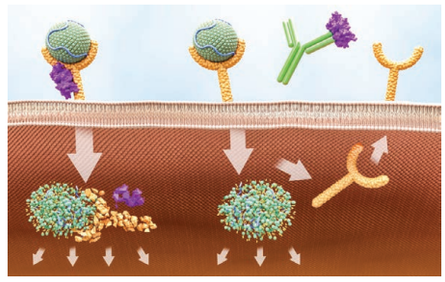
Lack of PCSK9i Use Impacts Cardiovascular Outcomes

Failure to take prescribed PCSK9 protein inhibitors (PCSK9i) impacts cardiovascular (CV) outcomes in patients with atherosclerotic cardiovascular disease (CVD), according to findings of a US study published in *Circulation: Cardiovascular Quality and Outcomes* [1].

Data from the Symphony Health claims database were used to investigate the composite rate of CV events (acute coronary syndromes, coronary interventions, heart arrest or stroke) in patients prescribed PCSK9i for the primary prevention of familial hypercholesterolaemia or secondary prevention of atherosclerotic CVD who rejected or abandoned their prescriptions, compared with the CV event rate in propensity score-matched patients who paid for their prescriptions. In total, 139 036 patients 18 years of age or over who were prescribed PCSK9i between August 2015 and December 2017 were included in the study.

The composite CV event rate was higher in patients who rejected versus paid for PCSK9i prescriptions (hazard ratio [HR] 1.10; 95% CI 1.01, 1.19) and in those who abandoned versus paid for



PCSK9i prescriptions (HR 1.12; 95% CI 1.01, 1.24; both p<0.05). Corresponding results were similar when paid was defined as receiving treatment for ≥338 days within one year (HR 1.16; 95% CI 1.02, 1.30 and HR 1.21; 95% CI 1.04, 1.38, respectively; both p<0.05).

PCSK9i rejection rates were higher in female patients, racial minorities, and patients with lower incomes.

"Rejection, abandonment, and disparities related to PCSK9i prescriptions are related to higher cardiovascular outcome rates," concluded the investigators. "Appropriately identifying and characterizing barriers to PCSK9i access, and developing approaches to overcome them, will reduce the clinical and economic burden for patients who are likely to benefit from PCSK9 inhibition and likely result in more cost-effective policies for payers," they said.

The US FDA approved PSCK9i for the management of cholesterol-related CVD in 2015 but "despite approved labeling and support by consensus statements, nearly all public and private insurers placed requirements of PA* for PCSK9i in response to the initial price tag of $14 000 per year," noted Dr Khurram Nasir from Yale University, New Haven, Connecticut, and colleagues, in an invited commentary published in *Circulation: Cardiovascular Quality and Outcomes* [2] "In its current form, there are clear unintended consequences of PA that are not only having a toll on patient care and satisfaction but possibly on preventable outcomes as underscored by Myers *et al* in the current study," they commented.

* prior authorisation

References available on request Healthcare.India@springer.com

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Multigene Testing in Acute Coronary Syndrome Optimises Drug Therapy

Multigene pharmacogenetic testing to optimise medication prescribing is a "potentially cost-effective strategy" in patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI), report researchers from the US.

The researchers used a hybrid decision tree/Markov model to evaluate the cost effectiveness of multigene testing (*CYP2C19* for antiplatelet therapy selection, SLCO1B1 for statin selection and *CYP2C9/VKORC1* for warfarin dosing), compared with single-gene testing (*CYP2C19* for antiplatelet therapy selection) and no genotyping (standard of care), for a hypothetical cohort of Medicare patients aged 65 years post-PCI for ACS. The analysis was conducted from Medicare's perspective.

The model predicted that multigene testing was associated with the highest number of events avoided and the highest discounted QALYs gained over 12 and 24 months and over a lifetime horizon. The incremental cost-effectiveness ratios for multigene testing, compared with standard of care, were $US59 876, $33 512 and $3780 for the three time horizons, respectively. At a willingness-to-pay (WTP) threshold of $100 000/QALY gained, multigene testing was cost effective, compared with standard of care, for all three time horizons. At a WTP threshold of $50 000/QALY gained, however, multigene testing was only cost effective at 24 months and over the lifetime. Single-gene testing was less effective and more costly, compared with multigene testing, at all time horizons. "This analysis offers valuable insight into the potential benefits that multigene testing could provide for Medicare beneficiaries post-PCI for ACS," conclude the researchers.

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Hypertension, Pre-hypertension, and Associated Risk Factors in a Subsistent Farmer Community in Remote Rural Central India

Ramin Asgary, Sophie Galson, Hari Shankar, Caitlin O'Brien, Shobha Arole

Eighty percent of global burden of hypertension is in low-income and middle-income areas. The authors aimed to assess the point prevalence of hypertension, pre-hypertension, associated risk factors, and awareness about high blood pressure in a subsistent farmer community in India.

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The World Health Organization (WHO) recently published a report highlighting the rapid rate of increase in the prevalence of non-communicable diseases, including cardiovascular disease (CVD), particularly in low- and middle-income countries (WHO 2011a). CVD is the leading cause of death worldwide, accounting for 17.1 million deaths in 2004. Eighty-two percent of these deaths were in low- and middle-income countries (WHO 2010). CVD accounts for roughly a third of deaths in low- and middle-income countries (Lawes *et al.* 2008) and is the leading cause of death among those over age 30 worldwide (Aje and Miller 2009; Gaziano 2005). Despite the increasing interest in non-communicable disease in the developing world, there is a lack of primary data collection. The Global Forum for Health Research (GFHR), the Institute of Medicine, and the WHO have created initiatives aimed at stimulating and supporting research on cardiovascular risk reduction in the developing world (Initiative for Cardiovascular Health Research in the Developing Countries, National Research Council 1999).

Hypertension (HTN) is the largest modifiable risk factor contributing to the increasing burden of CVD in the developing world and accounts for 13.5% of deaths worldwide (Lawes *et al.* 2008).

The prevalence of HTN in patients greater than 60 years old in the developing world is 65% (HTN Study Group 2001) and 80% of the global burden of HTN is in low-income and middle-income areas (Lawes *et al*. 2008).

The prevalence of HTN in adults in rural India has been estimated to be between 20 and 36% (Chow *et al*. 2007; Jonas *et al*. 2010; Mittal and Singh 2010; Subburam *et al*. 2009; Bhardwaj *et al*. 2010; Kaur *et al*. 2012, Singh *et al*. 1997, Kearney *et al*. 2005) and is increasing (Gupta 2008). An additional one-quarter of the rural population meet the criteria for pre-hypertension (Kumar and Mishra 2008; Bhardwaj *et al*. 2010). The rural villages surrounding Jamkhed, India provide a unique environment for estimating the prevalence of high blood pressure because this area has benefitted substantially from the work of the Comprehensive Rural Health Project (CRHP). The CRHP has trained thousands of community health workers (CHW's) to provide primary care to villagers (Walley *et al*. 2008; Jamkhed 2011). We aimed to evaluate the prevalence of high blood pressure, pre-hypertension (pre-HTN), and associated cardiovascular risk factors in a rural farmer community served by CRHP in order to provide information to local health agencies to develop appropriate and effective public health strategies.

Methods

Study Design

We performed a cross-sectional study of adults in six villages in Jamkhed, India measuring blood pressure and abdominal girth and administering a comprehensive questionnaire including both closed and open-ended questions to assess CVD risk factors during the summer of 2010. We utilized a simple proportional random selection method in each village to recruit participants with the assistance of the CRHP village health workers who live in the villages. The CRHP provided us with village maps with homes numerically labelled. We randomly selected the first house and then visited every third house thereafter. Any person who met the inclusion criteria in the selected homes was included in the study. Inclusion criteria were: (1) residing in the villages in Jamkhed covered by CRHP, and (2) 40 years or older. The CRHP faces competing health priorities and has limited resources. As the incidence of HTN and other CVD increases with age (Roger *et al*. 2012), an age cut off of 40 years was chosen to target limited therapeutic and human resources toward higher risk groups within this population. Informed consent was obtained orally in the local language, Marathi, using local interpreters. It was clarified that participation would not affect participants in any negative way, and they could retract their participation or answers at any time during and/or after participation. Questionnaire included demographic and risk factor data including dietary habits such as salt and carbohydrate intake, occupation, income, religion, cast, family or personal history of CVD or diabetes, and tobacco and alcohol use.

We measured blood pressure in each arm after a 5-min rest period in sitting position with arm rested at the level of the heart using two brand new validated manual auscultatory sphygmomanometers (non-mercury; Tempo, HOLTEX, S/N CE0483 model). The two values were then averaged. The sphygmomanometers were also calibrated and tested against the mercury ones for accuracy before their usage. Research team members were trained, supervised, and evaluated for reliability in proper measurement of blood pressure using the same devices before the start of data collection. High blood pressure was defined as systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg. We used the criteria for measurement of blood pressure from the United States Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7 2004). Pre-hypertension was defined as systolic blood pressure 120–139 mmHg or diastolic blood pressure 80–89 mmHg (JNC-7 2004). All individuals with first blood pressure above normal were referred to a local hospital for follow up and re-evaluation. Participants with either systolic or diastolic blood pressure above 150 mmHg or 100 mmHg, respectively, were re-evaluated by a medical provider in the clinic the following day.

We measured abdominal girth to the nearest centimeter in each individual using a plastic, non-disposable measuring tape at the mid-point between the lower rib margin and the iliac crest at the end of a normal mild exhalation in the standing position (Janssen *et al*. 2002, WHO 2008). High abdominal girth, a component of metabolic syndrome, has been shown to be associated with HTN and a risk factor for CVD independent of body mass index (Rexrode *et al*. 2001; Janssen *et al*. 2002; Ness-Abramof and Apovian 2008; Gruson *et al*. 2010). High abdominal girth was defined as greater than 88 cm in women and greater than 102 cm in men (NIH 1998; Janssen *et al*. 2002; Grundy *et al*. 2004). All measurements and questionnaires were applied by two research team members. One measured and the other verified and recorded. We also measured non-fasting blood sugar using finger sticks with a calibrated glucometer. We trained all community health workers accompanying the research team in proper measurement of blood pressure and abdominal girth to facilitate future follow up and service programs with regard to non-communicable diseases.

Study Outcomes and Statistical Analyses

The primary study outcomes were the rates of high blood pressure readings consistent with HTN or pre-HTN criteria. Secondary outcomes included the rates of large abdominal girth, tobacco use, alcohol consumption, non-fasting finger stick blood sugar, diet, and family and personal history of HTN and diabetes. Logistic regression analysis assessed the presence and degree of association between independent variables including

age, gender, occupation, income, tobacco use, as well as important clinical variables such as abdominal girth with the main outcomes of interest, and to control for potential confounders. Variables were included into the models when univariate analysis showed significance and when clinically sensible and plausible. Chi square, *t*-test, bivariate and multi-variable logistic as well as linear regression were used where indicated. SPSS Version 19.0 was used for data analysis.

Sample Size

Based on limited original literature, we hypothesized that our rural population would have a lower rate of high blood pressure than the national rate and or at least equal to other rural areas. We estimated that the rate of HTN in adults greater than 40 years is at least between 15 and 20% and that the difference between the prevalence of high blood pressure in a rural population versus the national or urban average in this age group would be around 20% (Midha *et al*. 2009; Pednekar *et al*. 2009). We set alpha = 0.05, power = 0.8 and calculated the sample size of $n = 195$ using the formula established by Krejcie and Morgan (1970). We added another 15% to our sample size to cover for potential lost data and to increase the power for other secondary outcomes of interest. The Institutional Review Board (IRB) at Mount Sinai School of Medicine approved this study. Additionally, this study was approved by the local Department of Health, India, and Jamkhed's CRHP.

Results

Demographics

A total of 224 men and women aged 40 years old and above were evaluated. Average age of subjects was 56.8 years (standard deviation, SD, ±11.76 years) with maximum of 85 years. Females comprised 57% of the study population. The majority were farmers and housekeepers. Large abdominal girth was diagnosed in 8.6% participants, the majority of whom were female. Over 80% of the participants classified themselves as smokers. The overwhelming majority was Hindu. Median annual income was 21,000 rupees or approximately 456 US dollars and the mean income was 31,217 rupees (SD ±27,303) with a range of 500–100,000 rupees. The majority of the subjects reported they consumed a carbohydrate rich diet that also has high salt content. Mean non-fasting blood glucose was 111.5 mg/dL and only 2 of the 133 subjects for whom finger sticks were obtained had a level >200 mg/dL. Only three subjects reported a family history of HTN, and only one was aware of and had concomitantly a high blood pressure reading.

HTN is the largest modifiable risk factor contributing to the increasing burden of CVD in the developing world and accounts for 13.5% of deaths worldwide.

Study Outcomes

Overall, 30.3% (68/224) of subjects met the criteria for high blood pressure and 38.3% (86/222) met criteria for pre-HTN by JNC-7 criteria. Four percent (10/226) had diastolic blood pressure greater than or equal to 100 mmHg and 4% (9/226) had systolic blood pressure greater than or equal to 160 mmHg consistent with stage 2 HTN by the JNC 7 guidelines. The point prevalence of large abdominal girth as a risk factor for pre-HTN and HTN was 8.5% (17/200). With increasing age, systolic blood pressure (SBP) was increased ($p < 0.01$) but not diastolic blood pressure (DBP). Higher income was not correlated with any of higher systolic or diastolic blood pressure. Applying chi-square tests, high blood pressure readings were not associated with large abdominal girth (defined as high or normal), gender, occupation or smoking history. Applying *t*-tests, high blood pressure was not associated with older age or higher income. Pre-HTN was associated with large abdominal girth ($p < 0.05$), but not gender, occupation or smoking history applying chi-square tests. *T*-tests revealed no association between pre-HTN and either older age or higher income. The association between age and blood pressure readings of above 135/85 mmHg and below 140/90 mmHg was not significant ($p = 0.08$). Older age was not associated with increased non-fasting blood glucose ($p < 0.08$). There was no association between gender and large abdominal girth. In this sample population, there was an association between gender and occupation, with females more likely to work as housekeepers and males more likely to be farmers ($p < 0.01$). There was also an association between sex and age ($p < 0.01$) where females were more likely to be younger, and an association between occupation and age (farmers were older; $p < 0.05$). There was no relationship between alcohol consumption and either high blood pressure readings or pre-HTN. Table 1 presents point prevalence of high blood pressure and pre-HTN stratified by sex, age, income, occupation, abdominal girth, tobacco and alcohol use; it also presents the results of the univariate analyses.

In multivariable regression analysis, when age, sex, abdominal girth, income, and occupation were in the model, high blood pressure was not predicted by increasing age, income, sex, large abdominal girth or occupation. In regression analysis, pre-HTN was only predicted by high abdominal girth but not age, sex, occupation, or income (Table 2).

Discussion

Given the increasing incidence of CVD and the known relationship between HTN and CVD, prevention and treatment of HTN could improve mortality and morbidity in rural India. Our data suggests the point prevalence of high blood pressure readings among adults 40 years and above in rural Jamkhed, India is 30.3%. This finding is similar to other epidemiologic studies in rural

Table 1: Demographics and point prevalence of high blood pressure, pre-hypertension stratified by sex, age, income, occupation, abdominal girth, tobacco and alcohol use.

Characteristic	*N*	Total %	HTN	Sig.	Pre-HTN	Sig.
Population prevalence (≥40 year)	224		30.3% (68/224)		38.3% (86/224)	
Sex				$p = 0.35$		$p = 0.58$
Men	95	42.5%	33.6% (32/95)		40.0% (38/95)	
Women	129		27.0% (36/129)		36.0% (47/129)	
Age (years)				$p = 0.08$		$p = 0.82$
40–59	129	57.5%	28.6% (37/129)		36.4% (47/129)	
60–79	88	39.2%	30.7% (27/88)		42.0% (37/88)	
≥80	6	2.6%	66.7% (4/6)		33.3% (2/6)	
Income (rupees) ($n = 140$)				$p = 0.26$		$p = 0.42$
0–20,000	64	46.4%	26.2% (17/64)		46.8% (30/64)	
20,001–40,000	37	26.4%	37.8% (14/37)		18.9% (7/37)	
40,001–60,000	22	15.7%	31.8% (7/22)		50.0% (11/22)	
60,001–80,000	5	2.9%	40% (2/5)		20.0% (1/5)	
≥80,001	12	8.8%	33.3% (4/12)		33.3% (4/12)	
Occupation ($n = 212$)				$p = 0.72$		$p = 0.63$
Farmers	112	52.8%	31.2% (35/112)		40.1% (45/112)	
Housekeepers	100	47.1%	29.0% (29/100)		37.0% (37/100)	
Abdominal girth ($n = 196$)						
Large Abd. girth prevalence[a]	17	8.6%	29.4% (5/17)	$p = 0.184$	58.8% (10/17)	$p < 0.05$[b]
Male >102 cm	6	3.0%	33.3% (2/6)		66.6% (4/6)	
Female >88 cm	11	5.6%	27.2% (3/11)		54.5% (6/11)	
Smoking status ($n = 105$)						
Smokers	86	81%	31.3% (27/86)	$p = 0.72$	36.0% (31/86)	$p = 0.38$
Male	61	57.5%	37.7% (23/61)		36.0% (22/61)	
Female	25	23.5%	16.0% (4/25)		36.0% (9/25)	
Alcohol status ($n = 35$)						
Alcohol users	15	42.8%	46.6% (7/15)	$p = 0.19$	26.7% (4/15)	$p = 0.25$
Male ($n = 24$)	15	62.6%	46.6% (7/15)		26.7% (4/15)	
Female ($n = 11$)	0	0%	0%		0%	

[a]Janssen *et al.* 2002; NIH 1998
[b]Significance level

Table 2: Multivariable analysis.

	HTN			Pre-HTN		
Predictor	**Adj. Odds Ratio**	**95% CI**	***p*-value**	**Adj. odds ratio**	**95% CI**	***p*-value**
Age years	1.01	0.97–1.04	0.50	1.004	0.97–1.03	0.78
Male vs female	2.17	0.65–7.20	0.20	0.76	0.24–2.46	0.65
Large Abd. girth (yes/no)	0.52	0.22–1.21	0.13	3.24	1.29–8.13	0.013[a]
Occupation farmer vs housekeeper	1.01	0.30–3.35	0.98	0.73	0.23–2.26	0.58
Income (Rupee)	1.00	1.00–1.001	0.21	1.0	1.00–1.001	0.53

[a]Significance level

India estimating a prevalence of HTN in the adult population between 13.6 and 35.8% (Singh *et al.* 1997; Kearney *et al.* 2005; Chow *et al.* 2007; Kumar and Mishra 2008; Bhardwaj *et al.* 2010; Mittal and Singh 2010). Since we targeted a high-risk population of adults aged 40 years and above, we anticipated a higher prevalence of HTN as compared to the adult population at large. However, our findings are consistent with other studies in rural central India targeting adults over age 40 with a prevalence of HTN between 26.7 and 33% (Subburam *et al.* 2009; Jonas *et al.* 2010). On the

other hand, our estimated prevalence of HTN is lower than the 38.7–46.6% prevalence in adults over age 35–40 found in urban communities (Mohan *et al*. 2007, Pednekar *et al*. 2009). The rate of high blood pressure in adults aged 40–59 of 28.6% in our study population is also similar to the current prevalence of HTN among the United States population aged 40–59 of 31% (Wang and Wang 2004; CDC-MMWR 2011) as well as that of other developed countries (Kearney *et al*. 2005). The rate of age-adjusted pre-HTN blood pressure readings was 36.4% and comparable to the rate of 34% reported in the United State (Wang and Wang 2004).

Only one of our participants with a high blood pressure reading was aware of his elevated blood pressure in contrast with 20–25% awareness reported from rural central and southern India (Jonas *et al*. 2010; Kaur *et al*. 2012). This low level of awareness about HTN might be due to a variety of reasons such as lack of recognition of chronic diseases prevalence in this community, lack of training and/or awareness among providers and health agencies, failure to measure or communicate blood pressure readings with patients, inadequate patient-physician counselling during acute or preventive visits, and the asymptomatic nature of HTN. In our study population, the rate of other cardiovascular risk factors such as smoking was also high but alcohol intake response rate was largely low, which we hypothesize might be due to stigma related to its reporting. Our point prevalence of larger abdominal girth, although associated with pre-HTN, was lower than the rate in developed countries (Janssen *et al*. 2002; Pasco *et al*. 2012). The lack of predication of HTN by age, abdominal girth, and occupation either alone or when grouped in a regression model could be due to around 15% of missing data from abdominal girth and occupation and a higher age cut off in our sample population. Farmers with presumed higher level of physical activity had the same risk as housekeepers for HTN and pre-HTN, which we hypothesize is due to a general higher level of physical activity among this rural population at baseline. Income level as one of the strong indicators of socio-economic status was not associated with either HTN or pre-HTN, likely due to a general low level of income among this population. The effect of other risk factors on the prevalence of HTN and pre-HTN such as psychological stressors (Hamer and Steptoe 2012) chronic life stressors and lack of social support (Everson-Rose and Lewis 2005; Gerin *et al*. 2005; Clougherty *et al*. 2009; Figueredo 2009; Spruill 2010), needs to be further evaluated. The existing literature in management of CVD and HTN emphasizes prevention (National Research Council 2010; Weintraub *et al*. 2011; Wood *et al*. 2011) and recognizes the significant contribution of additional risk factors in resource poor settings, including psychosocial stress (Everson-Rose and Lewis 2005; Gerin *et al*. 2005; Clougherty *et al*. 2009; Figueredo 2009; Hamer and Steptoe 2012; Spruill 2010).

Given the increasing incidence of CVD and the known relationship between HTN and CVD, prevention and treatment of HTN could improve mortality and morbidity in rural India.

As India undergoes epidemiologic transition, there should be greater emphasis on chronic disease management and prevention, particularly CVD (Gaziano 2005). Although affordable management strategies targeted toward hard to reach populations and addressing access issues in resource poor regions are significant issues to address, attention to health education with regard to chronic disease and simple preventive strategies to address modifiable risk factors using the already existing health education forums for communicable-diseases should not be overlooked. Once, possible strategy to increase awareness and treatment of HTN and other non-communicable diseases could be through the efforts of community health workers (CHWs). Programs such as CRHP and the Health Extension Program in Ethiopia have trained thousands of CHWs to deliver primary health care services to rural populations thereby significantly improving healthcare coverage (Wakabi 2008). They have had positive effects in a wide range healthcare delivery including management of common childhood diseases, offering and maintaining directly observed therapy for infectious diseases, increasing health care utilization, and improving care for patients with HIV (Liu *et al*. 2011). CHWs could be trained to address both prevention and management strategies for HTN including screening for HTN at visits with community members, encouraging and directing patients who meet criteria for high blood pressure to clinics for evaluation and therapy, coordinating care and assessing medical adherence in the community (Farzadfar *et al*. 2012). Proper data collection and surveillance is a major component to improve prevention and treatment programs for CVDs. The WHO recommends that countries incorporate three major components to non-communicable disease surveillance including collecting data on exposures, outcomes, and assessing health system capacity and response (WHO 2010). However, there remains a lack of surveillance data on non-communicable diseases in the developing world (WHO 2010; National Research Council 2010) due to low health expenditures, problems with reliable data collection, and lack of evaluation strategies which make it difficult to compare data across regions and to implement programs. Employing CHWs could be a feasible and cost-effective strategy to improve proper data collection.

In a recent report, the World Economic Forum ranked non-communicable diseases among the most severe threats to economic development alongside natural disasters, oil price

Cont'd on page 20...

The Impact of Measurement Methods on Office Blood Pressure and Management of Hypertension in General Practice

Julia Höller[1], Linda Elizabeth Villagomez Fuentes[2], Klaus Matthias[1], Reinhold Kreutz[2]

The use of unattended automated office blood pressure (uAutoOBP) versus attended automated (aAutoOBP) and manual auscultatory office blood pressure (AuscOBP) measurements is a topic of current controversy.

Hypertension is a global public health issue that affects more than 1 billion individuals [1] and a strong risk factor for cardiovascular diseases [2]. The 2018 European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension define hypertension as systolic blood pressure (SBP) values ≥ 140 mmHg, and/or diastolic BP (DBP) values ≥ 90 mmHg [2]. This definition is based on conventional office BP (OBP) measurements that are usually carried out by measuring OBP with auscultatory measurements with a conventional stethoscope or more recently with oscillometric semiautomatic or automatic methods. These measurements of OBP are typically carried out by a physician or a nurse during the visit to the office [3]. There is, however, an ongoing controversy and intensive discussion about the differences in OBP values as obtained not only by the different techniques but by also as to how the presence or absence of an attending person, e.g., physician or nurse, might affect the OBP values [4–14]. The fact that OBP measurements by a doctor or nurse might contribute to a pressure response resulting in higher OBP values due to an alerting reaction [15–17] is a well know phenomenon referred to as the "white-coat effect" [2, 18]. Consequently, the difference between the higher OBP and

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lower out-of- OBP values have been at least in part [19] attributed to this effect and thus to the attending vs. unattended status of OBP measurements [2].

The discussion on the differences between aAutoOBP and uAutoOBP measurements has recently been intensified after the report of the Systolic Blood Pressure Intervention Trial (SPRINT), that was conducted in 102 clinical sites in the United States and in which the OBP was measured by an unattended automated measurement technique [4, 20]. However, the method used for OBP monitoring in the study and its applicability in a real-world clinical setting in daily routine management has subsequently been a matter of controversy [2, 5, 21].

Two important studies by Filipovský *et al.* [22, 23] comparing the uAutoOBP with AuscOBP measurement technique in a specialized hypertension healthcare center [22] and the other taking place in four academic hypertension centers [23], reported a significant difference between both measurements. In another critical study, however, Bauer *et al.* [21] used the same measurement protocol as in SPRINT [4] but in a GP office setting. Unlike, the studies by Filipovský *et al.* [22, 23], this study showed no significant differences between uAutoOBP readings and AuscOBP measurements.

The primary objective of the current study was to evaluate differences between aAutoOBP and uAutoOBP measurements and to compare uAutoOBP measurements with AuscOBP differences in hypertensive patients in the GP setting. In addition, we analyzed the potential implications for hypertension management based on the 2018 ESC/ESH Guidelines recommendations for target OBP in the management of arterial hypertension [2].

Methods

Study Design

We conducted a single-center study in a large GP office in Germany (Audorfer Gemeinschaftspraxis, Oberaudorf, Germany). The Audorfer GP office treats approximately 10,000 patients per year, offering wide range of preventive, diagnostic and therapeutic services, with a particular focus on chronic diseases, such as cardiovascular diseases, diabetes and obesity. Four GPs working in this office participated in the study. All consecutive patients with hypertension during the study period between April/2018 and October/2018 were initially invited to participate during their routine clinical examination, by one of the four GPs.

The attended versus unattended status of automated OBP measurements had no impact on OBP values in GP.

Informed consent was obtained from each participant, after receiving a complete explanation about the nature of the present study. Only patients who gave their informed consent were included. Their personal information was protected following the regulations of personal data confidentiality and data pseudonomisation for analysis in agreement with the local General Data Protection Legislation ("Datenschutz-Grundverordnung", DSGVO). The protocol was in accordance with the 1975 Helsinki Declaration and approved by the Charité ethics committee. In total, 133 consecutive patients with a diagnosis of arterial hypertension that attended the GP office for routine clinical examinations were included. All patients had been visiting the GP office for at least 1 year. Patients with hypertensive emergencies or any other severe illness or emergencies at the time of presentation were excluded.

OBP Measurement

In agreement with a previous report [21], our study protocol did not interfere with the routine AuscOBP measurements used for routine patient care by the participating GPs. Thus, the number of measurements used was at the discretion of the physician (one in the majority of patients), and the devices used included OSO Kll, ERKA 2517, and BOSO Profitest sphygmomanometers.

For both aAutoOBP and uAutoOBP measurements, we used the validated Mobil-O-Graph® NG device (I.E.M GmbH, Stolberg, Germany) [24, 25]. During automated OBP measurements with the Mobil-O-Graph, OBP was measured three times in 30-s intervals. We used the mean of these three measurements for statistical analysis. All OBP measurement devices were calibrated within a year prior to the study.

In group 1, which included 42 patients (age range 34–89 years, 54.8% females and 45.2% males), automated OBP was measured with the Mobil–O-Graph using a proper size cuff bladder that was placed on the patient's upper arm. The following protocol for aAutoOBP and uAutoOBP measurements was used:

1. All patients were seated with the Mobil-O-Graph cuff in place in the same patient room, on an ergonomic examination chair, with their back and arms supported, with their feet placed flat on the floor, and without speaking during 5 min of rest.
2. For the aAutoOBP measurements, the device program was started after 5 min of rest by the medical assistance staff in the patient room by pressing the Start key of the device in front of the patient and with the staff personal remaining in the patient room throughout the measurements.
3. For the uAutoOBP measurements, an additional separate staff room was used in which a computer for remote control of the Mobil-O-Graph device by Bluetooth was available. First, the medical assistance staff selected the patient from the patient list on the computer, went inside the patient's room and activated the PAIr mode on the Mobil-O-Graph device. The patient was seated in the patient room and the Mobil-O-Graph cuff was placed as stated above. The entire medical assistance staff left the room. In the staff room, the Mobil-O-Graph

device and the computer being in Bluetooth communications mode were paired and the measurements were started after the patient rested for 5 min in the patient room.

4. The aAutoOBP and uAutoOBP measurements were performed in random order.

In the second group, including 133 patients (age range 32–93 years, 62.4% females, and 37.6% males) the participating GPs performed their routine AuscOBP measurements in the examination room. In addition, the patient was taken to a separate room to perform the uAutoOBP measurements with the Mobil-O-Graph using the same procedure described above for group 1.

The differences between aAutoOBP and uAutoOBP values were regarded as the primary endpoint of the study; we expected a maximal difference of 10 mmHg in SBP in the GP setting [21]. Thus, a sample size of 34 was required with a power of 80% power to detect this difference through a paired *t* test assuming that the standard SD is 20 mmHg with a α-significance level of 0.05. We increased the sample number to 42 patients (group 1).

Secondly, in an explorative analysis, we compared uAutoOBP to AuscOBP measurements by GPs (133 patients, group 2). In addition, we analyzed the OBP control rates in group 2, as recommended in the 2018 ESC/ESG guidelines [2]. Thus, we analyzed the percentage of patients achieving the overall recommended target of systolic OBP (SOBP) and diastolic OBP (DOBP) values below 140 and 80 mmHg; and the frequency of patients who achieved the lower target below 130 and 80 mmHg in the group of patients younger than 65 years and without chronic kidney disease (CKD). Finally, we determined the frequency of patients with resistant hypertension, i.e., as defined by OBP values of systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg in response to combination therapy with three first-line drugs including a diuretic [2].

Statistical Analysis

All statistical analyses were performed using version 25 IBM SPSS Statistics Software, Armonk, NY: IBM Corp and GraphPad Prism version 8 for Windows, GraphPad Software, La Jolla California, USA. Numeric data are presented as the arithmetic mean ± SD or as a proportion (percentage). We compared the OBP values using paired 2-sided t student tests in both studies. We constructed Bland–Altmann plots to compare aAutoOBP to uAutoOBP and AuscOBP to uAutoOBP. Bias (i.e., mean of the differences) and limits of agreement of 95% were derived from Bland-Altmann analysis. Additionally, we applied Pearson's correlation analyses to assess the association between variables. A stepwise multivariate regression analysis was then performed; using as dependent variables the SOBP and DOBO differences (Δ).Pearson's Chi-squared test was used for the analysis of control rates according to the recommended target OBP in the recent European guidelines. P values < 0.05 were regarded as statistically significant.

Results

Demographic and clinical characteristics of patients in group 1 (aAutoOBP vs. uAutoOBP, 42 patients) and group 2 (AuscOBP vs. uAutoOBP, 133 patients) are summarized in Table 1. The mean

Table 1: Demographic and clinical characteristics of the patients.

	Group 1 (n = 42)	Group 2 (n = 133)
Female	23 (54.8%)	83 (62.4%)
Male	19 (45.2%)	50 (37.6%)
Age (years)	71 (34–89)	72 (32–93)
Body mass index (kg/m^2)	29.0 ± 5.8	28.6 ± 4.9
Concomitant diseases		
Diabetes mellitus	7 (16.7%)	30 (22.6%)
Dyslipidemia	28 (66.7%)	86 (66.9%)
Stroke/transient ischemic attack	8 (19.0%)	15 (11.3%)
Coronary heart disease	6 (14.3%)	20 (15.0%)
Chronic heart failure	4 (9.5%)	10 (7.5%)
Atrial fibrillation	3 (7.1%)	11 (8.3%)
Chronic kidney disease	3 (7.1%)	7 (5.3%)
Antihypertensive medication		
Number of antihypertensive drugs	2 (0–4)	2 (0–5)
Angiotensin-converting enzyme inhibitor	14 (33.3%)	45 (33.8%)
Angiotensin receptor blocker	19 (45.2%)	59 (44.4%)
Beta-blocker	14 (33.3%)	54 (40.6%
Calcium channel blocker	18 (42.9%)	48 (36.1%)
Aldosterone receptor antagonists	0	2 (2.3%)
Diuretic	15 (35.7)	55 (41, 4%)
Other antihypertensive	2 (4.8%)	4 (3.0%)
Without antihypertensive therapy	4 (9.5%)	10 (7.5%)
Antihypertensive monotherapy	12 (28.6%)	38 (28.6%)
Antihypertensive dual therapy	13 (31.0%)	38 (28.6%)
Antihypertensive triple therapy	8 (19.0%)	33 (24.8%)
Antihypertensive quadruple therapy	5 (11.9%)	12 (9.0%)
Antihypertensive quintuple therapy	0	2 (1.5%)

Numeric data are presented as mean and proportion (percentage) other as median and range

age in group 1 and group 2 was 71 and 72 years, and 54.8% and 62.4% of the patients were females. The most common concomitant diseases in both groups were dyslipidemia, diabetes mellitus, stroke or transient ischemic attack, and coronary heart disease. In both groups, more than 90% of patients were treated with antihypertensive drugs, while the minority (28.6%) were treated with only one medication. As compared to males, female patients in group 1 were older (73 ± 11 vs. 64 ± 14 years, p = 0.03) but demonstrated similar SOBP (130.7 ± 15.3 vs. 132.8 ± 13.7 mmHg, p = 0.64) and DOBP (80.8 ± 11.1 vs. 85.6 ± 10.6 mmHg, p = 0.17). In group 2, male and female patients had similar age (72 ± 12 vs. 69 ± 10 years, p = 0.14) and demonstrated similar SOBP (139.9 ± 16.9 vs. 138.9 ± 16.1 mmHg, p = 0.74) and DOBP (82.4 ± 11.4 vs. 85.4 ± 11.4 mmHg, p = 0.15).

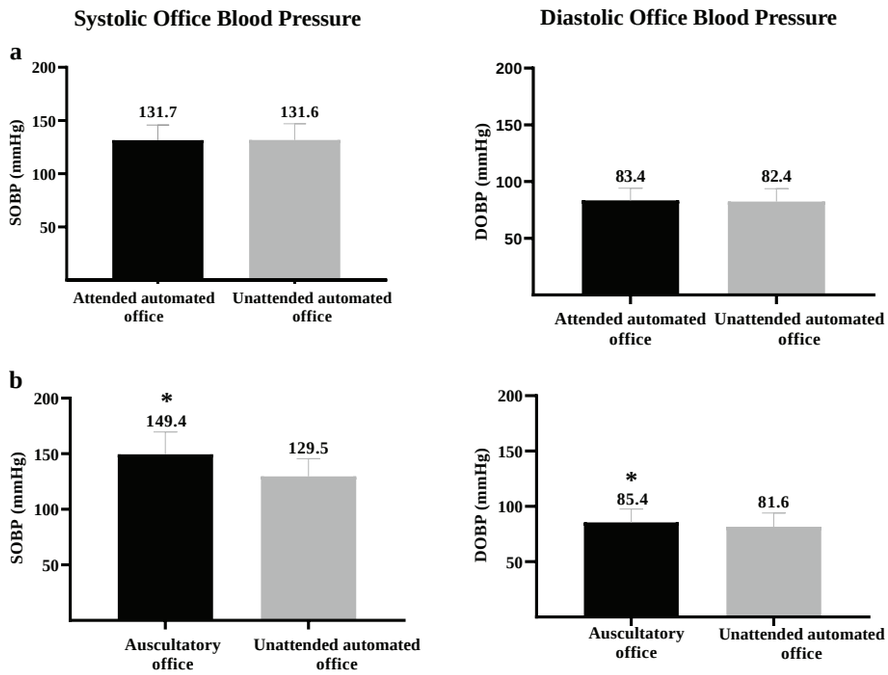

Fig. 1: Individual **a** systolic office blood pressure (SOBP) and diastolic office blood pressure (DOBP) values of attended-automated and unattended-automated measurements in group 1 (n = 42) and **b** SOBP and DOBP values of manual auscultatory and unattended-automated measurements in group 2 (n = 133). *$P < 0.0001$ vs. other group in panel.

Group 1: aAutoOBP vs. uAutoOBP

No significant differences between the two methods of aAutoOBP vs. uAutoOBP measurements were detected for both SOBP (131.7 ± 14.1 mmHg vs. 131.6 ± 15.2 mmHg, p = 0.84) and DOBP (83.4 ± 10.8 mm Hg vs. 82.4 mmHg, p = 0.05). The individual OBP values of the patients are shown in Fig. 1a. The coefficient of correlation between the two methods showed a highly significant correlation for both SOBP (r = 0.93, p < 0.001) and DOBP (r = 0.96, p < 0.0001, Online Resource 1a). ΔSOBP (0.1 ± 5.7 mmHg) was significantly correlated with uAutoSOBP (r = 0.38, p < 0.0001), but not with age and gender. ΔDOBP (0.9 ± 3.2 mmHg) was not significantly correlated with age, gender, aAutoDOBP or uAutoDOBP. Δ SOBP was similar in males and females (0.2 ± 6.6 and 0.5 ± 4.5 mmHg, p = 0.7). ΔDOBP was also similar in males and females (2.4 ± 2.1 mmHg and 2.7 ± 2.2 mmHg, p = 0.6). In a stepwise multivariate analysis including age and gender in the model, ΔSOBP remained independently correlated with uAutoSOBP (beta = − 0.1, p = 0.02). Bland–Altman plot illustrates the small inter-individual differences between attended and unattended automated SOBP and DOBP values (Fig. 2a). Limits of agreement were − 10.8 mmHg to 11.1 mmHg for SOBP and − 5.2 mmHg to 7.1 mmHg for DOBP.

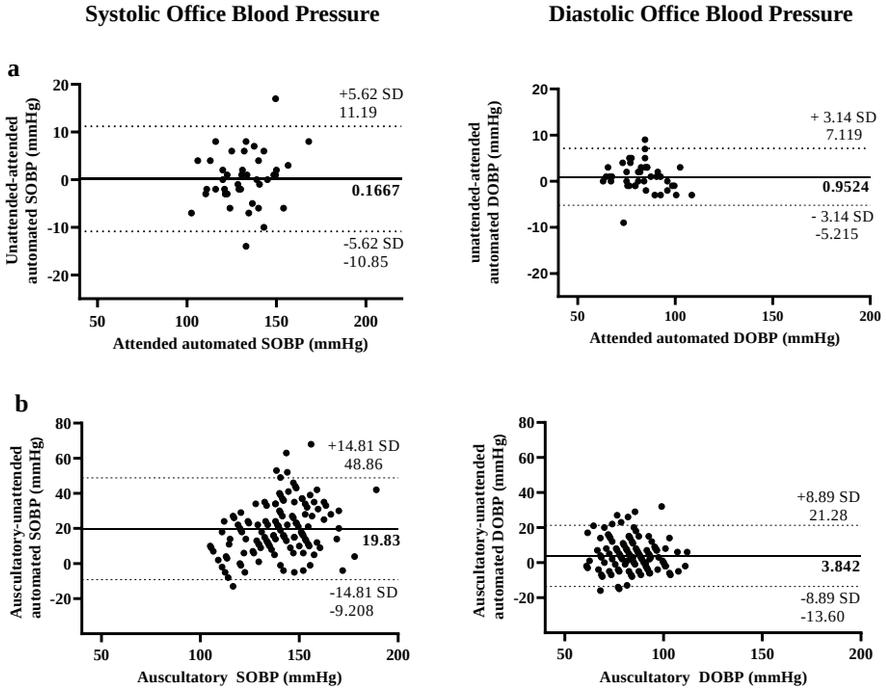

Fig. 2: Bland-Altman plots **a** comparing systolic office blood pressure (SOBP) and diastolic office blood pressure (DOBP) values of attended-automated versus unattended-automated measurements in group 1 (n = 42) and **b** comparing SOBP and DOBP values of auscultatory versus unattended-automated measurements in group 2 (n = 133). Solid lines, mean bias; dashed lines, 95% limits of agreement.

Group 2: AuscOBP vs. uAutoOBP

Significant differences between the two methods of AuscOBP vs. uAutoOBP measurements were detected for both SOBP (149.4 ± 20.1 vs. 129.5 ± 15.8 mmHg, $p < 0.0001$, Fig. 1b) and DOBP (85.4 ± 12.1 vs. 81.6 ± 12.3 mmHg, $p < 0.0001$, Fig. 1b). The coefficient of correlation revealed significant correlations between AuscOBP and uAutoOBP measurements for both SOBP ($r = 0.69$, $p < 0.0001$) and DOBP ($r = 0.73$, $p < 0.0001$; Online Resource 1b). ΔSOBP (19.9 ± 14.8 mmHg) was positively correlated with AuscSOBP ($r = 0.63$, $p < 0.0001$), but not with age ($r = 0.13$, $p = 0.14$) and gender ($r = 0.01$, $p = 0.90$). ΔDOBP (3.9 ± 8.9 mmHg) was positively correlated with AuscDOBP ($r = 0.34$, $p < 0.0001$) and inversely correlated with uAutoDOBP ($r = -0.39$, $p < 0.0001$), but not with age ($r = 0.03$, $p = 0.75$) and gender ($r = 0.15$, $p = 0.08$). ΔSOBP in females and males was similar (19.7 ± 13.3 and 19.9 ± 15.7 mmHg, $p = 0.91$). ΔDOBP was numerically but not significantly lower in females than in males, (2.1 ± 8.5 and 4.9 ± 9.0 mmHg, $p = 0.08$). In a stepwise multivariate analysis including age and gender in the model, ΔSOBP remained independently correlated with AuscSOBP (beta = 1.00, $p < 0.0001$) and ΔDOBP remained independently correlated with AuscDOBP (beta = 0.3, $p < 0.0001$). The corresponding Bland-Altman plots illustrate in Fig. 2b the inter-individual variability between AuscOBP and uAutoOBP for both, SOBP (a) and DOBP (b) values. The limits of agreement were wide, i.e. between − 9.2 and 48.8 mmHg for SOBP and − 13.6 and 21.2 mmHg for DOBP. In a further analysis, we evaluated the achieved OBP targets as recommended in the 2018 ESC/ESH guidelines in group 2. When AuscOBP measurements were considered, the observed systolic and diastolic OBP were below the overall recommended target of 140 and 80 mmHg in 27 patients (20.3%), while 5 of 38 patients (13.2%) achieved OBP values below the lower target of 130 and 80 mmHg in the corresponding group (Fig. 3). Resistant hypertension was observed in 13 patients (9.8%, Fig. 3). In contrast, when the uAutoOBP measurements were considered 61 patients (45.9%) and 11 patients (28.9%) of patients were controlled with values below 140/80 and 130/80 mmHg, while 5 patients (3.8%) were diagnosed with resistant hypertension (Fig. 3). Thus, control rates of hypertension were significantly lower based on the AuscOBP measurements, while the percentage of patients with resistant hypertension was higher (Fig. 3, $p < 0.0001$, respectively).

Discussion and Conclusion

The recent 2018 ESC/ESH Guidelines encourage, in contrast to the time-honored approach to rely only on OBP for the diagnosis on hypertension, the additional use of out-of-office BP measurement for the management of hypertension [2]. Hence, the guidelines recommend for the first time to base the diagnosis of hypertension on repeated OBP measurements or out-of-office BP measurement with ambulatory BP measurement (ABPM) and/or home BP measurement (HBPM) if logistically and economically feasible [2]. Among others, one important limitation of OBP measurements is based on the well-known "white-coat-effect" [1, 17]. The term white-coat hypertension, although originally defined for untreated individuals only, is now also used to describe discrepancies between OBP and out-of-office BP in patients treated for hypertension [2].

It is known that white-coat-hypertension can be present in up to 30–40% of the patients (> 50% in the very old patients) and its prevalence is higher in women, non-smokers and with increasing age [26, 27]. However, many studies suggest that the diagnosis of whit-coat-hypertension can be reduced or even eliminated with automated multiple OBP readings, and particularly when a doctor or nurse is not involved in the BP measurement, i.e., during uAutoOBP measurements [11–13, 26, 27]. An important study highlighting the potential to detect lower OBP values by uAutoOBP measurements was previously reported [22]. In this single-center study reported by Filipovský *et al.* [22] uAutoOBP measurements resulted in significantly lower systolic (− 15.0 mmHg) and diastolic (− 8.0 mmHg) OBP values as compared to AuscOBP measurements. Our results are thus in agreement with this study although our data with four participating physicians were obtained in a single-center GP setting, while the previous study was performed with three participating physicians in a single-center hypertension specialist clinic [22]. In a subsequent multicenter study involving 172 patients, the authors reported albeit still statistically significant, a smaller difference of 8.5 mmHg and

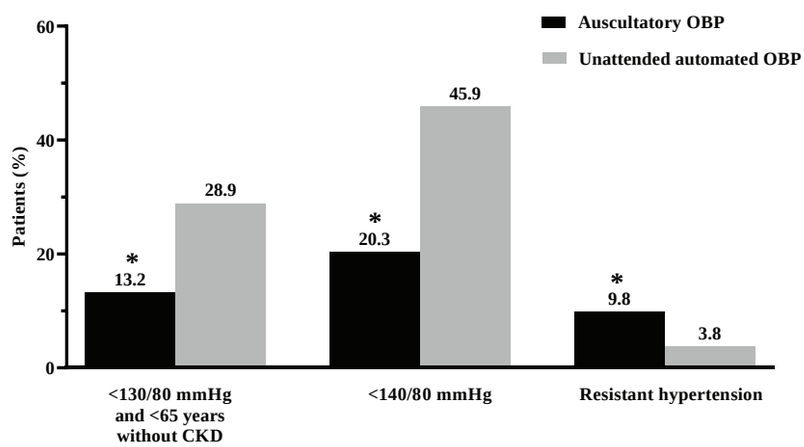

Fig. 3: Percentage Patients in group 2 that achieve blood pressure control or exhibit resistant hypertension. OBP, office blood pressure; CKD, chronic kidney disease. For the definition of resistant hypertension, see text [2]. *$P < 0.0001$ vs. other group in panel (Pearson's Chi-square test).

3.0 mm Hg between systolic and diastolic AuscOBP and uAutoOBP values [23]. However, in the previous studies yielding a difference of 15/8 mmHg automated measurements were conducted after five minutes of rest, while in the more recent study the conduction of the uAutoOBP measurements was carried out after only a short (one minute) rest period. This highlights the importance of the resting time preceding the measurements, even in the setting of measuring OBP in a separate room [28]. Nevertheless, the recent data reported by other authors [22, 23, 29] and our current data are at variance with the results obtained in a recent study in Germany involving 4 GPs´ offices [21]. In this study, no significant OBP differences between AuscOBP and uAutoOBP measurements were found in 107 subjects. Concerning the AuscOBP measurements, the measurements took place right before the automated OBP measurements in our study and the study by Bauer *et al.* [21]. However, in the latter study, the same person that performed the conventional OBP measurement was also responsible for the automated measurement and was also trained to use the device (i.e., Omron 907 BP monitor) and protocol of uAutoOBP measurement. Thus, this might have introduced bias by influencing at the same time, the performance of the physician during AuscOBP measurements. In contrast, in our study, the participating GPs who performed the AuscOBP measurements were not involved in automated OBP measurements, which was exclusively done by the medical staff (nurses) of the GP office. Therefore, by avoiding any interference with the conventional OBP measurements by GPs as much as possible, our study might better reflect the routine measurements of OBP as being applied by GPs in clinical routine. The potential impact on BP management between the different methods used is highlighted by our data on achieved OBP targets and the percentage of patients with resistant hypertension. Hence, the rates of achieved OBP targets were significantly higher, and the percentage of patients with resistant hypertension significantly lower when uAutoOBP measurements were considered. It appears appropriate to point out at this point that we obtained in parallel with a previous study [22] a pronounced difference between AuscOBP and automated OBP, while other recent studies observed smaller differences [23, 29]. Nevertheless, our data are compatible with a recent meta-analysis that identified a substantial pooled mean difference of +14.5 mmHg in routine, AuscSOBP compared to automated OBP measurements [11]. Thus, it seems well established that AuscOBP measurements give in general higher OBP values than automated OBP determinations [7, 11], which can have a substantial impact on hypertension management as shown. Furthermore, our study in the GP setting is in agreement with a recent meta-analysis demonstrating that, when the same measurement protocol and device are used, aAutoOBP provides similar OBP values as uAutoOBP [7].

However, some limitations of our study should be noted. First, although our study involved a large GP office with four participating physicians it nevertheless represents a single-center study with a small number of patients. Thus, a multi-center study and the enrollment of a large number of patients would have increased the validity of our findings. Moreover, we did not schedule multiple visits for OBP measurements as reported by Filipovský *et al.* [22]. This is a further limitation, because repeated visits allow a better determination of the reproducibility and potential impact of differences between OBP measurements, particularly regarding the white-coat effect during AuscOBP. Another limitation of the present study is the lack of standardization of the AuscOBP measurements in group 2. The rationale for this was based on our intention not to interfere with the routine procedures of the participating GPs [21].Thus, the conduction of AuscOBP measurements by the GPs should reflect their routine clinical practice. Consequently, based on our intention a bias was introduced into the comparison between the non-standardized AuscOBP and the very well standardized aAutoOBP measurements in group 2.

Hence, not only a potential white-coat affect due to the presence of the attending GP but also the less stringent methodology during the performance of AuscOBP might have contributed to the higher OBP values obtained by GPs. First, the number of AuscOBP measurements performed was only one in the majority of cases rather than three as recommended in the European guidelines [2]. Second, additional important factors such as the recommendation to investigate the patient seated in a quiet environment for 5 min before beginning the OBP measurements might have also not applied. This could have also contributed to the higher AuscOBP values observed in group 2. This limitation of AuscOBP measurements seems particularly relevant, since a large proportion of the global population spends overall only a few (less than five) minutes with their primary care physicians during their office visits [30].

Thus, in addition to the new concept that supports a wider use of out-of-office BP measurement in the 2018 ESC/ESH guidelines [2], the careful use of automated measurements- and for practical reasons possibly in the attended setting—should be the preferred method for OBP monitoring in routine clinical practice as suggested [7, 11].

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The protocol was in accordance with the 1975 Helsinki Declaration and approved by the Charité ethics committee.

Informed consent Informed consent was obtained from all participants before inclusion into the study.

References available on request Healthcare.India@springer.com

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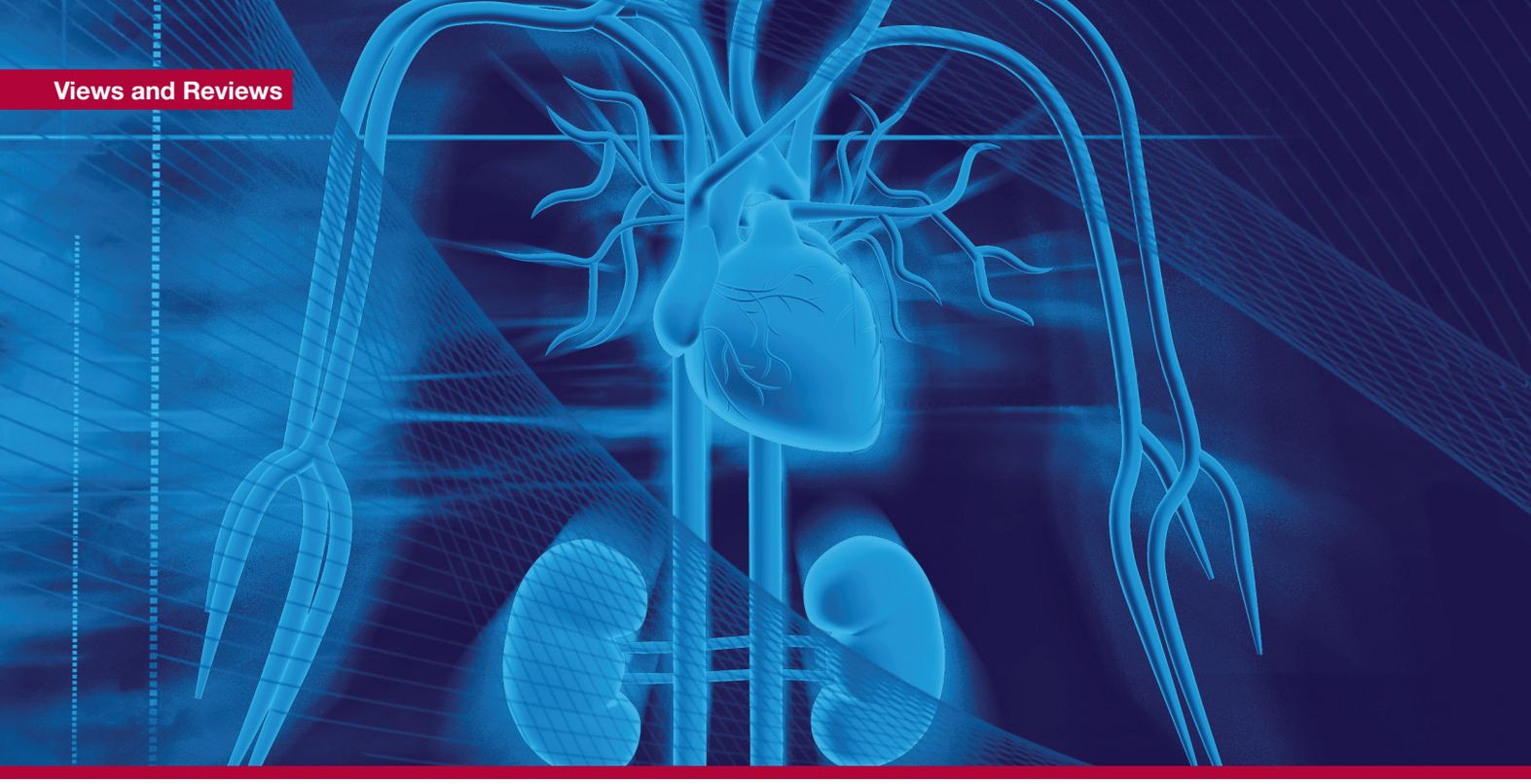

Atrial Fibrillation and Chronic Kidney Disease Conundrum: An Update

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Atrial fibrillation (AF) is the most common cardiac arrhythmia and it is frequently encountered in chronic kidney disease (CKD) subjects. CKD patients are already at high risk for cardiovascular (CV) complications and the addition of AF further aggravates the prognosis.

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Atrial fibrillation is the most common cardiac arrhythmia and it is frequently encountered in CKD subjects, encompassing a higher risk of stroke and systemic thromboembolism [1]. CKD patients are already at high risk for CV complications and the addition of AF further aggravates the prognosis. At the same time, data is missing regarding on how to best approach CKD patients with AF, due to lack of RCTs. The purpose of this review is to reinforce the symbiotic relationship between AF and CKD, to briefly summarize the current state of the therapeutic approach in this particular population and to highlight novel potential therapeutic strategies.

AF and CKD—Epidemiology and Relationship

Atrial fibrillation carries an important morbidity and mortality burden. The global estimate for AF burden in 2010 was 33.5 million. In patients >80 years old, AF is responsible for up to one-third of strokes, as the risk of both AF and subsequent stroke increases with age [2].

The mean global prevalence of CKD is estimated at 13.4% and it is more prevalent in women than in men. The prevalence of CKD is higher in developed areas such as Europe, USA, Canada and Australia, in comparison to areas where economies are growing [3]. It is estimated that 2 million people worldwide suffer

from ESRD and according to the latest report of USRDS, the prevalence of ESRD in USA reached 726,331 in 2016 [4].

Atrial fibrillation and CKD often coexist and have a close bidirectional relationship. The reported prevalence of AF among American CKD patients in 2016 was 23.8%. In an ambulatory clinical trial heart failure population, patients with concurrent AF had significantly greater renal impairment than those without AF [5]. AF increases the risk of incident CKD and the risk of death in patients with CKD. In a sub-study of the Chronic Renal Insufficiency Cohort (CRIC), incident AF doubled the risk of progression to ESRD, independent of baseline eGFR [6]. Patients with CKD and new-onset AF have a three- to sixfold greater rate of ischemic stroke, CV and all-cause death, myocardial infarction and heart failure [7].

At the same time, CKD is an independent risk factor for AF, and the incidence of AF increases with lower eGFR [8]. At enrolment in the CRIC study the prevalence of AF was 18% [9]. The prevalence of non valvular atrial fibrillation (NVAF) increases as CKD progresses, ranging from 21.3% in stages 1–2 to 28.3% in stages 4–5 [4].

AF and CKD—Common Risk Factors

Chronic kidney disease and AF share many risk factors. Conventional CV risk factors, such as older age, smoking, male sex, obesity, diabetes mellitus, hypertension and obstructive sleep apnea associate an increased risk of both CKD and AF. Among patients with ESRD, advanced age, hypertension, heart failure, peripheral arterial occlusive disease and chronic obstructive pulmonary disease were independently associated with the occurrence of AF and AF incidence was proportional to the number of risk factors a patient displayed [10].

Metabolic and hemodynamic derangements secondary to renal impairment and dialysis can predispose to AF. Several studies found an inversely proportional relationship between

Atrial fibrillation and CKD often coexist and have a close bidirectional relationship.

incident AF and urine albumin-to-creatinine ratio (UACR). In a study which included 10,328 participants, a UACR > 30 was associated with a double risk of developing AF [11]. Similarly, a meta-analysis which included 16,769 participants without prevalent AF, reported a strong association between incident AF and elevated UACR, which persisted after adjustment for subclinical CV diseases and temporary CV events [12].

Another important feature of CKD is secondary anemia, which is associated with a higher incidence of AF in all stages. Decreased oxygen carrying capacity caused by anemia is compensated by increasing the heart rate, stroke volume, cardiac output and myocardial mass, thus normalizing the wall stress. This mechanism, together with the increased neurohormonal activity present in anemic patients, can lead to arrhythmogenic remodeling and susceptibility for AF. Future prospective studies are needed in order to establish the potential role of erythropoiesis-stimulating agents in inhibiting new-onset AF in CKD patients [13].

Chronic kidney disease is correlated with a higher risk of infections secondary to immune dysregulation. In patients hospitalized for severe sepsis, renal failure was associated with a greater risk of incident AF [14].

Renal transplantation (RTx) is the treatment of choice for ESRD and the recovery of renal function can influence the extent and potential consequences of AF. In a meta-analysis of data from 8 cohort studies including 137,709 RTx recipients, the prevalence of AF previous to RTx was 7%, while 4.9% patients developed new AF. Allograft failure is more frequent in patients who already have or develop AF after RTx. Older age, higher body mass index, history of coronary artery disease/acute myocardial infarction were important risk factors for AF after RTx. AF was associated with death-censored allograft loss and stroke among RTx recipients [15].

Episodes of AF (generally paroxystic) are common during dialysis sessions, and this fact can be explained by both frequent swings in fluid and electrolytes balance and the activation of the autonomic nervous system (ANS), which act upon a favorable substrate represented by the remodeled atrium. In a prospective cohort study performed on 66 hemodialysis (HD) patients, AF was detected using implantable loop recorders in > 40% of patients, and it was more frequent during and immediately after dialysis. High pre-dialysis serum sodium and high dialysate calcium (> 2.5 mEq/L) were independently associated with the arrhythmia rate [16]. Low albumin levels at the time of dialysis initiation may be related with the occurrence of new AF [17] and there seems to be no major difference in AF incidence between peritoneal dialysis and HD [18].

CKD Leading to AF

There are kidney-specific mechanisms with effect on cardiac structure, endothelial function and vascular calcification.

Cardiac Structure

In CKD patients, chronic fluid overload (preload) and increased arterial stiffness (afterload) lead to left ventricular hypertrophy (LVH) with pronounced myocardial fibrosis, ventricular diastolic dysfunction and left atrial (LA) enlargement. CKD is associated with the raising activation of the Renin Angiotensin Aldosterone System (RAAS). Ang II promotes atrial fibrosis, modulates ion channels and increases atrial pressure. Atrial structural remodeling results in heterogeneous electrical conduction by forming reentrant activity, resulting in AF [19].

By stimulating the production of Ang II, inflammation can promote the development of atrial structural

remodeling and AF. As kidney function declines, there is an increase in concentration of proinflammatory markers such as CRP, fibrinogen, and IL-6. Chronic inflammatory states promote leukocyte activation and atrial remodeling. In a large cohort of CKD subjects, IL-6 was a strong independent risk factor for both preexisting (sixfold higher) and incident AF (two-fold higher) [20]. Despite this, it is still uncertain which inflammatory signaling pathways are involved and whether they have a direct role in AF promotion. The "NACHT, LRR and PYD domain containing protein 3" (NLRP3)-inflammasome is a key inflammatory signaling complex which regulates innate immunity and it is responsible for IL-18 and IL-1β release from innate immune cells. By releasing these cytokines, NLRP3-inflammasome plays a role in renal necro-inflammation, fibrotic tissue remodeling and tubular epithelial cell apoptosis, thus contributing to the progression of kidney disease. Moreover, a recently published study showed that NLRP3-inflammasome is enhanced in atrial cardiomyocytes of both AF patients and dogs subjected to atrial tachycardia pacing, and that cardiomyocyte-restricted activation of NLRP3 in mice promotes both the ectopic firing and AF maintaining substrate. A newly-developed selective inflammasome-inhibitor—MCC950—that interrupts the assembly of the NLRP3-inflammasome complex prevented AF-inducibility in mice. Therefore, targeting the NLRP3 inflammasome may be a novel therapeutic approach for AF of great clinical importance. Antagonizing IL-1 or Caspase-1, which are downstream effectors activated by the NLRP3 inflammasome, may also be of value against AF [21, 22].

Atrial structural remodeling, interstitial fibrosis and inflammation seem to also influence the connexins, gap junction proteins which are vital for the electrical coupling between cells. Alterations in the expression, phosphorylation and distribution of connexins 40 and 43 promote arrhythmias [23].

Transforming growth factor-β1 (TGFβ1), one of the major mediators of Ang II, promotes atrial fibrosis in heart failure, myocardial infarction and hypertension. In nephrectomized rats, CKD induced the activation of TGFβ1 and connexins remodeling, leading to hypertrophic cardiomyopathy, interstitial fibrosis, left atrial enlargement and AF [23].

Abnormalities in levels of phosphorus, fibroblast growth factor (FGF) 23 and vitamin D secondary to CKD can alter cardiac structure. FGF23 may induce pathological LVH by activating fibroblast growth factor receptor (FGFR) 4 on cardiac myocytes. Among patients with mild to severe CKD, there was a strong association of elevated FGF23 with AF independent of demographics, classic CV risk factors, severity of kidney dysfunction and proteinuria, and other markers of mineral metabolism [24].

Left atrium enlargement is an established predictor of adverse CV events, including AF development and impaired LA reservoir function precedes LA enlargement. A study including 358 participants, 19% with CKD (eGFR < 60 mL/min/1.73 m^2), demonstrated that CKD is associated with impaired LA reservoir function, independent of traditional AF risk factors, including left ventricle (LV) mass index and diastolic dysfunction [25]. Even though the possible cardiac chamber remodeling after the initiation of HD may improve CV outcomes, data regarding LA remodeling after dialysis intensification is limited, and mainly driven by echocardiographic measurements. Law *et al*. were the first to evaluate LA remodeling by cardiac magnetic resonance imaging (CMR) after the intensification of HD, on 57 dialysis patients without AF. After 52 weeks, there was no significant change in LA remodeling between the two HD regimens (4 h/session, 3×/week vs 7–8 h/session, 3×/week); changes in LA volumes had strong association with ventricular remodeling [26].

Endothelial Function

Patients with CKD display premature atherosclerosis, and albuminuria is linked to both endothelial and microvascular dysfunction. Oxidative stress and endothelial dysfunction caused by renal impairment may be involved in the increased risk of new-onset AF in patients with CKD [19]. Uremic toxins, especially protein-bound compounds such as indoxyl sulfate, play important roles in generating oxidative stress. CKD may induce AF by enhancing pulmonary veins arrhythmogenesis through the effects of indoxyl sulfate [27].

Vascular Calcification

Chronic kidney disease is associated with increased vascular stiffness determined by arteriosclerosis, which in turn imposes high ventricular afterload in systole, leading to hypertrophy and dilation of the LA. In diastole, reduced coronary perfusion promotes myocardial ischemia [28].

AF Leading to CKD

Atrial fibrillation is characterized by a proinflammatory and a prothrombotic state, that can reflect both on the heart and the kidney. By inducing myocardial fibrosis, it contributes to the decline of LV function and alteration of cardiac hemodynamics, which may accelerate the progression of CKD. On the other hand, AF induces renal fibrosis by downregulation of neutral endopeptidase expression. In the setting of AF, renal enzyme expression and histological appearance of renal tissue are altered. Moreover, the prothrombotic state can also determine kidney dysfunction through renal microinfarcts [6]. This can explain why high CHA_2DS_2-VASc scores showed a strong association with renal function and predicted the decline in eGFR in patients with AF and CKD [29].

Bearing in mind all these pathophysiological peculiarities when approaching a patient with AF and CKD is important, since this explains why the management can be so challenging in

this setting. The following sections of this paper aim to review some of the practical aspects regarding pharmacological and interventional therapies for AF in CKD.

Thrombotic Events and Oral Anticoagulant Therapy

In mild renal dysfunction, a prothrombotic state occurs via alterations in the secretion of PAI1 and vWF, which lead to the inhibition of the fibrinolytic system. Activation of RAAS further aggravates this procoagulant state through hyperfibrinogenemia and high levels of PAI1. Moreover, increased plasmatic levels of tissue factor are present in CKD, thus initiating the coagulation cascade. On the other hand, in advanced CKD, a bleeding tendency is promoted by impaired platelet aggregation, alterations in the coagulation system and the activation of the fibrinolytic system. Anemia, increased production of nitric oxide and the accumulation of uremic toxins are the main three factors responsible for platelet dysfunction in uremia. The inhibition of thromboxane and serotonin by uremic toxins and high levels of nitric oxide and prostacyclin secondary to endothelial dysfunction, impair platelet adhesion and aggregation [30].

These particular aspects should be taken into consideration when undertaking anticoagulant therapy in CKD patients.

Risk Scores in CKD

Current guidelines suggest oral anticoagulation therapy in order to reduce the risk of thrombotic events, based on risk scores such as CHA_2DS_2-VASc, HASBLED, $CHADS_2$, R_2CHADS_2, ATRIA, ORBIT, $HEMORR_2HAGES$. A major gap in this approach is that none of these scores has been validated for CKD patients.

In a cohort consisting of 58,451 anticoagulant-naïve patients, all risk prediction scores performed significantly better for patients with normal kidney function than in patients with CKD, and $HEMORR_2HAGES$ was the best bleeding risk score. The addition of KDIGO class to $CHADS_2$ or replacement of eGFR in the $HEMORR_2HAGES$ score with KDIGO class did not improve either model's discrimination or calibration [31].

Atrial fibrillation is characterized by a proinflammatory and a prothrombotic state, that can reflect both on the heart and the kidney.

Over 90% of HD patients have a CHA_2DS_2-VASc score ≥ 2 [32] and nearly 50% of them have a CHA_2DS_2-VASc score of 5–9 [33]. Chao *et al.* [34] suggested that for patients with ESRD and AF, anticoagulant treatment should be considered for those with a $CHADS_2$ score ≥ 4 or CHA_2DS_2-VASc score ≥ 6.

In ESRD, the use of various drugs (antithrombotic agents, nonsteroidal anti-inflammatory drugs), together with the permanent need for vascular access during HD sessions, contribute to an increased propensity to bleed. Renal replacement therapy (RRT) is associated with an increased risk of both gastrointestinal and cerebral hemorrhages [35].

Renal function is considered by all available bleeding calculators, but each of them uses different thresholds of eGFR and does not take into account the different bleeding risk among subjects on RRT and those not receiving dialysis. In a recent multicenter, prospective cohort study performed on 1745 patients from 38 dialysis centers, HASBLED, ATRIA, $HEMORR_2HAGES$ and ORBIT risk scores had poor predictive abilities, concluding that caution in interpretation is necessary if used in the dialysis population [36].

Vitamin K Antagonists (VKAs)

In CKD patients, VKAs are difficult to use because they frequently have vitamin K deficiency. Compared with patients with eGFR > 30 mL/min, those with a eGFR < 30 mL/min require dose adjustments, have a labile international normalized ratio (INR) and are more frequently over anticoagulated. The latter may accelerate progression of CKD via intratubular hemorrhage [37, 38].

The time in therapeutic range (TTR) seems to decrease with declining renal function, and one study reported that only 42% of those with an eGFR ≤ 29 mL/min/1.73 m^2 had a TTR ≥ 65% [39]. Nevertheless, CKD is an independent risk factor for the occurrence of stroke and death (every decrease of 10 mL/min was associated with a higher risk of stroke and death), independently from TTR [40]. Several studies performed in HD patients taking warfarin, reported different mean TTR values, all of them under 65%, with patients being more likely under-anticoagulated and with a higher mortality risk [41–43]. On the other hand, there were studies reporting that the majority of patients with severe CKD had rather supratherapeutic time, with the lowest TTR values for patients in their first full year of warfarin use [44].

Warfarin is 99% bound to plasma proteins and it is not dialyzable. It is minimally dependent on kidney for elimination and it is not influenced by renal impairment. However, patients with eGFR < 30 mL/min/1.73 m^2 have a 4.9-fold increase in the risk of bleeding when compared to patients with normal renal function treated with warfarin [45].

The platelet dysfunction associated with advanced CKD and the risk of warfarin-induced nephropathy, lowers the net benefit of warfarin use for the prevention of stroke in this setting. A meta-analysis including more than 48,000 patients with AF and CKD concluded that in non ESRD, warfarin lowered the risk of stroke and mortality, with no influence on bleeding events. On the other hand, in ESRD warfarin did not reduce the risk of stroke or mortality and increased the hemorrhagic events [46]. However, in a population of HD patients prospectively followed for 4 years, warfarin intake was associated with a 50% risk reduction in total mortality [47] and this finding has been confirmed by other studies [32, 41].

Another aspect we have to bear in mind is that warfarin use in ESRD is associated with an increased risk of calciphylaxis and accelerated vascular calcifications by interaction with Matrix Gla protein (MGP), which is activated through vitamin K-dependent mechanism and normally inhibits vascular calcification [28].

In light of the above, the percentage of ESRD patients with AF receiving VKAs is rather low with data from several studies reporting that warfarin is prescribed in up to 25% of ESRD patients [32, 41, 48].

Direct Oral Anticoagulants (DOACs)

Compared with VKAs, DOACs seem to have fewer diet and drug interactions, a more predictable effect without the need for INR monitoring, a faster onset of action and a shorter half-life. Secondary analyses of the Phase 3 DOACs trials concluded that in CKD patients dabigatran and apixaban were associated with a lower risk of stroke and systemic embolism when compared with warfarin and with lower risk of major bleeding for the latter, while dabigatran had similar hemorrhagic risk. Rivaroxaban and edoxaban proved to be non-inferior to warfarin in thromboembolic events and superior for the major hemorrhagic events [49]. These results led to an increased prescription of DOACs in patients with AF and CKD, with the most commonly used DOAC in 2015 being apixaban (10%), followed by rivaroxaban (9%) and dabigatran (3%). However, it is important to bear in mind that in real life there are notable differences regarding the safety and efficacy of DOACs: for example, a recent study reported that in patients with eGFR < 60 mL/min, there was an equal efficacy between DOACs and VKAs regarding stroke prevention, but with an excess of bleeding for the first group [50].

Direct oral anticoagulants need dose adaptations in the various CKD stages. Cockcroft–Gault equation is preferred for adjusting medication doses in renal dysfunction [51]. CKD-EPI and MDRD formulas better assess the degree of renal dysfunction, but the eGFR is not equivalent to the eCrCl derived from Cockcroft–Gault equation. In a study population of 831 patients with AF and moderate-severe CKD on DOACs, the eCrCl and MDRD eGFR equations correlated in 63.89% of the time. The use of the MDRD eGFR equation resulted in under-treatment in 26.9% of cases and in over-treatment in 9.3% of cases. The results for CKD-EPI eGFR were similar [52].

Moreover, there is a particular concern on acute-on-chronic kidney injury. Some authors suggest that DOAC therapy should be temporarily discontinued in patients with acute kidney injury, and bridging with parenteral agents should be taken into consideration depending on clinical context [53].

In ESRD oral anticoagulation is still an ongoing concern, as no prospective RCTs addressed this matter. Nevertheless, data from the Fresenius Medical Care records show that 23.5% of patients with AF and eGFR < 30 mL and 11.6% patients with AF on HD are taking DOACs [54].

The dependence on renal elimination, renal dosing, the dialysis clearance of DOACs and currently approved reversal agents as stated by the European Heart Rhythm Association are summarized in Table 1 [55].

In a study that evaluated 29,977 dialysis patients with AF treated with DOACs or warfarin, there was a higher risk of hospitalization and death from bleeding in the arm treated with dabigatran and rivaroxaban [56]. Another systematic review that synthesized the evidence for stroke and bleeding outcomes associated with DOACs compared with warfarin or aspirin in CKD and dialysis patients with AF, reported the same results regarding rivaroxaban and dabigatran, with no difference in major bleeding outcomes with apixaban compared to warfarin [57].

In a retrospective cohort study performed on 25,523 patients with ESRD and AF on dialysis, apixaban 5 mg BID was associated with a significantly lower risk of major bleeding, lower risks of stroke/systemic embolism and death compared with either reduced dose apixaban 2, 5 mg BID or warfarin [58].

In light of the above, the 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation recommends (class II level of evidence B-NR) warfarin or apixaban for oral anticoagulation in patients with ESRD or on dialysis. For patients with AF and moderate-to-severe CKD, treatment with adjusted doses of direct thrombin or factor Xa inhibitors may be taken into account [59].

Left Atrial Appendage Closure (LAAC)

Oral anticoagulant administration is effective for preventing stroke in patients with CKD and AF, but the risk of serious bleeding remains an important issue. The

Table 1: Renal dosing and elimination, dialysis clearance and reversal agents of DOACs.

Oral anticoagulant	Renal dosing	Renal elimination (%)	Dialysis clearance	Reversal agents
Rivaroxaban	15 mg QD[a]	35	No appreciable effect	Andexanet alfa
Apixaban	2.5 mg BID[b]	27	14%	Andexanet alfa
Edoxaban	30 mg QD[c]	50	No appreciable effect	No approved antidote (Ciraparantag-currently under investigation)
Dabigatran	150 mg or 110 mg BID[d]	80	50–60%	Idarucizumab

[a]If eCrCl < 50 mL/min; not recommended < 15 mL/min
[b]If eCrCl < 30 mL/min; not recommended < 15 mL/min
[c]If eCrCl < 50 mL/min; not recommended < 15 mL/min
[d]If CrCl < 50 mL/min; not recommended < 30 mL/min

site of thrombus formation is represented by the left atrial appendage and its exclusion is a non-pharmacological device-based therapy for stroke prevention. In terms of preventing the thrombotic complications, LAAC proved to be equivalent and even superior to oral anticoagulant therapy and CKD does not seem to influence the implant safeness and success rate [60–62]. Moreover, LAAC proved to be safe in ESRD patients too [63].

Oral anticoagulant administration is effective for preventing stroke in patients with CKD and AF, but the risk of serious bleeding remains an important issue.

Rate Versus Rhythm Control of AF

The decision of rate vs. rhythm control should be made based on a multidisciplinary approach involving a heart rhythm specialist, and AF related-factors (duration, LA size, LVH, left ventricular ejection fraction, age, comorbidities, reversible causes) as well as CKD-related factors (disease severity, relationship to HD session, pro-arrhythmic factors) should be considered. Younger age, relatively healthy patient, symptomatic AF, with recent onset, reversible causes, the interference with HD performance and a small LA size are arguments for a rhythm control strategy. When the patient is older with significant comorbidities, less symptomatic, and the AF is of longer duration associated with a larger LA, a rate control strategy is preferred. Beta blockers, calcium channel blockers and cardiac glycosides are the available therapeutic options regarding rate control. In a large retrospective cohort study on HD patients, Weir *et al.* classified beta blockers in two groups: high dialyzability beta blockers (acebutolol, atenolol, metoprolol) and low dialyzability beta blockers (bisoprolol, propranolol). Patients treated with a poorly dialyzed beta blocker (mainly bisoprolol) had significant lower mortality rate than those treated with a highly dialyzable beta blocker [64]. The main limitation of this study is that although its removal by dialysis is negligible, carvedilol was not included in the analysis because of limited coverage in Ontario. Moreover, Tieu *et al.* speculated that data regarding the dialysis clearance of beta blockers may be different after the implementation of modern high-flux dialysis membranes, and proved in their study that while indeed atenolol and metoprolol are highly dialyzable (72 ± 21 and 87 ± 28 mL/min), bisoprolol is also cleared during HD (44 ± 9 mL/min). All three of these beta blockers had markedly higher dialytic clearance when compared with carvedilol (0.2 ± 0.6 mL/min). Carvedilol is the only beta blocker that showed significant reduction in CV mortality and all-cause mortality in patients on HD. Taking all of the above into consideration, carvedilol seems to be the best choice, and bisoprolol the alternative [65]. Verapamil and digoxin may need dose adjustments. Regarding rhythm control, amiodarone does not appear to negatively affect survival, even in ESRD; it is unknown if CKD patients are at higher risk for organ toxicity. Both sotalol and flecainide need dose reduction according to eGFR. Only sotalol is dialyzable. If medical treatment fails to control the ventricular rate, atrioventricular nodal ablation with pacemaker implantation is an alternative, keeping in mind that in HD patients transvenous devices can lead to serious complications. Direct current cardioversion has a similar success rate regardless of eGFR, but given the high risk or recurrence of AF associated with CKD progression, long-term antiarrhythmic strategies may be necessary. CKD patients who underwent pulmonary veins isolation had a greater likelihood of AF recurrence, with an increased risk for delayed thromboembolic events, most likely because of the sympathetic hyperactivity inherent to CKD [66].

Renal Denervation (RDN)—A "One Stone Two Birds" Strategy?

Many of the above-mentioned risk factors for AF are associated with the activation of the ANS. AF onset is associated with combined sympatho-vagal activation. While sympathetic stimulation enhances triggered activity and automaticity, vagal activation increases the potential for reentry, by inducing nonhomogeneous shortening of the atrial effective refractory period. Therefore, ANS may play a central role in creating a substrate for atrial arrhythmia. During the past decade, both the importance of pulmonary veins and posterior left atrium in holding potential foci for generating AF and pulmonary vein isolation (PVI) as the cornerstone ablation strategy have been well established [67]. The contribution of sympathetic and parasympathetic innervations of the pulmonary veins and posterior left atrium to the occurrence of AF has also emerged as a potential novel therapeutic approach. RDN seems to be a promising therapeutic tool in cardiology, especially for the treatment of therapy-resistant hypertension. A recently published meta-analysis performed on hypertensive patients concluded that RDN as an adjunct to PVI was associated with a nearly 40% reduction in the burden of recurrent AF, for both paroxysmal and persistent AF [68]. Moreover, the AFFORD pilot study was the first to demonstrate that RDN without concomitant PVI may reduce AF burden in hypertensive patients [69].

On the other hand, increased sympathetic activity contributes to chronic kidney injury. In their study, Lubanda *et al.* created an experimental model of CKD and aimed to evaluate the impact of RDN on CKD progression. They did not observe significant changes in creatinine and urea but a lower aldosterone level was observed, which shows that by interfering with RAAS, RDN may have a mild protective effect [70].

If the aforementioned results were to be confirmed in future large-scale randomized trials, through its potential of reducing both AF burden and CKD progression, RDN could be of great clinical value in AF patients with CKD.

Summary and Conclusions

Atrial fibrillation and CKD have a double edged-sword relationship. On one hand, there are kidney-specific mechanisms which can alter cardiac structure and predispose to AF, and on the other hand the development of AF itself can accelerate the progression of CKD. Furthermore, the synergistic effect of these two entities raises serious issues concerning the balance between bleeding and thrombotic risk. Anticoagulant treatment can be challenging, especially in ESRD, where the net clinical benefit is still unclear. While advances have been made on this field, with the recent approval of apixaban for ESRD patients [59], the decision of rate vs. rhythm control lies mostly on general consensus, rather than on RCTs. Specific treatment targeting the pathophysiological connections between AF and CKD may be capable of improving the outcomes in this setting.

Compliance with ethical standards

Conflict of interest No conflicts of interests to declare.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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spikes, and global gaps in governance (World Economic Forum 2010). The cost due to premature deaths from heart disease, diabetes, and stroke in India is projected to be 237 billion dollars by 2015 (Prabhakaran and Yusuf 2010). Health care delivery in India remains challenging due to its large, aging population of 1.18 billion (Chanana and Talwar 1987, WHO 2011b) and limited resources in rural areas (Ghei *et al*. 2010; Patel and Nowalk 2010). Given the increasing prevalence of CVD and its related morbidity combined with the pace of increase in the population and demographic aging (Chanana and Talwar 1987), the real impact goes far beyond the economic impact and contributes to a drain of health resources, both in human resources and infrastructure considering the current lack of medical personnel (Liu *et al*. 2011).

There are several limitations to our study. We measured blood pressure once, without repeat measurements in the two or more office visits necessary to make a diagnosis of HTN. However, comparable anecdotal data from CHWs and previous data from Jamkhed hospital suggest our findings likely correlate with HTN prevalence. Additionally, approximately 8% of subjects had DBP and SBP above 100 and 160 respectively, which is diagnostic of HTN even in one reading. Due to lack of resources, we were unable to collect more comprehensive data on the effect of socio-economic factors, including housing, education, literacy level, and household size on blood pressure. Other limitations were lack of objective measurement of salt or calorie intake, objective assessment of physical activity and environmental factors, and basic data on social network and psychological stressors such as anxiety, depression, PTSD or chronic stress (Everson-Rose and Lewis 2005, Gerin *et al*. 2005; Clougherty *et al*. 2009; Figueredo 2009; Spruill 2010; Hamer and Steptoe 2012). We suggest further study to evaluate these factors.

Conclusion

In conclusion, the prevalence of high blood pressure and pre-HTN in rural villages of Jamkhed, central India is high and comparable to that in developed countries. Prevalence of other cardiovascular risk factors, such as tobacco use, are also high and awareness about HTN is lower than other rural areas in India. The role of other risk factors in this rural farming community such as social and psychological stressors and environmental factors needs to be further evaluated. The emergence of non-communicable disease in India poses a significant challenge which warrants a strong public health response with emphasis on prevention, improving awareness and health education, providing low cost and sustainable interventions for risk factor modification, and consistent treatment and follow up. Training and employing CHWs in the context of comprehensive rural health programs to provide such services using the existing model for controlling communicable diseases is feasible and warranted.

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Lp(a): Addressing a Target for Cardiovascular Disease Prevention

The aim of this study was to review the current recommendations for lipoprotein(a) (Lp(a)) screening, the evidence behind the thresholds for increased cardiovascular disease (CVD) risk, and the available data supporting Lp(a) lowering.

Lp(a) is almost entirely genetically determined and has an independent causal association with CVD.

Measurement of Lp(a) is challenging given the structural heterogeneity of apolipoprotein a (apo(a)), for which isoformin-sensitive immunoassays should be used. Current guidelines do not recommend treatment to lower Lp(a) but rather focus on intensified preventive measures including low-density lipoprotein cholesterol (LDL-C) lowering in patients with high Lp(a). Evidence suggests that levels higher than 50 mg/dL (125 nmol/L) identify significantly increased CVD risk. Mendelian randomization studies suggest that in order to have a clinically significant reduction in coronary heart disease, Lp(a) levels should be reduced by at least 60–70 mg/dL to attain a significant benefit. Ongoing studies of targeted therapy with antisense oligonucleotides (ASO) have shown promising reductions in Lp(a) up to 80%, but a cardiovascular outcomes trial is needed.

There is unquestionably an increased risk for CVD in patients with elevated Lp(a); however, measurement assay issues and the lack of Lp(a)-targeted therapies with proven outcome reduction limit the clinical utility of this important risk factor. Available evidence suggesting specific thresholds for clinically significant CVD risk are based on European or Caucasian populations, not accounting for important racial differences. Novel Lp(a)-targeted emerging therapies may need to account for an expected reduction of at least 60–70 mg/dL to achieve a clinically significant benefit.

Source: Vasquez, N. & Joshi, P.H. Curr Cardiol Rep (2019) 21: 102. https://doi.org/10.1007/s11886-019-1182-0. © Springer Science+Business Media, LLC, part of Springer Nature 2019.

Renal Denervation: Is It Ready for Prime Time?

Interventional cardiology and in particular the field of renal denervation (RDN) is subject to constant change. This review provides an up to date overview of renal denervation trials and an outlook on what to expect in the future.

After the sham-controlled SYMPLICITY HTN-3 trial dampened the euphoria following early renal denervation trials, the recently published results of the sham-controlled SPYRAL HTN and RADIANCE HTN trials provided proof-of-principle for the blood pressure-lowering efficacy of renal denervation. However, these studies underline the major issue of patients' nonadherence to antihypertensive medication as well as the need for reliable patient- and procedure-related predictors of response.

The second generation of sham-controlled renal denervation trials provided proof of principle for the blood pressure-lowering efficacy of RDN. However, larger trials have to assess long-term safety and efficacy.

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Who Should Receive a Wearable Defibrillator Vest at Hospital Discharge?

The aim of this review was to discuss the role of wearable cardioverter defibrillator (WCD) vests in preventing sudden cardiac death (SCD) in at-risk populations.

The impact of randomized-controlled trials with implantable cardioverter-defibrillators (ICD) therapy is well established in randomized clinical trials in ischemic cardiomyopathy. Although the benefits are not as clear in non-ischemic cardiomyopathy, meta-analyses show significant mortality benefits from immediate electrical cardioversion strategies. The role of WCDs in at-risk populations in whom ICD therapy is temporarily not indicated is not as well-established. Smaller cohort trials have shown efficacy in patients with newly-diagnosed cardiomyopathy, requiring temporary ICD explantation, and others with less common indications for WCD therapy.

The Vest Prevention of Early Sudden Death Trial was a landmark randomized control study seeking to examine the benefits of WCD therapy in at-risk population, and although the primary endpoint of reducing arrhythmic death was not reached, the structure of the trial and significant differences in total mortality make a compelling case for continued use of WCD therapies in our healthcare systems.

Source: Kachur, S. & Morin, D.P. Curr Cardiol Rep (2019) 21: 125. https://doi.org/10.1007/s11886-019-1215-8. © Springer Science+Business Media, LLC, part of Springer Nature 2019.

Consistency of Blood Pressure Control: a Useful Tool of Hypertension Assessment in a Vulnerable Population

Anthi Katsouli[1], Tanu S. Pandey[2], David Goldberg[2]

There is compelling data showing that the proportion of visits with blood pressure control below 140/90 is a graded predictor of hypertension-related outcomes.

There is strong evidence that treatment of hypertension reduces cardiovascular morbidity and mortality [1]. National Health and Nutrition Examination Survey (NHANES) and a national quality program, the Health Plan Employer Data and Information Set (HEDIS), use point prevalence of blood pressure with a cut point of less than 140/90 mmHg to assess control for the population and for clinical practices, respectively [2, 3].

There is compelling data showing that the proportion of visits with blood pressure control below 140/90 is a graded predictor of hypertension-related outcomes [4]. The implication of this study is that beyond point prevalence of hypertension control, consistency of control below 140/90 may be an important patient-centered goal of care.

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Methods

We conducted an electronic medical record (EMR) review of patients in a primary care clinic at John H. Stroger, Jr. Hospital of Cook County approved by our institutional review board. Patients seen over a 2-week period of a random month of the year were selected using a random sampling method. An established primary care patient was defined as one with five or more clinic visits in the three preceding years. A diagnosis of hypertension was determined from the problem list. The last five clinic blood pressures recorded by the clinic nursing staff were abstracted for established clinic patients with hypertension.

Blood pressure control was defined as < 140/90 mmHg. For each participant, we evaluated the number of visits with blood pressure control and control at the last visit. Consistent control was defined as control on 4 or 5 of the visits. We defined inconsistent control as those with 3 or fewer of the five visits with controlled blood pressure.

The distribution of clinical predictors was compared between subjects with consistent and inconsistent control with chi-square tests. Independent predictors were identified using multivariate logistic regression. We developed multivariate models defining the race/ethnicity as a dichotomous variable (African-American vs. other race/ethnicity) because the sample size of each non-African-American race/ethnicity was small. We used the number of visits during the 3-year timeframe as a dichotomous variable with a cut-point of 9 visits, as this bivariate association with consistency of hypertension control approached statistical significance at this level. We used backward elimination with a threshold of $p < 0.05$ for eliminating variables in the model. The outcomes were adjusted for age and gender in the model. We report the risk as an odds ratio with 95% confidence intervals. The statistical analysis was conducted using SAS 9.2 (English).

Results

We reviewed 258 charts; 150 (58%) met the inclusion criteria. Among the 108 excluded patients, 62 had hypertension

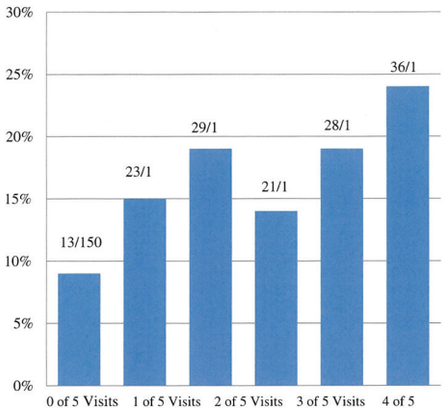

Fig. 1: Proportion of patients with blood pressure controlled to < 140/90 at the five recorded visits.

but fewer than five clinic visits. The mean age was 63 years (range 23–90), 58% were women, and 69% were African-American (13% Hispanic, 11% White, and 5% Asian). The most common comorbidities were dyslipidemia (79%) and diabetes (57%). Table 1 describes additional variables of the study population.

Eighty-three subjects (55%) had controlled blood pressure at the last visit. Figure 1 shows the subject's consistency of blood pressure control. Sixty-four individuals (43%) met the study definition of consistent control.

Table 1: Baseline characteristics of patients with inconsistent and consistent BP control.

	Inconsistent control (n = 87)	Consistent control (n = 63)	p value
Demographics			
Age			
≤ 54	31 (35.63%)	15 (23.81%)	0.3
55–64	16 (18.39%)	17 (26.98%)	
65–74	22 (25.29%)	20 (31.75%)	
≥ 75	18 (20.69%)	11 (17.46%)	
Gender			
Female	49 (56.32%)	38 (60.32%)	0.62
Male	38 (43.68%)	25 (39.68%)	
Race/ethnicity			
African-American	67 (77.01%)	36 (57.14%)	0.01
Others	20 (22.99%)	27 (42.86%)	
Current smoking			
Yes	8 (9.2%)	8 (12.7%)	0.49
No	79 (90.8%)	55 (87.3%)	
BMI (CDC categories)			
Normal	18 (20.69%)	9 (14.29%)	0.6
Overweight	26 (29.89%)	21 (33.33%)	
Obese	43 (49.43%)	33 (52.38%)	
Comorbidities			
Diabetes mellitus	52 (59.77%)	34 (53.97%)	0.48
Chronic kidney disease	27 (31.03%)	12 (19.05%)	0.1
Coronary artery disease	11 (12.64%)	12 (19.05%)	0.28
Stroke	6 (6.9%)	6 (9.52%)	0.56
Congestive heart failure	14 (16.09%)	15 (23.81%)	0.24
Dyslipidemia	67 (77.01%)	51 (80.95%)	0.56
Number of visits			
5–6	30 (35.29%)	13 (21.31%)	0.23
7–8	16 (18.82%)	10 (16.39%)	
9–10	18 (21.18%)	13 (21.31%)	
11–12	9 (10.59%)	12 (19.67%)	
≥ 13	12 (14.12%)	13 (21.31%)	
Number of visits			
< 9	48 (55.17%)	25 (39.68%)	0.06
≥ 9	39 (44.83%)	38 (60.32%)	
Number of hypertensive medications			
0–1	12 (13.79%)	15 (23.81%)	0.19
2	25 (28.74%)	14 (22.22%)	
3	26 (29.89%)	23 (36.51%)	
≥ 4	24 (27.59%)	11 (17.46%)	

Fifty individuals (33%) had control at 2 or 3 visits (sometimes controlled) and 36 individuals (24%) had control at 0 or 1 visits (never/rarely controlled). Among those with controlled hypertension at the last visit, 68% (n = 53) had consistent control. Among those with uncontrolled hypertension at the last visit, 10% (n = 7) had consistent control.

Discussion

In this retrospective chart review in a public hospital primary care clinic, the point prevalence of control on treatment (55%) is below the NHANES US population rate. We found that 43% met our definition for consistent control.

Using the frame of consistency of hypertension control may provide clinically meaningful information beyond the point prevalence of hypertension control. Given the known variability of blood pressure [5], it stands to reason that point prevalence would not fully predict consistent control. In our population, one-third of patients with point prevalence of control did not have consistent control. These are patients in whom we would recommend on-going careful monitoring. The frame of consistency may influence clinical decision-making, helping overcome clinical inertia [6]. The hypotheses that integration of consistency of blood pressure control alters clinical judgment, provider-patient communication, and is of value to aggregate assessment and clinical quality improvement are each testable.

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Compliance with Ethical Standards We conducted an electronic medical record (EMR) review of patients in a primary care clinic at John H. Stroger, Jr. Hospital of Cook County approved by our institutional review board.

Conflict of Interest The authors declare that they do not have a conflict of interest.

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Patient with Resistant Hypertension

Julian Segura

> The definition of resistant hypertension is based on office blood pressure (BP) measurements. Ambulatory blood pressure monitoring (ABPM) is mandatory in resistant hypertensive patients to define true and white-coat resistant hypertension, as the latter group has a better prognosis.

Clinical Case Presentation

A 68-year-old, Caucasian male was referred by his family physician for assessment of uncontrolled arterial hypertension. He started treatment 7 years ago with enalapril. In the previous year, amlodipine and hydrochlorothiazide were added due to poor control. Current treatment is enalapril 20 mg twice daily (in the morning and in the evening), amlodipine 10 mg once daily (at lunch) and hydrochlorothiazide 25 mg once daily (in the morning). He is also treated with atorvastatin 10 mg and long-acting insulin.

Family History

His father was hypertensive. He is the second of three brothers. All three are hypertensives.

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Clinical History

- Hypertensive known since the age of 60 years.
- Smoker up to 56 years old. Eat wine at meals.
- Type 2 diabetes with insulin requirements.
- Hypercholesterolemia in treatment with atorvastatin.
- Sleep apnoea syndrome treated with cPAP for 2 months.
- Grade 1 obesity.

Physical Examination

- Weight: 88 kg
- Height: 170 cm
- Body mass index (BMI): 30.5 kg/m^2
- Waist circumference: 105 cm
- Normal cardiopulmonary auscultation
- Abdomen without findings
- Extremities with palpable distal pulses, without oedema

Repeated clinic BP and heart rate (HR) measurements were performed (Table 1).

Haematological Profile

- Haematocrit: 39.7%
- Haemoglobin: 13.4 g/dL
- White blood cells: 5500/mm^3
- Platelets: 259,000/mm^3

Blood Biochemistry

- Fasting plasma glucose: 75 mg/dL
- Fasting lipids: Total cholesterol, 147 mg/dL; HDL cholesterol, 76 mg/dL; LDL cholesterol, 62 mg/dL; triglycerides, 47 mg/dL
- Renal function: Creatinine 0.8 mg/dL, estimated glomerular filtration rate (MDRD formula), 101.9 mL/min/1.73 m^2
- Serum uric acid 3.5 mg/dL
- Electrolytes: Sodium 142 mEq/L, potassium 3.93 mEq/L
- Urine analysis: Albumin/creatinine ratio, 14.7 mg/g.
- Liver function tests: Normal
- Thyroid function tests: Normal

12-Lead Electrocardiogram

Sinus rhythm with normal heart rate (80 bpm)

Diagnosis

According to office BP (Table 1) and ABPM values (Table 2 and Fig. 1), we classified this patient as true resistant hypertension.

Prescriptions

- Regular physical activity
- Restriction in sodium intake
- Addition of spironolactone 25 mg/day

Follow-Up Month 1

The patient has followed antihypertensive treatment for 1 month with enalapril 20 mg once daily (in the morning), amlodipine 10 mg once daily (at lunch), hydrochlorothiazide 25 mg once daily (in the morning) and spironolactone 25 mg once daily (in the morning). He does not refer any side effects.

Repeated clinic BP and HR measurements were performed (Table 3).

Blood Biochemistry

- Fasting plasma glucose: 129 mg/dL
- Renal function: Creatinine 0.84 mg/dL, estimated glomerular filtration rate (MDRD formula), 100 mL/min/1.73 m^2
- Serum uric acid 3.8 mg/dL
- Electrolytes: Sodium 141 mEq/L, potassium 4.49 mEq/L

ABPM (Table 4, Fig. 2) shows a decrease of 30 mmHg of the average systolic BP with respect to the baseline ABPM. No side effects have been observed, nor significant elevation of plasma creatinine or potassium levels. The treatment with spironolactone is therefore maintained.

Follow-Up 1 Year

Patient was reviewed in consultation after 6 months of treatment, maintaining clinical BP and home self-monitoring BP within normal limits. The patient is re-evaluated after 1 year of treatment with spironolactone.

Repeated clinic BP and HR measurements were performed (Table 5).

Haematological Profile

- Haematocrit: 36.6%
- Haemoglobin: 12.2 g/dL
- White blood cells: 6100/mm^3
- Platelets: 263,000/mm^3

Blood Biochemistry

- Fasting plasma glucose: 98 mg/dL
- Fasting lipids: Total cholesterol, 180 mg/dL; HDL cholesterol, 74 mg/dL; LDL cholesterol, 96 mg/dL; triglycerides, 52 mg/dL
- Renal function: Creatinine 1.0 mg/dL, estimated glomerular filtration rate (MDRD formula), 78 mL/min/1.73 m^2
- Serum uric acid 5.0 mg/dL
- Electrolytes: Sodium 140 mEq/L, potassium 4.63 mEq/L
- Urine analysis: Albumin/creatinine ratio, 2.1 mg/g
- Liver function tests: Normal

Discussion

Resistant hypertension is defined as high BP that remains uncontrolled (>140/90 mmHg) despite the use of effective doses of three or more different classes of antihypertensive agents, including a diuretic [1, 2].

Table 1: Repeated clinic BP and HR.

Systolic BP (mmHg)	Diastolic BP (mmHg)	HR (bpm)
180	87	58
163	83	57
159	94	58

Table 2: 24-h ambulatory blood pressure monitoring.

	24-h period	Daytime period	Night-time period
Systolic BP (mmHg)	163	170	146
Diastolic BP (mmHg)	85	90	74
HR (bpm)	67	69	62

Table 3: Repeated clinic BP and HR.

Systolic BP (mmHg)	Diastolic BP (mmHg)	HR (bpm)
137	81	60
123	88	65
126	78	61

Table 4: 24-h ambulatory blood pressure monitoring.

	24-h period	Daytime period	Night-time period
Systolic BP (mmHg)	133	142	115
Diastolic BP (mmHg)	78	82	67
HR (bpm)	65	66	62

Table 5: Repeated clinic BP and HR.

Systolic BP (mmHg)	Diastolic BP (mmHg)	HR (bpm)
153	75	67
147	71	70
139	67	66

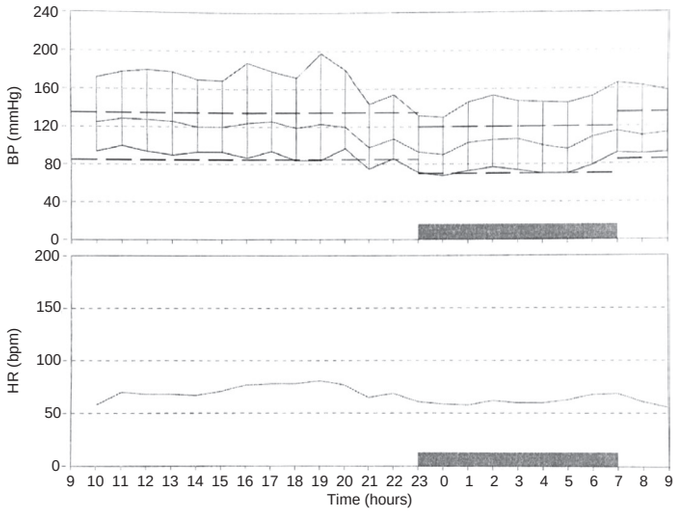

Fig. 1: 24-h ambulatory blood pressure monitoring. *BP* arterial blood pressure, *HR* heart rate, *bpm* beats per minute, *Time (hours).*

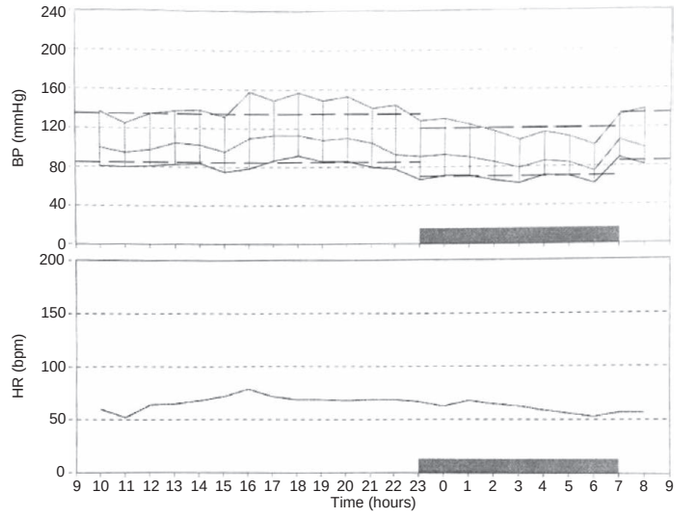

Fig. 2: 24-h ambulatory blood pressure monitoring. *BP* arterial blood pressure, *HR* heart rate, *bpm* beats per minute, *Time (hours).*

Select the correct sentence:

1. Resistant hypertension is defined as high blood pressure that remains uncontrolled despite the use of effective doses of three or more different classes of antihypertensive agents, including a diuretic.
2. Resistant and refractory hypertensions are synonymous terms.
3. Definition of resistant hypertension is based on ABPM values.
4. ABPM is not a useful tool in the management of resistant hypertensive patients.

The first American Heart Association Scientific Statement on resistant hypertension included patients whose BP was controlled (<140/90 mmHg) with four or more medications within the category of resistant hypertension [3]. Refractory hypertension has been used to refer to an extreme phenotype of antihypertensive treatment failure, considering increased blood pressure levels (>140/90 mmHg) despite the use of optimal doses of five or more different classes of antihypertensive agents, including chlorthalidone and a mineralocorticoid receptor antagonist [4].

The definition of resistant hypertension is based on office BP measurements. However, the use of ABPM has allowed for the recognition of the white-coat effect as being responsible for a relatively large proportion of resistant hypertensive patients. Data from the Spanish ABPM Registry shows that prevalence of resistant hypertension in a large population of treated hypertensive outpatients followed in different clinical settings (mostly in primary care) is around 15%, using the current definition, and around 12% if we consider only patients with office BP >140/90 mmHg (excluding patients with normal BP but treated with ≥4 antihypertensive drugs) [5]. Thus, ABPM is mandatory in resistant hypertensive patients to define true and white-coat resistant hypertension, as the latter group has a better prognosis than the former one [6, 7]. In the Spanish ABPM Registry, from 8000 resistant hypertensive patients detected by office BP, only 62.5% had 24-h values ≥130 and/or 80 mmHg; the remaining 37.5% were considered as having white-coat resistant hypertension, so-called pseudo-resistant hypertension [5]. True and pseudo-resistant hypertensives show differences in both clinical and ABPM parameters: male sex, longer duration of hypertension, worse cardiovascular risk profile (including a higher proportion of smokers, diabetics and target organ damage, e.g. left ventricular hypertrophy, microalbuminuria or impaired renal function) and history of a previous cardiovascular event were all more frequent in true resistant hypertension than in white-coat resistant. Most of these variables remained significant in a multivariate analysis, and they probably reflect the consequences of long-lasting sustained high BP. However, their capacity to discriminate between true and pseudo-resistant hypertension in clinical practice is probably low, and ABPM must be considered mandatory to clearly distinguish both hypertensive phenotypes [5].

Resistance to antihypertensive therapy is related to:

1. Inadequate doses or combinations of drugs
2. Non-compliance
3. Volume overload
4. All are correct

Although the differential diagnosis of resistant hypertension is beyond the scope of this chapter, it is worth mentioning a broad list of factors that may contribute to the genesis of this resistance: (1) inadequate antihypertensive treatment (non-compliance, inadequate doses, inappropriate combinations, failure to modify lifestyle), (2) false resistance (isolated office hypertension, pseudo-hypertension, improper BP measurement), (3) volume overload (due to excessive sodium intake, inadequate diuretic therapy and/or progressive chronic kidney disease) and

(4) sleep apnoea, drug-induced resistant hypertension or secondary hypertension (primary aldosteronism, renal artery stenosis, renal parenchymal disease, pheochromocytoma) [8].

Optimal treatment for resistant hypertension is based on identification and reversal of contributing factors. Accordingly, it is mandatory to make a thorough search for non-compliance to treatment and to evaluate the adequacy of the treatment regimen, drug interactions and associated conditions [8].

Select the correct sentence about management of true resistant hypertension:

1. Doxazosin is the most recommended therapeutical option.
2. Spironolactone has demonstrated to be a useful tool for BP control.
3. Bisoprolol is the preferred option.
4. None are correct.

Recommendations for the pharmacological treatment of resistant hypertension remain largely empiric, because of the lack of systematic assessments of three or four drug combinations. Specific pharmacological recommendations include the use of mineralocorticoid receptor antagonists. Spironolactone has demonstrated to be a useful tool for BP control in true resistant hypertension [9–11].

More recently, the ASPIRANT trial showed that the addition of spironolactone in patients with resistant hypertension using a mean of 4.5 antihypertensive drugs led to a significant decrease of systolic BP at both office and ABPM after 8 weeks of treatment [12]. Finally, the PATHWAY-2 trial shows that spironolactone is the most effective add-on drug for the treatment of resistant hypertension. In this double-blind, placebo-controlled, crossover trial, a total of 335 patients were included. Patients received 12 weeks of once daily treatment with each of spironolactone (25–50 mg), bisoprolol (5–10 mg), doxazosin modified release (4–8 mg) and placebo in a preassigned randomized order, in addition to their baseline antihypertensive drugs. The average reduction in home systolic blood pressure by spironolactone was superior to placebo, superior to the mean of the other two active treatments and superior when compared with the individual treatments [13].

This case is a good example of the usefulness of ABPM in the diagnosis and follow-up of patients with resistant hypertension (Table 6, Fig. 3). The effect on BP control of the addition of spironolactone in the antihypertensive treatment regimen is also shown.

Table 6: 24-h ambulatory blood pressure monitoring.

	24-h period	Daytime period	Night-time period
Systolic BP (mmHg)	122	126	114
Diastolic BP (mmHg)	61	63	56
HR (bpm)	67	69	64

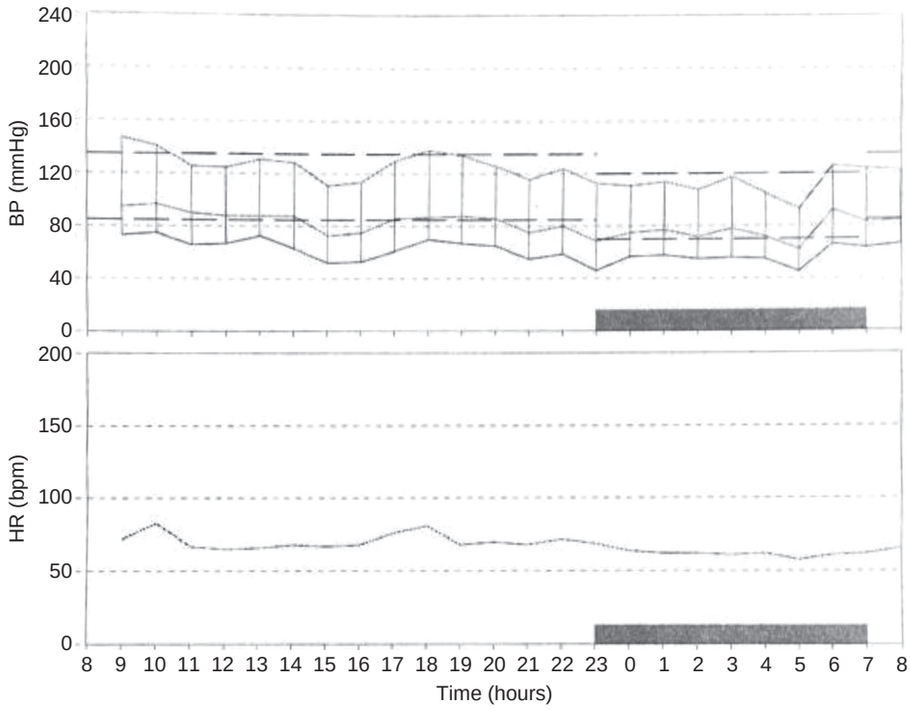

Fig. 3: 24-h ambulatory blood pressure monitoring. *BP* arterial blood pressure, *HR* heart rate, *bpm* beats per minute, *Time (Hours).*

Take-Home Messages

- The definition of resistant hypertension is based on office measurements. However, the use of ambulatory BP monitoring (ABPM) has allowed for the recognition of the white-coat effect as being responsible for a relatively large proportion of resistant hypertensive patients.
- ABPM is mandatory in resistant hypertensive patients to define true and white-coat resistant hypertension, as the latter group has a better prognosis than the former one.
- Spironolactone has demonstrated to be a useful tool for ameliorating BP control in true resistant hypertension.

References available on request
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Practice Guide

New American and European Hypertension Guidelines, Reconciling the Differences

Alejandro de la Sierra

In this review, the main differences between American and European recommendations are highlighted, along with the arguments exposed by both groups of experts and their possible impact affecting clinical practice in hypertension management.

Among all the risk factors involved in mortality and disability worldwide, hypertension is the one with the greatest impact, regarding its responsibility in the development of cardiovascular disease, which represents the main cause of death in all developed and many developing countries [1].

The scientific evidence supporting the benefits of pharmacological treatment of hypertension has been developing for more than 60 years. Many hypertensive patients have participated in clinical trials, most of them with a high quality of design, showing the benefits of such treatments in the prevention of both the onset and progression of cardiovascular disease, as well as in the prevention of mortality due to cardiovascular causes.

Both official agencies, depending on governmental organizations and scientific societies, have developed recommendations for the diagnosis, evaluation, and treatment of hypertension, resulting in a way of trying to assist physicians who usually take care of hypertensive patients, either in primary care or in referral units. Among the different clinical guidelines produced in several parts of the world (at local, national, or international levels), there is no doubt that the initiatives developed either in the United States or in Europe are those raising a greater expectation and a wider diffusion.

The history of clinical guidelines in the US begins with the Joint National Committee (JNC), an organization created in 1972 by the US government through the National Institutes of Health (NIH). The first report, known as JNC 1, was published in 1977, and since then the recommendations have been updated periodically until the year 2003, when the seventh report was released [2]. Although a group of panelists were working on

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a new report, in mid-2013, the NIH decided to transfer the responsibility of creating new guidelines to the corresponding scientific societies. In the case of hypertension, these were the American College of Cardiology (ACC) and the American Heart Association (AHA). The result was the publication, at the end of 2017, of an extensive clinical guide [3]. European guidelines were first released in 2003 by the creation of a joint committee from the European Society of Hypertension and the European Society of Cardiology. New updated versions were published in 2007, 2013, and more recently in 2018 [4].

These two recent published guidelines from US and Europe have created some controversy, as they contain different recommendations from the same clinical situations, after reviewing what apparently is the same evidence. It should be recognized that both guidelines contain more similarities than differences, and that some of these differences can be attributed to local epidemiological aspects or related to particularities about the type of health care provided on both sides of the Atlantic Ocean. However, differences that affect some fundamental aspects also appear. These include the classification of blood pressure and diagnosis of hypertension, the evaluation of cardiovascular risk, the usefulness of out-of-office blood pressure (BP) measurements, as well as therapeutic aspects such as treatment initiation, blood pressure goals, first-line drugs, or the use of combination therapies as the initial treatment. In this review, we will briefly discuss some of these differential aspects between the two guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Blood Pressure Categories and Definition of Hypertension

Previous versions of both American [2] and European [5] guidelines defined hypertension with BP values ≥ 140/90 mmHg. The JNC VII introduced the term pre-hypertension to define subjects with BP between 120–139 and/or 80–89 mmHg[2]. The term was based on the concept that the residual risk for developing hypertension among these subjects was very high, approaching 85–90% [6].

In its current version [4], the European guidelines maintain the same classification of BP categories contained in previous documents [5]. Hypertension continues to be defined as BP greater than 140/90 mmHg, with hypertensive patients divided into three categories (grades 1, 2, or 3), depending on the magnitude of BP elevation. Normotensives are also separated as optimal (< 120/80 mmHg), normal (120–129/80–85 mmHg), or high-normal (130–139/85–89 mmHg) categories. According to the European experts, the review of the literature does not justify any modification.

The American guidelines [3] substantially modified the threshold values for hypertension definition to ≥ 130/80 mmHg, which represents the most important change in the last 20 years. The categories within the hypertensive group are reduced to two (stage 1, defined as BP values between 130–139 and/or 80–89 mmHg and stage 2, ≥ 140/90 mmHg). Within the non-hypertensive categories, subjects with systolic BP (SBP) between 120 and 129, and diastolic BP (DBP) < 80 mmHg, are classified as having elevated BP. Normal BP is considered when values are < 120/80 mmHg (Table 1 contains both classifications).

The American experts justify this reduction in the threshold value for hypertension definition mainly on epidemiological reasons. First, hypertension continues to be the main risk factor producing death and disability. Secondly, several meta-analyses indicate that the risk of coronary events and stroke among subjects with SBP between 130 and 139 is 1.5–2 times higher compared to those who have SBP below 120. Moreover, although this increased risk attenuates with advanced age, it is still present in older adults [7]. According to this data, the American experts consider an urgent need to establish preventive measures in these groups, both to reduce the impact of cardiovascular disease and to avoid future progression towards more advanced stages of BP elevation. In contrast, the European point of view is more conservative. Data on antihypertensive treatment in individuals with BP levels below 140/90 mmHg has not shown a questionable benefit. In regard to this, the European experts do not consider defining an individual as belonging to an "abnormal" category (hypertension) if there is not a clear indication for treatment.

The epidemiological impact of this change in the definition of hypertension stated in the American guidelines has been quantified in the US, where the prevalence of hypertension would increase from 32 to 46% [8].

Table 1: Blood pressure classification in the ACC/AHA and ESC/ESH guidelines.

ACC/AHA				ESC/ESH			
Category	SBP		DBP	Category	SBP		DBP
Normal	< 120	and	< 80	Optimal	< 120	and	< 80
Elevated	120–129	and	< 80	Normal	120–129	and/or	80–84
Stage 1 hypertension	130–139	or	80–89	High-normal	130–139	and/or	85–89
Stage 2 hypertension	≥ 140	or	≥ 90	Grade 1 hypertension	140–159	and/or	90–99
				Grade 2 hypertension	160–179	and/or	100–109
				Grade 3 hypertension	≥ 180	and/or	≥ 110
				Isolated systolic hypertension	≥ 140	and	< 90

Evaluation of Cardiovascular Risk in the Hypertensive Patient

Several factors are recognized to influence the total cardiovascular risk in hypertensive patients. Some of them, such as smoking, diabetes, or dyslipidemia, are more prevalent in hypertensives in comparison to the general population. The presence of such comorbidities has a double implication. To start with, patient management includes treatment of all potentially modifiable risk factors, not only BP elevation. On the other hand, the initiation and intensity of the antihypertensive treatment may be influenced by other risk factors and thus by the total cardiovascular risk.

The sixth report of the JNC [9], which appeared at the end of 1997, mentioned for the first time a risk stratification for hypertension. Patients were classified into three categories: A, B and C, based on the estimation of their absolute risk. Each with different therapeutic recommendations, depending on which category an individual was placed in. This concept was also adopted by the European guidelines, first appearing in 2003 and maintained until the last version.

Both the ACC/AHA [3] and the ESC/ESH [4] guidelines consider the evaluation of total cardiovascular risk as an important tool affecting the onset and the intensity of antihypertensive treatment. The American guidelines proposes the use of a calculation derived from the equation of a *pooled cohort* [10], which comprised the Framingham cohort, the ARIC study (Atherosclerosis Risk in Communities), the Cardiovascular Health Study, and the CARDIA study (Coronary Artery Risk Development in Young Adults). This equation calculates the risk of a first fatal or non-fatal cardiovascular event at 10 years based on a series of parameters including BP, lipid levels, the presence of diabetes, age, sex, race, smoking, and treatments received for such conditions. Its main advantage is that the equation is also useful in African Americans and that it predicts the risk of any cardiovascular event, fatal or not.

The European guideline continues to use the equations provided by the SCORE (Systematic Coronary Risk Evaluation) study [11], which calculates the risk of a fatal cardiovascular event. Its main advantage is that it has been developed on the basis of the European population, hence equations are adapted to specific European countries (the risk is heterogeneous between northern and southern European countries). Its greatest disadvantage is that the risk is restricted to fatal episodes. Since it is well known that the fatality of many of these episodes is clearly influenced by the quality of care provided, especially in regard to early detection and management, including revascularization. In the European guidelines, this limitation is mentioned and an approximate calculation of the risk of non-fatal episodes is provided, multiplying the risk value obtained in SCORE by 3 in men, and by 4 in women [4].

In the risk classification proposed by the European guidelines, there are two particularities that were not considered in the American guidelines. First, it is stated that some patients should be considered directly as having very high risk due to the presence of documented cardiovascular disease (even if it is asymptomatic), or to the presence of diabetes, chronic kidney disease, or very high values of a single risk factor (grade 3 hypertension, family hypercholesterolemia, etc.). Secondly, it includes hypertension-mediated silent organ damage (left ventricular hypertrophy, microalbuminuria, arterial stiffness, etc.), as risk modifiers, although these elements are not included in the risk calculation of the SCORE system. Consistent in both guidelines is that the risk calculation will be decisive, together with the degree of elevation of BP in the initiation of antihypertensive treatment.

Out-of-office Blood Pressure Measurement

The use of home BP monitoring (HBPM) and ambulatory BP monitoring (ABPM) is for the first time recognized in the US guidelines as an important tool for both diagnosis and management of elevated BP. In individuals whose BP at the office is between 130 and 160 and/or between 80 and 100 mmHg, the use of HBPM or ABPM is recommended to confirm such BP elevation or to discard white-coat hypertension [3]. Moreover, in this latter group, the initiation of antihypertensive medication is not recommended. In parallel, in normotensive subjects with elevated BP (120–129/< 80 mmHg), HBPM or ABPM could be indicated to detect masked hypertension, also with a recommendation of antihypertensive treatment initiation in those without-of-office BP above 130/80 mmHg.

The same recommendation applies to hypertensive patients receiving antihypertensive treatment. In those not controlled with three different antihypertensive drugs, HBPM or ABPM should be performed, as one-third of them could have white-coat-resistant hypertension [12]. Furthermore, in treated and controlled patients, which remain at high cardiovascular risk or with persistent silent organ damage, the possibility of MUCH (masked uncontrolled hypertension) should be ruled out. Again, almost one-third of such patients may have this condition [13], which carries an important risk of increased mortality [14], thus requiring treatment intensification [3].

The European guidelines [4] continues to mention, as in previous editions, that office measurement remains the standard method for the diagnosis and monitoring of the hypertensive patient. With emphasis on the need for measuring BP after 1 min and 3 min of standing position in sensitive populations, such as the elderly, diabetics, or other clinical conditions that favor orthostatic hypotension. This condition is defined as a fall in BP > 20 mmHg for SBP or > 10 mmHg for DBP. With respect to HBPM and ABPM, the European guidelines already highlighted the potential value of such measurement methods in previous versions [5]. This is reinforced in the 2018 document [4] following the recommendations of a

previous position paper from the ESH [15]. The main recommendations are similar to those of the US guidelines, considering treatment initiation and treatment intensification in patients with masked hypertension and MUCH, respectively. With respect to white-coat hypertension, although recognizing that antihypertensive treatment is not routinely recommended, it could be appropriate for white-coat hypertensives with a high cardiovascular risk, due to the presence of other cardiovascular risk factors or hypertensive-mediated organ damage.

The main differences between the two guidelines refer to normal values of out-of-office BP. The European guidelines retain classical values of 135/85 mmHg for home and daytime BP, 130/80 mmHg for 24-h BP, and 120/70 mmHg for night-time BP, derived from previous observational studies. In contrast, the US guidelines were obliged to reduce the threshold for normality of out-of-office BP, in accordance to the new hypertension definition based on office BP values below 130/80 mmHg. However, these new values do not clearly derive from any previous evidence. Table 2 contains the thresholds of both guidelines.

Antihypertensive Treatment Initiation—Impact of Blood Pressure, Age, and Total Cardiovascular Risk

Both European and American guidelines base the decision concerning treatment initiation on the degree of BP elevation and the absolute cardiovascular risk. The review of evidence from randomized controlled trials shows that the relative risk reduction obtained with treatment is constant in all risk strata. Moreover, absolute risk reduction is proportional to the baseline risk [16].

Table 2: Thresholds for hypertension definition based on clinic, home, and ambulatory blood pressure.

	ACC/AHA	ESC/ESH
Clinic	130/80	140/90
Home	130/80	135/85
Daytime	130/80	135/85
24-h	125/75	130/80
Night-time	110/65	120/70

Both guidelines also agree when considering that pharmacological treatment must always be accompanied by personalized advice on lifestyle changes. This advice should be emphasized at not only the first visit but also each time the patient has contact with a health care provider. Weight loss in overweight individuals, reduction of salt intake, adoption of a healthy diet with increase in the consumption of fruits and vegetables and a parallel reduction in processed foods, promotion of physical exercise, and smoking cessation are all measures that should be implemented in the management of hypertensive patients.

Pharmacological treatment initiation is recommended by both European and American guidelines in hypertensive patients with BP ≥ 160/100 mmHg (HTA grades 2 and 3 of the European classification). According to the American guidelines, all patients with BP ≥ 140/90 mmHg (stage 2 hypertension) should receive antihypertensive treatment, regardless of age or baseline cardiovascular risk. The only exception is the presence of normal HBPM or ABPM (white-coat hypertension). In the European guidelines, treatment of patients with grade 1 hypertension (140–159/90–99 mmHg) is influenced by age and the total baseline cardiovascular risk. The recommendation in patients with high or very high cardiovascular risk (with cardiovascular disease, chronic kidney disease or target organ damage) is, like in the American guidelines, to initiate pharmacological treatment without delay. In patients with lower risk, antihypertensive treatment is considered reasonable if BP remains above 140/90 mmHg after 3–6 months of lifestyle changes.

In addition, in patients older than 65 years, pharmacological treatment is recommended only with systolic BP ≥ 160, although such a possibility is considered for those with systolic BP between 140 and 160 mmHg aged 65–80 years, provided that the patient is in acceptable general health conditions and the treatment is adequately tolerated.

Differences in the definition of hypertension also extrapolate to distinct recommendations in individuals with systolic BP < 140 mmHg. As already mentioned, the group with BP 130–139/80–89 mmHg is classified as having stage 1 hypertension in the US and pharmacological therapy is recommended for those with established cardiovascular disease or with an absolute cardiovascular risk of more than 10% at 10 years, by using the pooled cohort equation. The remaining individuals are advised to adopt lifestyle changes and to be periodically monitored for the progression to stage 2 hypertension.

These individuals, classified as having high-normal BP in the European guidelines (categories are not exactly the same as the range of DBP in Europe is 85–89 mmHg), are equally advised to adopt healthy lifestyles and, in general, antihypertensive treatment is not recommended, with the exception of those with documented coronary heart disease. Table 3 summarizes the recommendations of both guidelines with respect to treatment initiation.

It is relatively surprising that both guidelines refer to the same randomized controlled trials to produce different recommendations. There are two aspects which deserve attention. On the one hand, the greater aggressiveness of the American guidelines, aligned with changes in hypertension definition, is intended to reduce the burden of hypertensive disease and the consequences of cardiovascular disease, thus prevailing the epidemiological perspective. In the current context of a generally safe, well-tolerated, and affordable antihypertensive medication, it is reasonable to expect more advantages than disadvantages in taking such a decision. There is no doubt that a general reduction of BP in the general

Table 3: Antihypertensive treatment initiation.

	ACC/AHA	ESC/ESH
BP ≥ 160 and/or ≥ 100	Lifestyle changes and antihypertensive treatment	Lifestyle changes and antihypertensive treatment
BP 140–159 and/or 90–99 with high or very high risk	Lifestyle changes and antihypertensive treatment	Lifestyle changes and antihypertensive treatment
BP 140–159 and/or 90–99 with low risk	Lifestyle changes and antihypertensive treatment	Lifestyle changes Consider antihypertensive treatment if BP remains elevated after 3–6 months
BP 130–139 and/or 80–89[a]	Lifestyle changes and antihypertensive treatment if CVD or elevated CV risk (> 10% in 10 years)	Lifestyle changes Consider antihypertensive treatment in very high risk patients due to coronary heart disease

CVD cardiovascular disease
[a]In the European guidelines, this recommendation applies to patients with SBP 130–139 and/or DBP 85–89

population, including hypertensive patients, will translate into a reduction of cardiovascular deaths and disability.

The European perspective is more focused on the individual patient than in the global population. The most conservative attitude tries to avoid treatment in individuals where the benefit has not been unequivocally proven. In fact, the most important recent evidence in hypertension, the SPRINT (Systolic Blood Pressure Intervention Trial) study [17], does not have a uniform impact in both guidelines. The SPRINT trial, promoted by the NIH and developed entirely in the US, included patients older than 50 years with systolic BP ≥ 130 mmHg (more than half had values between 130 and 140 mmHg). Results demonstrated that the group randomized to a systolic BP < 120 mmHg significantly reduced the occurrence of both total mortality and cardiovascular events. Obviously, the trial strongly influenced the new American guidelines, while from the European perspective it has received more criticisms. Among them, it has been argued that most patients included were previously under antihypertensive treatment and so this systolic BP between 130 and 140 mmHg cannot be considered as their baseline BP. According to this argument, the results of the trial could not be extended to the untreated population at the time of treatment initiation.

Therapeutic Objectives of Antihypertensive Treatment

For the first time, the ACC/AHA guidelines [3] recommended values below 130/80 mmHg as a therapeutic target for all hypertensive patients. This recommendation is classified as class I and therefore mandatory, for patients with a high cardiovascular risk (established cardiovascular disease or a predicted risk of cardiovascular events higher than 10% in 10 years) and reasonable (class IIb recommendation) for those with lower risk.

In adopting this strategy, more aggressive than that of previous guidelines, the results of the aforementioned SPRINT trial [17], demonstrating a clear benefit in patients randomized to a lower BP target, have been of great influence. Differences in BP between the therapeutic target of the intensive treatment group of the SPRINT trial (< 120 mmHg) and that proposed by the guidelines (< 130 mmHg) is justified by the unattended BP measurement method used in SPRINT. It has been suggested that this measurement method results in lower BP values in comparison to standard attended measurements [18]. From a practical point of view, values of 120 mmHg obtained with the unattended measurement would be close to 130 in clinical practice.

It could be criticized that the generalization of all the hypertensive population of such BP treatment target does not correspond with the SPRINT data, where only patients older than 50 years with additional cardiovascular risk factors were included. Besides, both diabetics and patients with a previous stroke were excluded from the SPRINT. Two previous studies [19, 20] with the same treatment design (comparison of an intensive versus a conventional BP target) in diabetics and patients with a previous lacunar stroke did not result in a clear benefit, with the exception of some secondary endpoints (prevention of stroke in diabetics and prevention of hemorrhagic cerebrovascular events in patients with a previous stroke). In this context, and also aligned with the new hypertension definition, the authors of the American guidelines considered that this evidence, along with the results of several recent meta-analyses, was important enough to establish a goal below 130/80 mmHg for the majority of the hypertensive population.

The European guidelines are less strict regarding therapeutic goals but also more detailed, with different targets depending highly on age. In fact, the general recommendation is structured into two sentences. It is stated that the first therapeutic objective should be to reduce BP to values below 140/90 mmHg, but an immediately followed second objective of values below 130/80 mmHg is mentioned, providing that antihypertensive treatment is well tolerated. The European guidelines also emphasize that a reduction of SBP below 120 mmHg should be avoided and in patients older than 65, a reasonable target is to maintain SBP between 130 and 140 mmHg.

The main conclusion is that both recommendations, ACC/AHA [3] and ESC/ESH [4], are similar, and are only different in how they are formulated. The American perspective is more pragmatic, containing clear and concise recommendations for most hypertensive patients. The European guidelines are more cautious. They try to achieve the

same objectives, but avoid a possible negative impact of excessive BP reduction, especially in older and frail patients. The consequences of either one of the strategies in hypertension control and disease-related complications should be analyzed in the future.

First-line Antihypertensive Drug Classes and Agents

The selection of first-line therapeutic agents has usually been divergent between American and European guidelines. While the European guidelines included several antihypertensive drug classes (diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-receptor blockers) as suitable for treatment initiation [5], previous reports from the JNC [2] advocated for a preferential use of diuretics, alone or in combination. In their current version, both guidelines converged to this wide approach considering several drug classes as first-line agents. The only discrepancy refers to beta-blockers, which are still considered first-line agents in the European guidelines, but restricted to specific indications, such as angina, post myocardial infarction, congestive heart failure, supraventricular arrhythmias requiring heart rate control, or young women who are planning pregnancy.

Another additional difference relates to the selection of the diuretic agent. While both guidelines advocate for the preferential use of thiazide and thiazide-like diuretics, with respect to loop diuretics, only the ACC/AHA guidelines recommend a preferential use of clorthalidone versus hydrochlorothiazide. Chlorthalidone has been the thiazide-like diuretic used in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study [21], resulting in similar benefits when compared to the ACE inhibitor lisinopril, or the calcium channel blocker amlodipine. Having said that, a recent meta-analysis comparing both drugs did not result in any significant advantage of chlorthalidone [22].

Monotherapy or Combination Therapy for Treatment Initiation

The classical approach to antihypertensive treatment recommended a single agent for treatment initiation, and the addition of other agents if BP control was not achieved. This stepped-care strategy was questioned in the previous JNC VII [2], where two-drug combination was proposed for treatment initiation in selected patients. Accordingly, previous versions of the European guidelines [5] also introduced the possibility of initial combination therapy in patients with hypertension grades 2 or 3, or with high cardiovascular risk. In the current version of both American and European guidelines, combination therapy has become the preferred option for treatment initiation for the majority of patients. In the ACC/AHA guidelines [3], this is the recommended option for patients with stage 2 hypertension (values above 140/90 mmHg). In the ESC/ESH guidelines [4], this is the preferred option for most patients, excluding frail, older patients, or those with grade 1 hypertension and low cardiovascular risk.

With regard to the components of such combinations, both guidelines recommend the use of ACE inhibitors or angiotensin-receptor blockers (but never combining both classes), with either diuretics or calcium channel blockers. The European guidelines add some particularities, by considering that these combinations should be, if possible, administered in one single pill, given its beneficial impact of treatment adherence [23]. In addition, the use of a triple therapy on patients not controlled with two-drug combinations is also advocated to be administered in a single pill containing an ACE inhibitor or an angiotensin-receptor blocker; a diuretic and a calcium channel blocker.

Conclusions

In summary, the main differences between ACC/AHA and ESC/ESH guidelines derive from the new definition of hypertension stated in the US with values ≥ 130/80 mmHg, while European guidelines retain the classical threshold of 140/90 mmHg. This difference in definition carries variant approaches with respect to treatment initiation and therapeutic objectives. US guidelines are clearer, pragmatic, and the main objective is to reduce the burden of hypertension-related disease by trying to detect risk individuals at an earlier stage, all while being more interventionist in reducing the risk of such individuals and accordingly, the cardiovascular health of the general population. In contrast, the European perspective is more conservative, less focused on epidemiological issues, but more addressed to the individual patient. In turn, trying to personalize the treatment, as to avoid such treatment for those who will not obtain a clear benefit, or for those who an excessive BP reduction may be harmful to. Two different strategies are confronted. The coming years will help elucidate which one better fits to the reduction of cardiovascular morbidity and mortality.

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Suboptimal Performance of Cardiovascular Magnetic Resonance Imaging for the Assessment of Myocardial Viability at the Early Phase of an Acute Coronary Syndrome: Usefulness of SPECT Myocardial Perfusion Imaging

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> LGE-imaging for the quantification of irreversible myocardial injury has been extensively validated in coronary heart disease. However, dynamic changes of LGE have been described following an acute coronary syndrome, which may impair the analysis of myocardial viability.

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Case

A 55-year-old man was referred to our intensive cardiology care unit for acute dyspnea and chest pain. The EKG showed atrial fibrillation, a QS pattern in the inferior leads, and ST segment depression in the anterior leads (V1 to V5) in the setting of an elevated cardiac-specific troponin. Trans-thoracic echocardiography (TTE) showed left ventricular ejection fraction (LVEF) of 25%. Coronary angiography revealed severe multi-vessel disease (Fig. 1). Cardiovascular magnetic resonance imaging (CMR) was performed at day 5 with serum creatinine at 148 µmol/L. Late gadolinium enhancement (LGE) image indicated several segments with more than 50% scarring (Fig. 2). Rest-redistribution-thallium-201-SPECT was performed (Fig. 3) and indicated a less significant impairment of segmental myocardial viability (Fig. 4). Successful revascularization was performed using coronary artery bypass grafting (CABG). TTE was performed 10 days after CABG and indicated a LVEF at 50%.

Discussion

LGE-imaging for the quantification of irreversible myocardial injury has been extensively validated in coronary heart disease. However, dynamic changes of LGE have been described following an acute coronary syndrome (ACS) [1], which may impair the analysis of myocardial viability [1]. Several reasons can account for infarct size overestimation such as technical parameters or altered gadolinium-based contrast agents (GBCA) washout rate due to altered glomerular filtration rate [2]. An alternative mechanism leading to LGE accumulation in the viable myocardium is an increase in GBCA distribution volume caused by interstitial volume increase as a

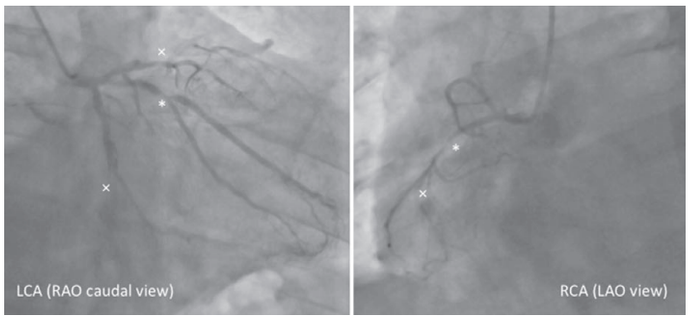

Fig. 1: Coronary angiography shows severe multiple vessel disease with Chronic Total Occlusion of right, circumflex, left anterior descending coronary artery (*white* X), and 70% narrowing of ramus intermedius artery (*white cross*). *LCA*, left coronary artery; *LAO*, left anterior oblique; *RAO*, right anterior oblique; *RCA*, right coronary artery.

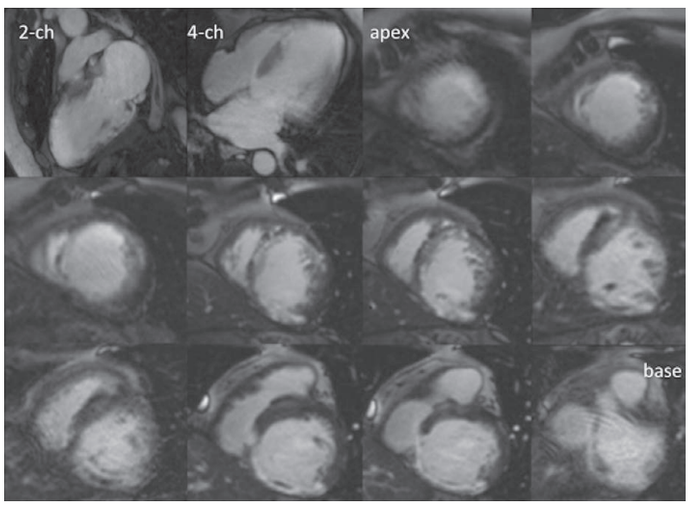

Fig. 2: Assessment of myocardial viability by short-axis image Inversion-recovery prepared T1-weighted 2D gradient-echo sequence 10 minutes after intravenous administration of a gadolinium chelate (Dotarem; Guerbet, Roissy CdG Cedex, Paris, France).

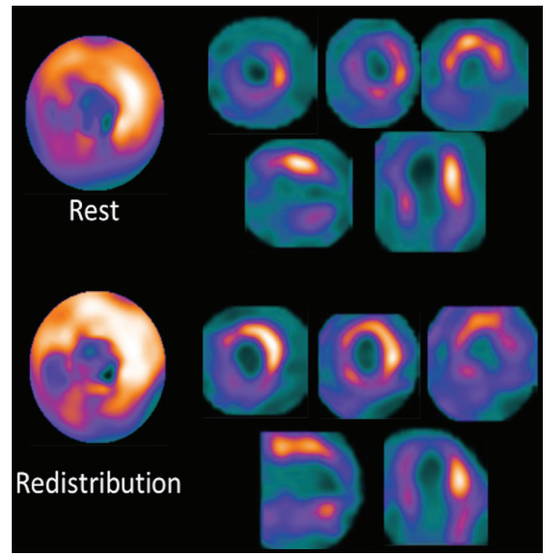

Fig. 3: Assessment of myocardial viability by rest-redistribution thallium-201 SPECT. The figure shows 4-hour-redistribution thallium-201 imaging.

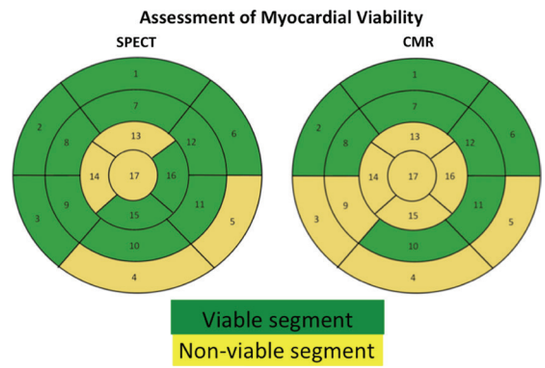

Fig. 4: Comparison of myocardial viability analysis by segment between SPECT and CMR.

consequence of myocardial edema. In this setting, LGE reduction could be partly explained by the resorption of edema in the first week following an ACS [3]. Because CMR is the optimal technique to assess LV remodeling while SPECT has outstanding sensitivity for the detection of myocardial viability, multimodality imaging might be considered at the early phase of an ACS in the setting of severe CAD with low LVEF.

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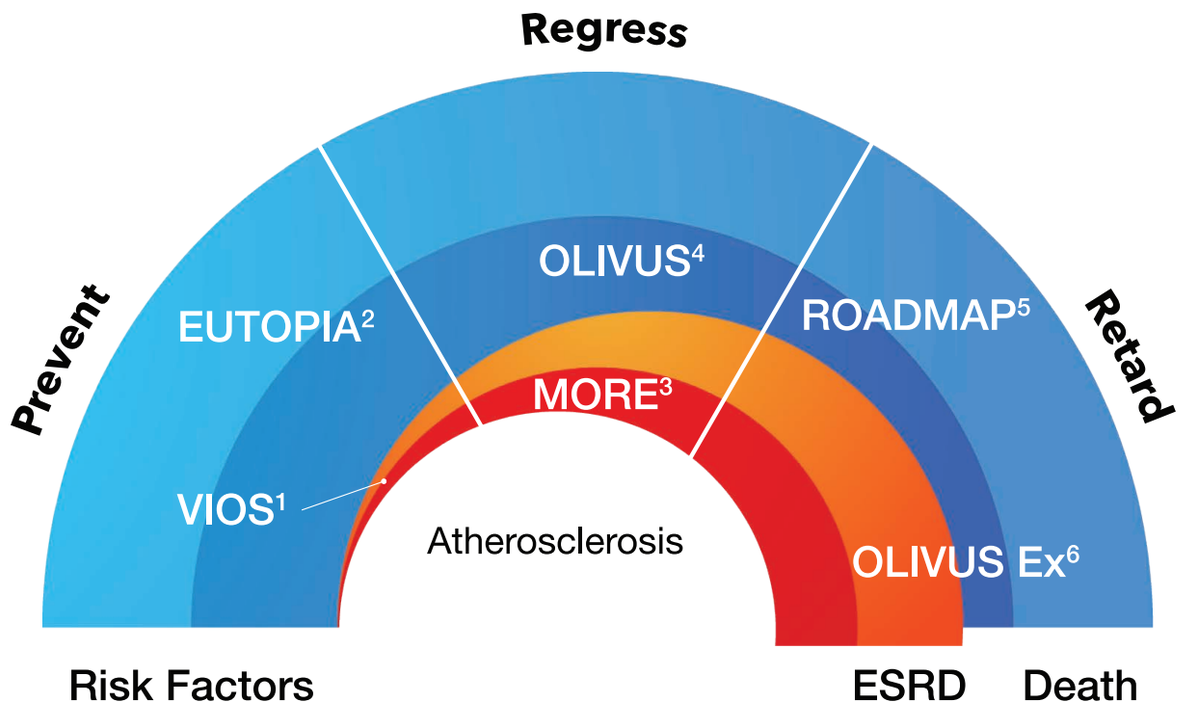

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