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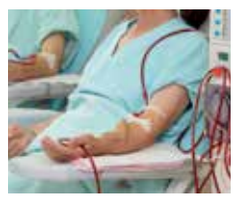

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Habitual Coffee Intake Reduces All-Cause Mortality by Decreasing Heart Rate

It is well known that subjects with metabolic syndrome show an elevated resting heart rate. The researchers previously reported that elevated heart rate was significantly related to all-cause mortality, and that coffee consumption was inversely associated with metabolic syndrome. The authors hypothesized that higher coffee consumption may decrease all-cause mortality by reducing resting heart rate. The team performed a longitudinal epidemiological study in Tanushimaru (a cohort of the Seven Countries Study). A total of 1920 residents aged over 40 years received health checkups in 1999. The authors measured components of metabolic syndrome, and eating and drinking patterns were evaluated by a food frequency questionnaire. We followed up the participants annually for 15 years. During the follow-up period, 343 of the participants died. Of these, 102 subjects died of cancer, 48 of

cerebro-cardiovascular diseases, and 44 of infectious diseases. Multivariate analyses revealed that higher coffee consumption was inversely associated with resting heart rate. Kaplan–Meier curves found lower mortality rates in the higher coffee consumption groups. In the lower coffee consumption groups, elevated hazard ratios of all-cause death were observed in the increased heart rate quintiles, whereas heart rate was not associated with all-cause death in the higher coffee consumption groups. These significant associations remained after further adjustment for confounders. This prospective study suggests that higher coffee consumption may have a protective effect against all-cause death due to reducing resting heart rate.

Source: Nohara-Shitama, Y., Adachi, H., Enomoto, M. et al. Heart Vessels (2019). https://doi.org/10.1007/s00380-019-01422-0. © Springer Japan KK, part of Springer Nature 2019.

Myocarditis After ICI Therapy More Common than First Thought

Myocarditis is an uncommon, but potentially fatal side effect of immune checkpoint inhibitors (ICI), according to a retrospective review.[1]

Researchers from the U.S. and Canada created a multicentre registry to provide data on 35 patients who developed myocarditis after receiving ICI treatment between November 2013 and July 2017. These patients were compared to a random sample of 105 ICI-treated patients who did not develop myocarditis.

The prevalence of myocarditis was determined to be 1.14% (11 patients), which developed after a median duration of 34 days after starting ICI therapy.* Steroids were administered as the initial treatment in almost 90% of these myocarditis cases.

Compared with controls, patients who developed myocarditis were more likely to have received combination ICI (1.9% vs 34.3%), had a higher prevalence of diabetes mellitus (13% vs 34%).

The main outcome of interest – major adverse cardiac events (MACE) – was a composite of cardiovascular death, cardiac arrest, cardiogenic shock, and haemodynamically significant complete

heart block. Over 102 days of median follow-up, 16 patients (46%) developed MACE, of whom 6 patients had a normal LVEF.** The researchers noted that "*the implication of this finding is that clinicians should not rely on ejection fraction as a discriminator of severity in ICI-associated myocarditis*".

However, "*by contrast, we did find that the degree of troponin elevation was useful in determining adverse cardiac outcomes*", added the researchers. Specifically, a final/discharge troponin T value of ≥1.5 ng/mL was associated with a 4-fold increased risk of MACE.

In an accompanying editorial, Dr Carlo Tocchetti (Federico II University, Naples, Italy) and his colleagues stated that ICI therapies – such as monoclonal antibodies that target CTLA-4, PD-1 and PD-L1,† "*have revolutionized antineoplastic protocols*".[2]

They added that the results from the above-mentioned are "*particularly important, because most of the new trials using ICIs in adjuvant care are testing combination therapies*", and that "*a global cardio-immuno-oncologic assessment seems important to detect potential toxicities of newer immunotherapies*".

* Based on data from 964 patients at Massachusetts General Hospital who received ICI therapy during the stated time period.

** LVEF = left ventricular ejection fraction

† CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1

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Predictors of Heart Disease Knowledge Among Older and Younger Asian Indian Adults

Ritin S. Fernandez[1,2], Bronwyn Everett[3,4], Subbaram Sundar[5]

Coronary heart disease (CHD) has been estimated to be the leading cause of mortality in developing countries in 2010, particularly among Asian Indians. When compared to other populations globally, Asian Indians less than 40 years of age are at an increased risk of myocardial infarction. The objective of this study was to identify the predictors of knowledge of heart disease among younger and older Asian Indians adults.

Ritin S. Fernandez
ritin@uow.edu.au

[1] School of Nursing, University of Wollongong, Northfields Avenue, Wollongong, NSW 2520, Australia

[2] Centre for Research in Nursing and Health, St George Hospital, Kogarah, NSW, Australia

[3] Centre for Applied Nursing Research, School of Nursing and Midwifery, University of Western Sydney, Parramatta, NSW, Australia

[4] Ingham Institute, South Western Sydney Local Health District, Sydney, NSW, Australia

[5] Toongabbie, NSW, Australia

Coronary heart disease (CHD) has been estimated to be the leading cause of mortality in developing countries in 2010, particularly among Asian Indians [1]. Data obtained from the global burden of disease indicates that the highest incidence of mortality due to CHD is among South Asians and has increased by 87.8% from 704,833 deaths in 1990 to 1,323,551 in 2010 [2]. High mortality rates due to CHD has extensively been reported among Asian Indians in England [3, 4] the United States (U.S.) [5], Canada [6, 7], Singapore [8, 9], Mauritius [10, 11], South Africa [12], and Trinidad [13].

When compared to other populations globally, coronary heart disease occurs 5–10 years earlier among Asian Indians [14]. Evidence from the literature indicates that the median age for the first presentation of acute MI is 53 years for Indians and 63 years for European and Chinese populations [15]. Asian Indians less than 40 years of age are at an increased risk of myocardial infarction regardless of whether they live in India or have migrated to another country [15]. In addition to the development of premature CHD, the presence of risk factors namely hypertension and diabetes have worse outcomes in Asian Indians with CHD

compared to the global population [15]. This immense burden of CHD has major implications on the productive workforce.

Given the high incidence of CHD among Asian Indians and particularly at a younger age it is important that they have the necessary knowledge about the facts relating to heart disease. Knowledge can serve as a powerful and effective tool to develop and enhance the health literacy levels among people. While there is extant literature on the knowledge of people relating to CHD in other populations [16–20], there is limited literature among Asian Indians. In a survey undertaken in Canada less than half the women identified smoking and less than a quarter identified hypertension or high cholesterol as a risk factor for heart disease [17]. In contrast, results from a study undertaken in the U.S. found 91.9% of the participants knew that being overweight was a risk factor for CHD. The participants also identified having a family history of heart disease (88%), and having high blood pressure (84%) were causes of heart disease [20].

In a large cross-sectional study undertaken in South Asians to assess their knowledge, only 20% of the participants were fully aware of the four key modifiable risk factors of heart disease namely fatty food consumption, smoking, obesity and exercise [21]. Similar findings were reported in another study where the majority of respondents could identify only up to two risk factors for CHD [22]. In a more recent study assessing knowledge about CHD, high blood pressure and cholesterol levels were perceived by the community as important risk factors for CHD however, diabetes was not considered an important risk factor [23]. Another study [24] reported that although 81% of respondents had one or more CHD risk factors, the majority indicated that they knew little or nothing about CHD. The results from published studies indicate that overall knowledge about heart disease among Asian Indians remains poor. What is missing in the literature is whether this knowledge gap is different between the older and younger Asian Indians particularly given that CHD affects Asian Indians at a younger age. For the purpose of this study young adults were defined as those 40 years of age and under

The aim of this study was to identify the predictors of knowledge of heart disease among younger and older Asian Indian adults.

Methods

Participants

This prospective cross sectional study was undertaken using convenience sampling. People of Asian Indian descent, aged 18 years and over and able to read English, who attended the health promotion stall at the Australia India Friendship Fair in Sydney in 2012 were invited to participate in the study. Participants were informed of the study by an assistant and were provided with an information sheet. All participants were assured that all information provided would be kept confidential. Completion of the questionnaire was considered to be consent. Numerical unique identifiers and password-protected files were used to maintain participant privacy and confidentiality. Approval to undertake the project was obtained from the University of Western Sydney Human Ethics Review Committee; Parramatta Australia.

The results from published studies indicate that overall knowledge about heart disease among Asian Indians remains poor.

Data Collection

Data were collected using an English language self-administered questionnaire comprising of demographic details, cardiovascular risk factors and knowledge relating to heart disease. Demographic details relating to gender, age and educational attainment was collected. Blood pressure was measured using the automatic device Dinamap™ 1846 SX monitoring system (Critikon, Norderstedt, Germany). Random blood glucose level was measured using a portable sensor (Accu-Chek Advantage™; Roche Diagnostics, Indianapolis, IN) and whole-blood obtained from a capillary (finger stick) sample from each participant. Waist circumference and weight were measured according to recommended procedures [25]. All measurements were undertaken by trained research assistants.

Measures

Knowledge of heart disease was measured using the 25-item Heart Disease Facts Questionnaire (HDFQ). Participants had to respond to each statement with a true, false, or I don't know answer. The HDFQ has been previously used in ethnic populations [26]. The HDFQ has demonstrated high internal consistency (Kuder–Richardson r = 0.77) and test–retest reliability (r = 0.89) [26]. The Cronbach's alpha for the HDFQ in this study was 0.916.

Data Analyses

Data were analysed using SPSS version 21.1. Given that Asian Indians less than 40 years of age are at an increased risk of myocardial infarction regardless of whether they live in India or have migrated to another country the data was analysed for those 40 years of age and below, and those over 40 years. The total score was calculated as the sum of correct responses. Categorical data have been presented as percentages and continuous data are presented as means and standard deviation (SD). Univariate logistic regression was undertaken to determine the relationship of each independent variable with the overall knowledge of CHD. All variables with $p \leq 0.25$ in the univariate analysis were included in a standard multiple logistic regression analysis to determine those factors independently associated with overall CHD knowledge. Separate

regression analyses were conducted for younger and older adults. The following predictor variables were included in the model (1) gender (2) level of education (3) duration of residence in Australia (4) weight (5) BMI (6) history of high blood pressure, (7) history of high blood sugar (8) smoking status and (9) history of high cholesterol. Results of only the multiple regression analysis are reported. Statistical significance was set at $p < 0.05$.

Results

Demographic Characteristics of Participants

A total of 180 people visited the health promotion stall, however only 144 completed the survey. Data were analysed from all 144 participants all of whom had migrated to Australia. The mean age of the younger participants was 32.2 years (±4.9) and that of the older adults was 55.7 years (±10.2). There were significantly greater number of males in the older group and significantly greater number of females in the younger group. Approximately 80% of the participants in both age groups had a bachelor's degree or higher. Seventy-two percent of the younger adults and half (50%) the older adults were in paid employment (Table 1).

Table 1: Participant demographics.

	18–40 years (n = 73)	41–81 years (n = 71)	p value
	n (%)	n (%)	
Gender			
Male	33 (45.2)	44 (62)	0.04
Female	40 (54.8)	27 (38)	0.04
Educational attainment[a]			
High school certificate	11 (15.5)	15 (22.7)	0.35
Bachelors degree	36 (50.7)	32 (48.5)	0.61
Masters degree	24 (33.8)	17 (25.8)	0.24
Doctorate	0	2	0.29
Currently in paid employment	53	35	0.005
Duration of residence in Australia (years)	7.3 (8.0)	15.1 (16.1)	0.000

[a]Missing data

Table 2: Personal risk factors for heart disease.

Risk factor	18–40 years (n = 67)	41–81 years (n = 63)	p value
	Mean (SD)	Mean (SD)	
Systolic blood pressure	118.7 (12.5)	134.3 (918.2)	0.000
Diastolic blood pressure	76.2 (9.6)	83.8 (13.4)	0.000
Blood sugar level	5.7 (1.1)	6.5 (2.9)	0.034
Waist (cm)	90.2 (13.3)	96.1 (17.1)	0.034
Weight (kg)	70.8 (14.8)	74.7 (19.3)	0.207
	Frequency	Frequency	
History of high blood pressure	19	34	0.007
History of high blood sugar	18	30	0.03
History of high cholesterol	26	31	0.32
Smokers	19	22	0.51

Risk Factors for Heart Disease

Systolic and diastolic blood pressure, blood glucose levels and waist circumference were significantly higher in the older adults (Table 2). Similarly, having a history of high blood pressure or diabetes was significantly greater among the older adults. There were no differences in weight, history of high cholesterol or smoking status between the two groups (Table 2).

Knowledge Relating to Heart Disease

All six modifiable risk factors for heart disease namely smoking, high blood pressure, diabetes, high cholesterol, physical inactivity and overweight were identified by 45.2% of those aged below 40 and 53.5% of those aged above 40 years of age respectively. Among the younger cohort only 70% identified smoking, 71% identified high blood pressure, 76% high cholesterol, overweight and physical inactivity and 64% diabetes as a risk factor for heart disease. In contrast, among the older cohort 80% identified smoking and high blood pressure, 83% high cholesterol, 83% being overweight, 77% physical inactivity and 78% diabetes as a risk factor for heart disease (Table 3). Overall, older adults had higher total HDFQ knowledge scores (mean 16.4 ± 7.1) compared to their younger counterparts (mean 14.6 ± 7.0), however, these results were not statistically significant ($p = 0.13$).

Predictors of CHD Knowledge Among the Younger Cohort

The following variables with $p \leq 0.25$ in the univariate analysis were included in the standard multiple logistic regression analysis for the younger cohort: history of diabetes, history of high cholesterol, smoking status, history of blood pressure, highest educational level, waist circumference (cm), weight (kg) and BMI. The multiple regression model to predict knowledge of CHD among the younger cohort was significant and accounted for 31.3% of the variance ($R^2 = 0.423$, $R^2_{Adj} = 0.313$, $F(8,42) = 3.81$, $p = 0.002$. The unique contribution of each variable (sr^2) in the final model is presented in Table 4. Only one variable smoking status was significant and was

Table 3: Knowledge relating to heart disease.			
	18–40 years (n = 67)	**41–81 years (n = 63)**	**Significance level (p)**
Number (%) of correct responses			
A person always knows when they have heart disease	43 (64.2%)	36 (57.1%)	0.41
If you have a family history of heart disease, you are at risk for developing heart disease	41 (62.1%)	43 (70.5%)	0.40
The older a person is, the greater their risk of having heart disease	32 (50.0%)	36 (58.1%)	0.29
Smoking is a risk factor for heart disease	45 (70.3%)	47 (79.7%)	0.35
A person who stops smoking will lower their risk of developing heart disease	40 (62.5%)	44 (71.0%)	0.23
High blood pressure is a risk factor for heart disease	47 (71.2%)	50 (80.6%)	0.23
Keeping blood pressure under control will reduce a person's risk for developing heart disease	44 (67.7%)	50 (80.6%)	0.08
High cholesterol is a risk factor for developing heart disease	50 (76.9%)	52 (83.9%)	0.27
Eating fatty foods does not affect blood cholesterol levels	52 (81.3%)	47 (78.3%)	0.69
If your 'good' cholesterol (HDL) is high you are at risk for heart disease	37 (57.8%)	39 (62.9%)	0.44
If your 'bad' cholesterol (LDL) is high you are at risk for heart disease	40 (62.5%)	42 (70.0%)	0.41
Being overweight increases a person's risk for heart disease	50 (76.9%)	50 (83.3%)	0.32
Regular physical activity will lower a person's chance of getting heart disease	50 (76.9%)	47 (77.0%)	0.52
Only exercising at a gym or in an exercise class will lower a person's chance of developing heart disease	49 (75.4%)	42 (71.2%)	0.42
Walking and gardening are considered exercise that will help lower a person's chance of developing heart disease	45 (69.2%)	48 (80.0%)	0.26
Diabetes is a risk factor for developing heart disease	40 (64.5%)	46 (78.0%)	0.11
High blood sugar puts a strain on the heart	43 (68.3%)	46 (76.7%)	0.28
If your blood sugar is high over several months it can cause your cholesterol level to go up and increase your risk of heart disease	37 (58.7%)	39 (67.2%)	0.44
A person who has diabetes can reduce their risk of developing heart disease if they keep their blood sugar levels under control	33 (52.4%)	42 (71.2%)	0.05
People with diabetes rarely have high cholesterol	30 (47.6%)	33 (55.9%)	0.01
If a person has diabetes, keeping their cholesterol under control will help to lower their chance of developing heart disease	38 (61.3%)	46 (78.0%)	0.05
People with diabetes tend to have low HDL (good) cholesterol	20 (31.7%)	21 (36.8%)	0.67
A person who has diabetes can reduce their risk of developing heart disease if they keep their blood pressure under control	28 (44.4%)	37 (64.9%)	0.05
A person who has diabetes can reduce their risk of developing heart disease if they keep their weight under control	37 (58.7%)	42 (73.7%)	0.69
Men with diabetes have a higher risk of heart disease than women with diabetes	11 (17.7%)	12 (21.1%)	0.69

independently related to knowledge related to CHD (b = −10.6, $p = 0.001$, $sr^2 = 0.16$).

Predictors of CHD Knowledge Among the Older Cohort

The following variables with $p \leq 0.25$ in the univariate analysis were included in the standard multiple logistic regression analysis for the older cohort: history of diabetes, history of high cholesterol, smoking status, history of blood pressure, highest educational level and duration of residence in Australia. The multiple regression model to predict knowledge of CHD among the older cohort was significant and accounted for 37.4% of the variance ($R^2 = 0.412$, $R^2_{Adj} = 0.374$, $F(6,93) = 10.86$, $p = 0.000$. The unique contribution of each variable (sr^2) in the final model is presented in Table 4. Only two variables, smoking status and duration of residence, were significant and were independently related to knowledge related to CHD (b = −7.4, $p = 0.000$, $sr^2 = 0.24$; b = 0.13, $p = 0.001$, $sr^2 = 0.069$ respectively).

Discussion

Heart disease affects young Indians therefore knowledge about heart disease among this cohort is vital. Although numerous studies have reported on knowledge about heart disease among Asian Indians, there is limited literature investigating the knowledge levels of younger and older Asian Indians

Table 4 : Multiple regression model to identify predictors of knowledge of CHD.

Predictors	18–40 years						41–81 years					
	B	SE	Beta	t	Sig.	sr^2	B	SE	Beta	t	Sig.	sr^2
History of diabetes	−4.492	3.250	−0.248	−1.382	0.174	0.026	−1.867	1.304	−0.140	−1.431	0.156	0.013
History of high cholesterol	−0.761	2.278	−0.046	−0.334	0.740	0.002	−1.832	1.455	−0.138	−1.258	0.211	0.010
Smoking status	−10.660	3.092	−0.481	−3.447	0.001	0.163	−7.744	1.404	−0.492	−5.517	0.000	0.192
History of blood pressure	1.832	3.605	0.090	0.508	0.614	0.004	2.431	1.339	0.185	1.816	0.073	0.021
Highest educational level	1.043	1.108	0.113	0.941	0.352	0.012	0.499	0.733	0.060	0.680	0.498	0.003
Waist circumference (cm)	0.047	0.123	0.079	0.382		0.002						
Weight (kg)	0.103	0.097	0.233	1.058		0.015						
BMI	−0.067	0.166	−0.063	−0.406		0.002						
Duration of residence in Australia							0.135	0.041	0.278	3.319	0.001	0.070

particularly when Asian Indians less than 40 years of age are at an increased risk of myocardial infarction regardless of whether they live in India or have migrated to another country.

Overall, there was no statistically significant difference in knowledge amongst older and younger participants. However, older adults had significantly higher knowledge about diabetes and blood pressure compared to the younger adults. Various reasons could be postulated for these results. Firstly, the incidence of diabetes and blood pressure among the older adults was higher therefore their health literacy levels also could be high as they could be receiving explanation regarding their illness from their health professionals. Only 45.2% of those aged below 40 and 53.5% of those aged above 40 years of age identified the six cardiac risk factors, namely smoking, high blood pressure, diabetes, high cholesterol, physical inactivity and overweight.

When compared to other studies reported in the literature [19, 27, 28], the knowledge levels relating to risk factors for CHD in this study are much higher. For example in a study conducted on 777 participants in Nepal only 29.7% identified hypertension and 11% identified overweight and physical activity as causes, whereas only 2.2% identified high blood sugar as causative factors for CHD [27]. Similarly, limited public knowledge and awareness of CHD have been reported in Jordan [19] and Ireland [28]. Despite extensive advertising and educational campaigns, mainly in English, to stop the use of cigarettes there were still a third of the participants who continued to smoke perhaps suggesting that current educational and public awareness campaigns relating to heart disease are not taken seriously by these participants. While knowledge can enhance the health literacy levels among people, it is well established that "knowledge" is not really enough to make people change health behaviors [27–29].

The result relating to smoking status as a predictor for CHD knowledge is consistent with the literature where participants were more likely to have better CHD knowledge scores if they were non-smokers.

Other factors such as personal stressors, peer pressure and addiction could be reasons why participants continued to smoke [30–32]. It is therefore important that along with increasing the knowledge levels, other multiple modalities to assist with smoking cessation are also implemented. Such strategies may include the use of lay people in health promotion programs because they share the same language, culture, and ethnic attributes which provides them with a better understanding of the health needs of their community [33]. The use of pharmacotherapies [34, 35], telephone counselling [36], and web- and computer-based smoking cessation programs have been demonstrated to change behaviours relating to smoking [37].

What is interesting is that among both cohorts, those with risk factors for CHD namely history of high blood pressure, high cholesterol and high blood sugar had poor knowledge relating to heart disease. It could be postulated that the knowledge deficits identified could be as a result of ineffective provider communication, low health literacy or poorly targeted messages. This lack of knowledge among those with risk factors for heart disease remains of concern particularly as Asian Indians exhibit higher rates of hypertension and diabetes [38]. It is therefore vital that public health initiatives should include tailored persuasive messages in multiple Indian languages, highlighting the benefits and advantages gained when a behaviour is adopted.

Among the younger adults only smoking status was identified as an independent predictor of CHD knowledge while for the older adults smoking status and duration of residence in Australia were significant predictors of CHD knowledge. The result relating to smoking status as a predictor for CHD knowledge is consistent with the literature where participants were more likely to have better CHD knowledge

scores if they were non-smokers [19, 28]. Although numerous studies [27, 39–41] have investigated the determinants of CHD knowledge, duration of residence has not previously been identified as a predictor of higher CHD knowledge. However, it has been well established that longer duration of residence in the adopted country is a risk factor for heart disease [42, 43]. It could be postulated that since the older cohort were residing for a longer period of time in Australia they had more exposure to the health promotion messages which could in turn increase their knowledge of heart disease. Other studies have reported that having tertiary qualifications and being overweight were predictors of CHD knowledge [19, 28], however in this study both these variables were not found to be predictors of CHD knowledge.

Improving knowledge relating to heart disease remains an important goal, as it is integral to promoting healthy lifestyles and preventing disease.

The gaps in knowledge surrounding cardiac risk factors that could be treated with medications [44–46] raises an important question about what is the best method to increase the knowledge of all Asian Indians about heart disease particularly as they are more vulnerable to the condition. It is evident from this study that despite this cohort being well educated, CHD prevention messages may not be reaching this group. These findings suggest that alternate educational approaches are warranted to meet the specific informational needs of minority patients. There is evidence to indicate the presence of low health literacy among patients who require health care the most [47]. Therefore, educational approaches should be developed while keeping in mind issues of health literacy. Efforts should be made to use simple everyday language and be tailored to educate patients as patients largely rely on health professionals for first-hand information. Resources including plain language educational materials in multiple languages must be developed to ensure that information provided is understood. In addition, the methods of education should encourage the patient to clarify information that is provided. In addition to increasing knowledge other behavioural strategies such as motivational interviewing, one–one or group counselling and brief interventions delivered by trained professionals have been reported to reduce risk factors for heart disease [48]. The use of mobile-health and web based technologies to support people in behaviour modification can also serve as an useful adjunct to other strategies [49, 50].

The major strength of the study was the use of a validated questionnaire developed in English specifically for the Indian population to assess heart disease knowledge. The questionnaire was simple and used a true false format which increased the response rates. Despite the results obtained in this study, the limitations inherent in undertaking such a study need to be acknowledged. Firstly the sample size was small and included only those who attended the health promotion stall which may limit the generalizability of our results. Secondly, the length of time the participant had the risk factor was not evaluated and this could have influenced their knowledge of heart disease. In addition, the data collection method is subject to recall and social desirability bias. Another limitation of the study was that the survey was self-administered in English which excluded immigrants mainly the older people who were not able to read English.

Improving knowledge relating to heart disease remains an important goal, as it is integral to promoting healthy lifestyles and preventing disease. Further research should include an assessment of health literacy of participants and knowledge relating to heart disease prevention. Research relating to heart disease knowledge among adults under the age of 40 from other populations is warranted in order to provide comparative data.

Conclusions

Although suboptimal, there were no statistically significant differences in the level of knowledge among older and younger Asian Indians. Nevertheless, the results of this study have helped to identify segments of the population who need to be targeted for aggressive educational strategies.

Author Contribution: Ritin S. Fernandez: Development of research project, research proposal, ethics application, data collection, contribution to writing the paper; Bronwyn Everett: Development of research project, data collection, Recoding dataset, development of publication; Subbaram Sundar: Development of research project, research proposal, data collection, development of publication. All authors have reviewed the submitted document and approve the manuscript submission.

Compliance with Ethical Standards

Conflict of interest: All authors declare that they have no conflict of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

References available on request Healthcare.India@springer.com

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New Approaches in Hypertension Management: a Review of Current and Developing Technologies and Their Potential Impact on Hypertension Care

Jamie Kitt[1], Rachael Fox[1,2], Katherine L. Tucker[2], Richard J. McManus[2]

Hypertension is a key risk factor for cardiovascular disease. Currently, around a third of people with hypertension are undiagnosed, and of those diagnosed, around half are not taking antihypertensive medications. The World Health Organisation (WHO) estimates that high blood pressure directly or indirectly causes deaths of at least nine million people globally every year.

Katherine L. Tucker

Katherine.tucker@phc.ox.ac.uk

[1] Radcliffe Department of Medicine (Cardiovascular Division), University of Oxford, Oxford, UK

[2] Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Primary Care, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG, UK

Hypertension has been identified by WHO [1] as one of the most significant risk factors for morbidity and mortality worldwide and is responsible for the deaths of approximately nine million people annually [1]. In the UK, the National Institute for Health and Care Excellence (NICE) [2] defines high blood pressure (BP), also known as hypertension, as a clinic blood pressure of 140/90 mmHg or higher confirmed by a subsequent ambulatory blood pressure monitoring daytime average (or home blood pressure monitoring average) of 135/85 mmHg or higher.

High blood pressure does not just develop in older adults. Over 2.1 million people under 45 years old had high blood pressure in England in 2015 [3]. This is important because treating hypertension results in significant reductions in risk of subsequent cardiovascular disease [4, 5]. Despite strong evidence for such treatment, studies suggest that many people remain sub-optimally controlled [6]. New approaches, including new technologies, are therefore needed to improve screening, detection and control of raised blood pressure in the community.

Screening

High blood pressure is largely asymptomatic, especially in the early stages, leading to its description as a 'silent killer' [1]. The asymptomatic nature of hypertension in conjunction with its disease burden necessitates routine blood pressure screening. In the UK, NICE guidelines recommend blood pressure measurement at least yearly among normotensive adults [3] and currently hypertension is largely identified in this way by physicians routinely or opportunistically assessing blood pressure in a primary care clinic setting [7]. However, it has been estimated that between a third and a half of hypertensive patients remain undiagnosed, indicating the need for better screening [8]. Developments in non-physician-based blood pressure measurements utilising new technologies may provide an opportunity for increased detection of hypertension.

Self-screening allows patients to measure their own blood pressure outside of physician consultations, either in their own home or with public validated solid cuff automatic sphygmomanometers that require no training, just simple instructions for use [7]. In Japan, the market penetration of home blood pressure monitoring is such that it is estimated that more than enough monitors have been sold for one per household. In the UK, at least 1:10 normotensive adults have measured their own blood pressure at some time in the past [9]. A recent systematic review [7] identified three studies of self-screening, which utilised public blood pressure cuffs in a variety of settings including pharmacies and grocery stores (Hamilton 2003 [10], Houle 2013 [11], Nykamp 2016 [12]). The majority of these were conducted in North America, where out-of-office blood pressure self-screening stations in pharmacies and work places are estimated to be used more than one million times a day [13]. Providing additional blood pressure self-monitoring equipment in physician waiting rooms has been proposed in the UK to increase blood pressure screening [14], and such monitors are available in around a third of practice in the UK [15]. Whilst several studies to date show promising results for feasibility, patient autonomy, convenience, and increased detection of hypertension (Hamilton 2003 [10], Houle 2013 [11] and Tompson 2017 [14]), a number of barriers are yet to be overcome before widespread community self-screening can be recommended. These include limited privacy, poor awareness of the availability of the facilities, and a lack of education regarding the asymptomatic nature of hypertension and the benefits of screening [14].

Advances in technology have allowed for the development of new 'cuff-less' BP monitoring devices however, which continuously monitor BP without disruption to daily activities.

Breaking away from traditional cuff-based measurement of blood pressure, the widespread accessibility of smartphones and mobile health applications also offer new potential for the ubiquitous monitoring of parameters such as blood pressure. Recently, for example, the Cardiogram® application on the Apple® watch has been evaluated for its utility at using deep learning algorithms to predict hypertension from inputs of heart rate and step count. Data were collected from 6115 app users for an average of 9 weeks and predicted hypertension moderately well [16]. This particular 'app' can now utilise multiple other wearable devices such as Fitbit®, Garmin® and Android devices; however, further research into its diagnostic utility is required. Furthermore, in the UK at least, current market penetration of smartphones into elderly populations is not sufficient for these techniques to be widely available in this key age group, but they have definite potential to aid detection of hypertension in younger adults [Ofcom communications market 2018]. In addition, cognitive deficits and visual or hearing impairments, which are more prominent in the older population, can decrease the accessibility of smartphone applications. It seems likely that further advances in technology will increase the spread of such techniques, but the need for long-term treatment of hypertension means that a formal diagnosis of hypertension is likely to remain paramount.

Hypertension Diagnosis

Once a person has been screened and found to have high blood pressure, ambulatory blood pressure monitoring (ABPM) is regarded as the most accurate way to diagnose hypertension and is recommended by guidelines to routinely to confirm elevated blood pressure readings [2, 17, 18]. Ambulatory monitors typically involve portable, automated cuffs worn continuously that measure blood pressure every 15–30 min during the day and 15–60 min overnight [19]. Despite their utility in diagnosis, ambulatory monitors may not be available to many clinicians and patients due to cost and time limitations [19] and can be uncomfortable and disruptive to daily life and sleep [9, 20]. Advances in technology have allowed for the development of new 'cuff-less' BP monitoring devices however, which continuously monitor BP without disruption to daily activities. Cuff-less BP monitoring devices utilise smartphone or wearable sensor technologies that can estimate BP from ECG signals, photoplethysmogram (PPG) signals (using infrared light on the finger to estimation of skin blood flow), or a combination of both [21]. For example, one system developed consists of a wearable wrist band to collect PPG signals, a wearable heart rate belt to collect ECG signals, and a smartphone. The signals from the wearable device communicate via Bluetooth with the smartphone to synchronise their measurements and continuously stream the wearer's blood pressure. Other devices that have been developed utilise

sensors in T-shirts [22], placed behind the ear [23] and in a computer mouse [24] to calculate and record blood pressure measurements.

As with screening, the use of 'smartphone apps' is increasingly popular to aid in diagnosis. One U.S. survey of 'app users' showed that 31% of mobile phone owners used their phone to look for health information, with the largest proportion (52%) among smartphone users [25]. Although this is a hugely expanding field, with >180 apps now existing to measure blood pressure, in only 3.8% (7/184) of the blood pressure apps was any involvement of medical experts mentioned in its development and very few apps have been robustly evaluated [25]. Moreover, at present, no mobile apps have formally obtained approval for use as measuring/diagnostic devices by the U.S. Food and Drug Administration or European Commission. The American Heart Association (AHA) has stated that there are too many errors with smartphone blood pressure apps [26] with mobile app-based blood pressure measurements being inaccurate four out of five times when one popular mobile application was tested [25, 26].

A vital issue with both the apps and novel non-invasive devices is the lack of a universally agreed standard for the validation of this technology, and current protocols simply do not include them. There are plans to rectify this [27•] with some apps exploring clinical validation [28, 29] so the future does look brighter. At present, however, there is limited incorporation of this technology into widespread clinical practice as a result of this key issue [26].

Hypertension Management

Around 14% of the adult population in England and Wales currently appear on primary care hypertension registers [8] which equates to over seven million people. This provides a significant market for technology to assist in control. Currently, 60% of those on hypertensive registers are controlled [30], and only 50% of those starting on a new antihypertensive remaining taking it after 6 months [3]. In this cohort of people, the technology to facilitate management has been available for some years but has only recently acquired a solid evidence base. Options considered in this section range from self-monitoring and tele-monitoring to virtual clinics and artificial intelligence (AI)-assisted management.

Self-monitoring of blood pressure can improve blood pressure control and is an increasingly common part of hypertension management.

1. Self-monitoring of blood pressure can improve blood pressure control and is an increasingly common part of hypertension management. It is well tolerated by patients and has been shown to be a better predictor of end organ damage than clinic measurement [2, 20, 32, 33]. Trials of self-monitoring show improved blood pressure control, mainly in the context of additional co-interventions such as pharmacist intervention or nurse-led education [34]. A caveat to self-monitoring is that it relies on good communication between patients and physicians, and perhaps 50% of patients do not tell clinicians they are self-monitoring or share the readings with their physician, in a meaningful manner [35]. A solution to this may be the remote monitoring of blood pressure readings measured at a patient's home, i.e. tele-monitoring, something explored more below.

Another option to enhance ongoing self-monitoring compliance could be BP monitoring apps. These can communicate between smartphone and BP monitor allowing the patient to control (e.g. start/stop/configure) the BP measurement procedure from the app and to download automatically the current or previous BP readings. BP estimation is computed in the device microchip using the oscillometric signal, which is sampled and filtered from device pressure sensors, during the cuff inflation or deflation. Examples of BP self-monitoring analytics subsequently available include tracking the average BP over time, alerting on concerning BP trends, e.g. high/low readings, or normal/abnormal circadian BP patterns (dipper/non-dipper trend). When an app is used to communicate with a clinician, this becomes a type of tele-monitoring (see below).

Self-monitoring can also be combined with self-titration of medication, a process known as self-management. Trials undertaken before the current generation of mobile devices have shown that self-management can lead to improved blood pressure control through medication optimisation in both hypertensive and higher risk populations [36•, 37•].

2. Tele-monitoring is a particular application of telemedicine—the transfer of data remotely—which in this case consists of automatic data transmission of BP readings. It can also be combined with the transfer of other parameters such as heart rate, oxygen saturations, and pacemaker/defibrillator data from the patient's home or workplace to a professional healthcare environment such as a primary care clinic/surgery or the hospital [38]. Several tele-monitoring systems are available which differ in their modality of data collection, transmission, and reporting and by the presence/absence of additional features such as reminders for BP measurement to be performed or medication reminders. Randomised controlled trials [39•] performed in recent decades have tested the effectiveness of home blood pressure tele-monitoring for the improvement of hypertension control and associated healthcare outcomes. In a large meta-analysis [39•], all studies included demonstrated a high degree of acceptance of the technologies by

doctors and patients, good adherence to tele-monitoring programs and confirmed that the technology has the potential to enhance hypertension management, improve patient outcomes, and reduce healthcare costs, particularly when considering long-term follow-up.

Another meta-analysis demonstrated that BP tele-monitoring in conjunction with co-intervention, such as medication titration by a case manager or education/lifestyle counselling, led to significantly larger and persistent (up to 12 months) BP reductions when compared with self-BP monitoring alone without transmission of BP data and counselling [34].

Until recently, the key evidence missing from trials of self-monitoring and tele-monitoring was whether the use of such data by clinicians actually led to lower blood pressure. In 2018, the TASMINH4 trial [40•] showed that GPs using self-monitored blood pressure to titrate antihypertensives, with or without tele-monitoring, achieved better blood pressure control for their patients than those using clinic readings. As with previous trials, the mechanism of action appeared to be medication optimisation. The tele-monitoring group achieved lower blood pressure quicker than the self-monitoring group, but readings were not significantly different at the primary end point of 1 year. Forthcoming work shows that patient and clinician experience was largely positive from tele-monitoring with some important caveats in particular patients. Cost-effectiveness analysis suggests that self-monitoring in this context is cost-effective by NICE criteria, i.e. costing well under £20,000 per QALY [Grant S *et al*. BJGP 2019, *In Press; and* Monaghan M *et al*. Hypertension 2019, *In Press*].

Interactive digital interventions now offer the ability to provide users with additional support over and above simple tele-monitoring which can also result in lower blood pressure than usual care [41]. This can include, for example, multi-media demonstrations of lifestyle advice utilising video and web links. The 'Home BP' trial will report later in 2019 on the effectiveness of a web-based digital intervention with a lifestyle module testing the efficacy over and above usual care [42]. Where a digital intervention utilises mobile phone technology to underpin tele-monitoring, this is increasingly termed as 'M-health'.

3. 'Virtual clinics/visits' provide a system-level option for the use of such technology and comprise structured asynchronous online interactions between a patient and a clinician to extend medical care beyond the initial office visit. A study by Levine *et al*. in 2018 showed that for primary care patients managed for hypertension with a virtual visit vs. a real-life in-person visit, there was no significant adjusted difference in systolic blood pressure control, number of specialist visits, emergency department presentations, or inpatient admissions [43].

Hypertension is a risk factor for atrial fibrillation (AF), and half of those with AF have hypertension, making blood pressure measurement an important aspect of care in these patients.

4. Other novel advances in hypertension management

Artificial intelligence underpins interfaces such as Alexa® and Siri® which can wirelessly update medication lists and set reminders (e.g. alarm reminders to take medications to improve adherence to treatment), and although there is a current dearth of evidence of the efficacy of these, it seems likely that their use will increase over time. Incorporation of tele-monitored data on blood pressure into digital healthcare programmes can now also allow combination with other physiological variables including blood glucose, heart rate and exercise allowing adaptation of management recommendations based on pre-determined variables including user demographics, indicated morbidities and comorbidities, self-identified barriers and actions recorded over the course of a programme or set by a physician. Examples of this include the 'WellDoc Hypertension and diabetes management platform' and 'Omada Health's digital program'.

Implementation of Technology in Special Groups

Hypertension is an ideal area for the use of new technology but does require consideration of a number of special groups, the most important of which are discussed below:

Atrial Fibrillation

Hypertension is a risk factor for atrial fibrillation (AF), and half of those with AF have hypertension [44], making blood pressure measurement an important aspect of care in these patients. However, the accuracy of current methods of blood pressure monitoring is limited in those with AF as demonstrated in a recent meta-analysis [45]. This is particularly an issue in the elderly where AF can affect over 10% of the population. Validation studies of automated blood pressure devices typically exclude those with AF, resulting in a lack of evidence regarding the accuracy of these devices to measure BP when AF is present, which is turn makes reliable out-of-office BP measurement, including home and ambulatory BP monitoring more difficult in this population. As a result, NICE [2] and European guidelines [17] currently both recommend manual measurement of blood pressure when AF is present, making self-monitoring very difficult [46]. A more recent systematic review analysed studies containing 14 different automated BP devices to determine if

their accuracy in the presence of AF has improved as technology and detection algorithms have advanced [45]. In this study, of the devices compared, four were newer automated BP devices that incorporated the latest algorithms to detect AF, but the marketing for these devices appeared misleading as despite claiming 'AF detection' and 'BP measurement' within the same device, there was no evidence to suggest that they were more accurate at measuring BP in the presence of any atrial arrhythmia. This particular review [45] concluded that BP devices known to be accurate for patients in sinus rhythm cannot be assumed to maintain accuracy when used to measure BP in those with AF. Consequently, measurement, and thus management of BP, in patients with AF remains an area in which further development of new technology is required to enable more precise monitoring and management.

Pregnancy

Hypertension in pregnancy results in substantial maternal morbidity and mortality worldwide [47, 48]. Furthermore, hypertension during pregnancy has been linked to the development of chronic hypertension and an increase in lifetime cardiovascular risk of at least double [49]. Self-monitoring of BP in pregnancy has been shown to be feasible and to have the potential to detect hypertensive disorders sooner than standard care [50]. Two large trials are currently recruiting (BUMP1 and BUMP2, https://clinicaltrials.gov/ NCT03334149) and aim to assess whether self-monitoring improves the detection and/or control of hypertension in pregnancy. Moreover, a recent feasibility trial of self-management of BP following hypertensive pregnancy [35] demonstrated that self-management using a purpose-designed app offers great promise in optimising post-partum BP management. This app allowed women to record self-monitored BP, to receive reminders to monitor their BP, and provided real-time automated medication titration feedback based on NICE guidance at that time [49] regarding self-titration and safety. Feasibility testing suggested that this technique was acceptable, as women self-monitored daily with 85% adherence and a median accuracy of 94% and there was a significant improvement in blood pressure control. This was most marked at 6 weeks, and interestingly, the difference in diastolic readings persisted to 6 months despite all but one woman finishing therapy [35]. These findings have prompted further follow-up of the women originally in this study and a larger, pilot study on self-management in the post-partum hypertensive cohort, both commencing later in 2019.

Hypertension during pregnancy has been linked to the development of chronic hypertension and an increase in lifetime cardiovascular risk of at least double.

Children

The first report on paediatric hypertension by the National Heart, Lung, and Blood Institute (NHLBI), published in 1977 [51] declared that "Detection and management of hypertension in children and the precursors of hypertension in adults are the next major frontier". The report also recommended annual BP measurement in all children ≥ 3 years. Unfortunately, nearly 40 years later, the diagnosis of hypertension is missed in the majority of cases, and familiarity with paediatric hypertension among clinicians is extremely poor. This is therefore an area where the technology described above could make a real difference. However, the issues of validation of the technology are even more acute in the paediatric population because children's vasculature and arm size are not the same as those of adults. The new universal standard provides recommendations aiming to improve this [27•].

Developing Countries

New technology offers huge promise in low- and middle-income countries and is being embraced by projects such as CRADLE. This team have developed and validated several devices [52, 53] which were developed specifically to meet the World Health Organisation criteria for use in a low-resource setting. The newest device is low cost at approximately $20 per device, has low-power requirements, and can be charged using a standard mobile phone charger [54]. It is also robust and capable of accurately detecting abnormalities in vital signs, including during pregnancy [55]. Severe bleeding, severe infection, and blood pressure disorders [55] are the most common cause of deaths in pregnancy, and such devices have the potential to be life-saving. Resources are the biggest issue in the developing world however where many hospitals do not currently have appropriate monitoring equipment, let alone the newest technology.

Future Research Needed

Whilst much has been achieved in terms of research to date, several areas are clearly lacking in the kind of evidence needed in primary and secondary care alike. The most pressing need is perhaps for new technologies to be assessed and clinically validated [27•] prior to widespread implementation in the general population.

As healthcare is moving towards greater patient involvement and responsibility, including self-monitoring and self-screening of hypertension, we need to understand how best clinicians and patients alike can integrate these advances into daily practice.

Much previous research around blood pressure monitoring and management has excluded those with additional or complex needs such as the very old, multi-morbid, or pregnant women. It is important to complete research in these populations, as there may be differences in accuracy in some

groups [56, 57] and the implications of, for instance, white coat hypertension, may be very different in pregnancy compared with the general population.

Conclusions

Hypertension has been identified by WHO as one of the most significant risk factors for morbidity and mortality worldwide [1], and despite strong evidence for treatment, studies suggest that many people remain sub-optimally controlled [6]. New approaches, including new technologies, are therefore needed to improve screening, detection and control of raised blood pressure in the community. Breaking away from traditional cuff-based measurement of blood pressure, the widespread accessibility of smartphones and mobile health applications offers new prospects for ubiquitous monitoring of parameters such as blood pressure, but evidence of both accuracy and efficacy is currently lacking.

Current market penetration of smartphones into the elderly is not sufficient for widespread implementation of technology such as smartphone apps in this age group, but M-health has definite potential to aid screening and diagnosis in younger adults, pregnant women, children and adolescents as well as older populations as the technology becomes more commonplace. A key issue with both apps and novel non-invasive devices are the lack of a universally agreed standard for the validation of this technology, and current protocols simply do not include them. There is thus limited incorporation of this technology into clinical practice at present [26], and this must be addressed as a matter of urgency by European, UK, and American regulators.

Until recently, the key evidence missing from trials of self-monitoring and tele-monitoring was whether the use of such data by clinicians actually led to lower blood pressure. Now trial data combined in meta-analyses provides strong evidence for BP tele-monitoring in conjunction with co-interventions, such as medication titration or education/lifestyle counselling. Further work is needed to ensure the most appropriate and beneficial aspects of technology are effectively utilised within the health system as this could improve care whilst reducing the need for face to face clinical appointments.

Compliance with Ethical Standards

Conflict of Interest: Dr. Tucker reports grants from National Institute for Health Research (NIHR) (Applied Research Programme grant), the NIHR Collaboration for Leadership in Applied Health Research and Care Oxford at Oxford Health NHS Foundation Trust, Research Capacity funding and the National School for Primary Care Research, outside the submitted work. Dr. McManus reports grants from NIHR, during the conduct of the study, and grants from Omron, outside the submitted work. Drs. Kitt and Fox declare no conflict of interest relevant to this manuscript.

Disclaimer: The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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How Digital Health can be Applied for Preventing and Managing Hypertension

The aim of this study was to summarize available data on digital health strategies for the prevention and management of hypertension, discussing the state-of-the-art, current limitations, and future perspective of this approach.

Technology is developing at a fast pace and is providing a number of novel solutions for cardiovascular patients, in particular in the field of digital health. Even if the benefit of these approaches is intuitive, the methodological heterogeneity of the available studies and their small sample size have made it difficult to provide robust evidence regarding the usefulness and cost-effectiveness of digital health technologies. Recently, studies with larger sample sizes and some meta-analyses have provided more convincing data on the favorable impact of such strategies.

Digital health solutions may offer a chance to improve primary prevention and for timely diagnosis and effective management of hypertension. Results

from small studies are promising, but there is a strong need for larger, long-term, and well-designed clinical trials to make these novel solutions really applicable in real-life patients' care.

Source: Parati, G., Pellegrini, D. & Torlasco, C. Curr Hypertens Rep (2019) 21: 40. https://doi.org/10.1007/s11906-019-0940-0. © Springer Science+Business Media, LLC, part of Springer Nature 2019.

Waist-to-height Ratio Index for Predicting Incidences of Hypertension: the ARIRANG Study

Several anthropometric indices such as body mass index (BMI) and waist circumference (WC) have been examined as indicators of cardiovascular diseases, in both adults and children. However, the waist-to-height ratio (WHtR) is considered a better predictor for the detection of cardiovascular risk factors, than BMI. We investigated the association between the WHtR and incident hypertension.

A total of 1718 participants, aged 39–72 years, were recruited in this longitudinal study. Participants were divided into 2 groups according to the development of hypertension during 2005–2008 (baseline) and 2008–2011 (follow-up). Logistic regression models were used to evaluate the WHtR as a significant predictor of hypertension.

During the 2.8 years of follow-up, 185 new cases of hypertension (10.8%) were diagnosed, with an incidence rate of approximately 4% per year. The WHtR was significantly higher in the participants who had developed hypertension than in those who had not (0.54 ± 0.05 vs. 0.51 ± 0.05, $p < 0.001$).

After adjusting for age, sex, smoking status, alcohol intake, regular exercise status, total cholesterol, and systolic blood pressure, at the baseline, the logistic regression analysis indicated that the participants with the highest quartile of the WHtR (WHtR ≥ 0.54) were 4.51 times more likely to have hypertension than those with the lowest quartile (odds ratio 4.51; 95% confidence interval 2.41–8.43; $p < .0001$). The area under the curve for the WHtR, in identifying hypertension risk, was significantly greater than that for the BMI ($p = 0.0233$).

A positive association between WHtR and the incidence of hypertension was observed in Korean adults. The findings of the present community-based prospective study suggest that the WHtR may be a better predictor of incident hypertension.

Source: Choi, J., Koh, S. & Choi, E. BMC Public Health (2018) 18: 767. https://doi.org/10.1186/s12889-018-5662-8. © The Author(s). 2018.

Artificial Intelligence in Nuclear Cardiology: Adding Value to Prognostication

Radionuclide myocardial perfusion imaging (MPI) continues to be an accurate and reproducible method of diagnosing obstructive coronary artery disease (CAD) with predictive, prognostic, and economic value. We review the evolutionary potential of machine learning (ML), a subset of artificial intelligence, as an adjunct to MPI.

Applying the broad scope of ML, including the integration of deep learning, can leverage the knowledge representation and automated reasoning to detect and extrapolate patterns from high-dimensional features of MPI.

There is growing evidence to suggest superior abilities of ML over parametric statistical models for predicting the presence of obstructive CAD, the need for revascularization, and the occurrence of major adverse cardiac events including cardiac death.

ML is uniquely positioned to provide the next great advancement in the field of nuclear cardiology for improving patient-specific risk stratification.

Source: Seetharam, K., Shresthra, S., Mills, J.D. et al. Curr Cardiovasc Imaging Rep (2019) 12: 14. https://doi.org/10.1007/s12410-019-9490-8. © Springer Science+Business Media, LLC, part of Springer Nature 2019.

The Influence of Dietary Salt Beyond Blood Pressure

Excess sodium from dietary salt (NaCl) is linked to elevations in blood pressure (BP). However, salt sensitivity of BP varies widely between individuals and there are data suggesting that salt adversely affects target organs, irrespective of BP.

High dietary salt has been shown to adversely affect the vasculature, heart, kidneys, skin, brain, and bone. Common mediators of the target organ dysfunction include heightened inflammation and oxidative stress. These physiological alterations may contribute to disease development over time. Despite the adverse effects of salt on BP and several organ systems, there is controversy surrounding lower salt intakes and cardiovascular outcomes.

The goal of this study is to review the physiology contributing to BP-independent effects of salt and address the controversy around lower salt intakes and cardiovascular outcomes. The researchers will also address the importance of background diet in modulating the effects of dietary salt.

Source: Robinson, A.T., Edwards, D.G. & Farquhar, W.B. Curr Hypertens Rep (2019) 21: 42. https://doi.org/10.1007/s11906-019-0948-5. © Springer Science+Business Media, LLC, part of Springer Nature 2019.

Generalizability of SPRINT-CKD Cohort to CKD Patients Referred to Renal Clinics

Roberto Minutolo[1], Luca De Nicola[1], Ciro Gallo[2], Paolo Chiodini[2], Michele Provenzano[1], Giuseppe Conte[1], Carlo Garofalo[1], Silvio Borrelli[1], Collaborative Study Group on the Conservative Treatment of CKD of the Italian Society of Nephrology

The Systolic Blood Pressure Intervention Trial-CKD substudy (SPRINT-CKD) has suggested a lower blood pressure (BP) target in CKD patients. However, it is questionable whether the SPRINT-CKD results may be generalized to CKD patients under nephrology care.

Roberto Minutolo(✉)
roberto.minutolo@unicampania.it

[1]Division of Nephrology, Department of Scienze Mediche e Chirurgiche Avanzate, University of Campania "Luigi Vanvitelli", Via M. Longo 50, 80138 Naples, Italy

[2]Medical Statistics Unit, University of Campania, Luigi Vanvitelli, Naples, Italy

Strict blood pressure (BP) control in chronic kidney disease (CKD) patients is a mainstay to lower mortality and progression of renal disease to ESRD [1, 2]. However, the optimal goal of blood pressure (BP) in CKD population is still debated [3]. Recently, the pre-specified subgroup analysis of CKD patients enrolled in the Systolic Blood Pressure Intervention Trial (SPRINT-CKD) explored the effects of a systolic blood pressure (SBP) target < 120 mmHg in comparison with SBP < 140 mmHg in 2646 non-diabetic patients at high cardiovascular (CV) risk with eGFR 20–59 mL/min/1.73 m^2 [4]. Targeting SBP to < 120 mmHg reduced mortality risk by 28% without significant protection against CV risk [hazard ratio (HR) 0.81; 95% confidence interval (95% CI) 0.63–1.05]. However, the effect on renal events was neutral (HR 0.90; 95% CI 0.44–1.83), while risk of acute renal failure and hyperkalemia increased [4]. According to these findings, a more stringent BP target (< 130/80 mmHg) has been recommended by the most recent hypertension guidelines [5] and critically reappraised in the setting of CKD population [6].

Despite the outstanding findings of that landmark study for the nephrology community, some critical aspects must be considered when translating the results

of SPRINT trial in the context of clinical practice. It is well known, in fact, that RCTs typically have lower event rates in part because the patients enrolled are perhaps much better taken care and in part because of inclusion of highly selected population with stable conditions and at lower risk. These limitations likely occurred also in SPRINT trial in which CKD patients enrolled were mainly recruited in general population where a low eGFR may be the result of kidney senescence rather than a marker of true renal disease [7–10]. Furthermore, very stringent exclusion criteria were applied (i.e., heart failure, diabetes, severe proteinuria, eGFR < 20 mL/min/1.73 m^2) that actually account for about one-half of CKD population now followed in renal clinics [11–14]. Therefore, as previously acknowledged and discussed [4, 15], the risk profile of SPRINT-CKD participants is different from CKD patients treated in nephrology practice, and the claimed 'high risk' population selected in the trial could not mirror the true cardio-renal risk of patients followed in renal clinics. The underrepresentation of CKD patients among RCTs has been recently highlighted by Maini *et al.* that have shown as 46% of trials investigating CV disease excluded patients with CKD [16].

Based on the above considerations, we hypothesize that SPRINT-CKD cohort is not comparable to patient population followed in renal clinics. Therefore, we designed the present study to quantify the gap between the phenotype of patients enrolled in SPRINT-CKD and CKD population followed in daily clinical practice by assessing the representativeness of the SPRINT-CKD cohort in terms of patients' risk profile and outcomes in comparison with those observed in Italian CKD patients under nephrology care.

Methods

Study Population

This is a pooled analysis of four prospective cohorts enrolling consecutive patients with CKD stage I–V referred to 40 Italian nephrology clinics [17–20]. As previously described [21], the four cohorts shared similar exclusion criteria and data collection including demographic information, history of CV disease, height, weight and BP, laboratory results and medication pattern. BP measurement was performed with the same methodology in the four cohorts. During the physician's visit, office BP was measured with the patient seated three times at 5-min intervals. The office BP measurement values reported herein are the mean of the three values. Glomerular filtration rate (eGFR) was estimated by the four-variable MDRD equation and Chronic Kidney Disease Epidemiology Collaboration equation; since creatinine was not standardized to isotope-dilution mass spectrometry values, we reduced creatinine values by 5% [22]. Institutional review boards of participating centers approved the four studies and informed consent was obtained from all individual participants included in the studies.

A more stringent BP target (< 130/80 mmHg) has been recommended by the most recent hypertension guidelines and critically reappraised in the setting of CKD population.

To allow comparability between SPRINT-CKD and our pooled cohort, we implemented the same selection criteria adopted in SPRINT [4]. Specifically, we included patients ≥ 50 years old, SBP 130–180 mmHg on 0 or 1 medication, SBP 130–170 mmHg on up to 2 medications, SBP 130–160 mmHg on up to 3 medications, SBP 130–150 mmHg on up to 4 medications, eGFR of 20–59 mL/min per 1.73 m^2, and presence of clinical CV disease (other than stroke). Patients with diabetes mellitus, 24 h proteinuria ≥ 1 g/day, previous stroke, symptomatic heart failure, diagnosis of autosomal dominant polycystic kidney disease (ADPKD), and receiving immunosuppressive therapy were excluded. Cancer diagnosed and treated within the past 2 years was an exclusion criteria already adopted by the four Italian cohorts [17–20].

For comparison we only used data of CKD patients randomized to the control arm of SPRINT-CKD, because BP management in this group mirrors daily clinical practice where SBP target < 140 mmHg is usually pursued. Furthermore, in our cohort, we limited the analysis of outcomes to the events occurring no later than 4.8 years after enrolment, i.e. the maximum follow up available in SPRINT-CKD [4].

Outcomes

We implemented the same endpoints reported in the SPRINT trial: (1) a composite of myocardial infarction, acute coronary syndrome, stroke, heart failure and CV death (2) all-cause mortality and (3) end-stage renal disease (ESRD), as a composite of chronic dialysis, transplantation or 50% eGFR decline [4]. To establish the underlying cause of death and to determine CV deaths, we used death certificates and autopsy reports, whereas hospital records were used to identify the diagnosis of non-fatal CV events based on the International Classification of Diseases, Ninth Revision, Clinical Modification [21]. Patients were followed-up until 31 December 2015, death or end-stage renal disease (ESRD), and were censored on the date of the last nephrology clinic assessment.

Statistics

Continuous variables were reported as either mean ± standard deviation (SD) or median and interquartile range (IQR) based on their distribution, while categorical variables were expressed as percentage. Median follow-up was estimated by the reverse Kaplan–Meier approach [23].

Since a formal comparison of patient

characteristics between SPRINT-CKD trial and our pooled cohort was beyond our purpose, we did not apply any statistical test. Incidence rates of adverse events were calculated as percent per 1 year in order to be consistent with data reported in SPRINT-CKD study [4] and compared using mid-p exact method (R software 3.3.1, R Foundation for Statistical Computing, Vienna, Austria). The datasets analyzed during the current study are not publicly available due policy rules of the coordinating center but are available from the corresponding author on reasonable request.

Results

From the initial pooled cohorts (n = 3225), we deleted 338 duplicate patients, 27 patients without data on SPRINT selection criteria and 13 patients lost to follow-up with a final number of 2847 evaluable patients (Fig. 1). Among these patients, only 571 (20.1%, 95% CI 18.6–21.5) were identified as eligible for SPRINT-CKD trial. Eligibility rate increased in parallel with age and declined with worsening of eGFR, systolic BP and proteinuria, while no difference was detected for gender (Fig. 1).

It is worth noting that statin and aspirin prescription was by far less frequent in Italian patients than in SPRINT-CKD control arm.

Baseline risk profile

Demographic and baseline clinical characteristics of the Italian patients potentially eligible to SPRINT and the SPRINT-CKD patients (standard BP arm) are reported in the Table 1. In this table, we included the same variables reported in SPRINT-CKD trial [4]. Age and gender distribution were similar while CV risk profile was worse in Italian pooled cohort, as testified by higher prevalence of CV disease, mainly subclinical, higher Framingham risk score, and more severe dyslipidemia (total cholesterol and triglycerides). Renal damage was also more severe in Italian patients due to higher proteinuria and lower eGFR; in particular, 25% of patients had eGFR 45–59, 50% had eGFR 44-30 and 25.2% had eGFR 20–29 mL/min/1.73 m^2. SBP in the Italian cohort was slightly lower (142 ± 10 mmHg on average with values ≤ 132 mmHg in 27.5%, 133–144 mmHg in 35.7% and ≥ 145 mmHg in 36.8%). The number of antihypertensive drugs at baseline was similar in the two groups; drugs acting on renin-angiotensin system (RAS) (converting enzyme inhibitors and/or angiotensin II receptor blockers), calcium channel blockers and loop diuretics were the most frequently prescribed classes (75%, 45% and 33%, respectively) in Italian patients. The same occurred in the standard arm of SPRINT-CKD; however, the use of these three classes was less frequent (57%, 37% and 15%, respectively). It is worth noting that statin and aspirin prescription was by far less frequent in Italian patients than in SPRINT-CKD control arm.

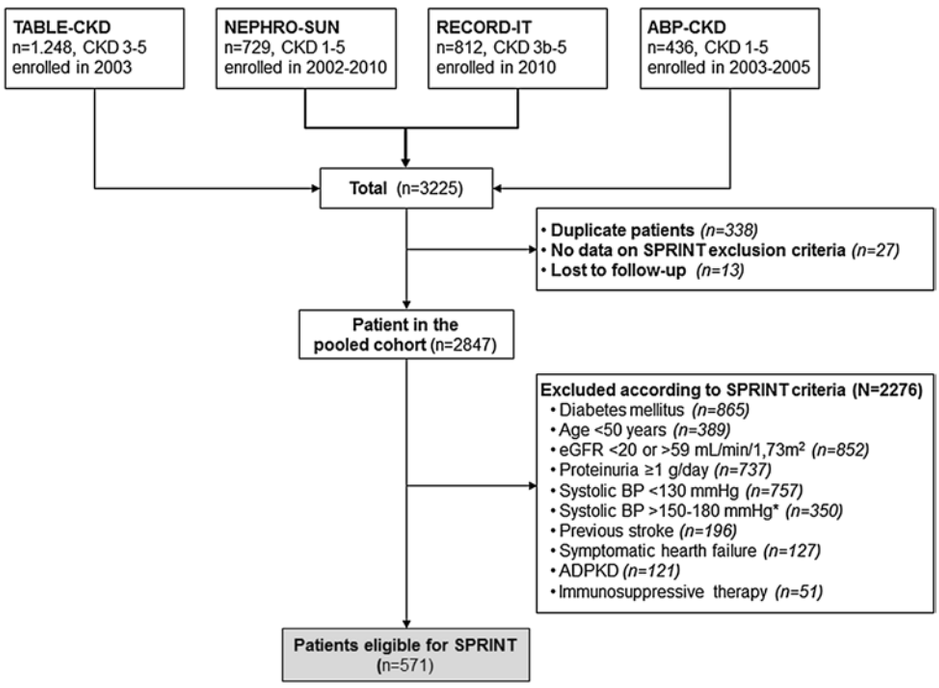

Fig. 1: Flowchart of the study. *Upper limit of systolic BP varied from 150 to 180 mmHg according to the number of antihypertensive drugs (see "Methods").

Outcomes

At a median follow-up of 4.0 years (IQR 2.7–4.8), we registered 86 CV events (50 fatal), 78 all-cause death with annual incidence rates higher than those observed in the SPRINT-CKD control group (Table 2). Furthermore, in our cohort we observed 59/571 (10.3%) ESRD events (eGFR reduction > 50%, n = 30 and chronic dialysis, n = 29) in comparison with only 16/1316 (1.2%) reported in the SPRINT-CKD control arm (eGFR reduction > 50%, n = 12 and chronic dialysis, n = 4); accordingly, ESRD incidence rate was about sixfold higher in our cohort (P < 0.001).

Patients not fulfilling the SPRINT selection criteria were younger and had more frequent clinical CVD, lower SBP, and similar Framingham risk score. Lower eGFR and higher proteinuria reflected the presence of specific SPRINT exclusion criteria (GFR < 20 mL/min/1.73 m^2 and/or proteinuria > 1 g/day). RAS inhibitors calcium channel blockers and loop diuretics were the most frequently prescribed classes (77%, 46% and 43%, respectively). This large group of uneligible patients showed the worst outcome in terms of ESRD incidence but not for CV events and mortality (Table 2).

Table 1: Baseline characteristics of the SPRINT-CKD control group and Italian CKD patients potentially eligible for SPRINT trial.

	SPRINT standard group	Italian CKD cohort eligible for SPRINT
Number	1316	571
Age (years)	71.9 ± 9.5	72.1 ± 9.4
Age ≥ 75 years (%)	43.8	43.8
Women (%)	39.6	42.2
Body mass index (kg/m^2)	29.5 ± 5.8	27.4 ± 4.8
Current smoker (%)	8.1	11.2
Clinical CVD (%)	19.5	25.7
Subclinical CVD (%)	9.2	62.2
Framingham risk score (%)	27.2 ± 24.7	31.9 ± 14.6
Framingham risk score > 15% (%)	78.2	87.5
Systolic BP (mmHg)	139.1 ± 16.1	141.7 ± 10.4
Diastolic BP (mmHg)	75.1 ± 12.2	80.4 ± 9.8
Creatinine (mg/dL)	1.43 ± 0.38	1.79 ± 0.50
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	47.9 ± 9.5	38.1 ± 10.6
Plasma glucose (mg/dL)	98 ± 12	97 ± 14
Total cholesterol (mg/dL)	185 ± 41	196 ± 36
LDL cholesterol (mg/dL)	109 ± 35	112 ± 33
Triglycerides (mg/dL)	125 ± 69	136 ± 65
Proteinuria (mg/day)	NA	190 [70–430]
Urinary ACR (mg/g)	14 [6–44]	NA
Antihypertensive medications (n)	2.11 ± 1.01	2.14 ± 1.00
No antihypertensive therapy (%)	4.7	3.9
Statin use (%)	53.4	29.2
Aspirin use (%)	55.5	21.4

Data are mean ± SD, median [IQR] or percent
CVD cardiovascular disease, *BP* blood pressure, *ACR* albumin/creatinine ratio, *NA* not available
Subclinical CVD defined as coronary artery calcium score ≥ 400 Agatston units or ankle brachial index (ABI) ≤ 0.90 or left ventricular hypertrophy (LVH) by ECG or echocardiogram. In Italian cohort subclinical CVD includes only LVH, because coronary artery calcium score and ankle brachial index was not measured.

Table 2: Outcome of the SPRINT-CKD control group and Italian CKD patients potentially eligible for SPRINT trial.

	SPRINT standard group (n = 1316)		Italian CKD cohort eligible for SPRINT (n = 571)		
	Events (n)	Incidence rate (percent per 1 year)	Events (n)	Incidence rate (percent per 1 year)	P
CV outcome	131	3.19	86	4.18	0.076
All cause death	95	2.21	78	3.64	0.001
ESRD	16	0.41	59	2.80	< 0.0001

CV outcome includes myocardial infarction, acute coronary syndrome, stroke, heart failure and cardiovascular death; ESRD includes chronic dialysis, transplantation or 50% eGFR decline

Discussion

In this study we found that SPRINT-CKD results may only be generalized to a small minority of Italian patients (20%) referred to renal clinics. SPRINT-CKD investigators correctly highlighted that study results cannot immediately translated to other CKD sub-populations not included in the trial (diabetic patients, proteinuric and ADPKD) [4]; on the other hand, these categories are of greater interest being characterized by high risk and accounting for most CKD patients followed in renal clinics [11–14]. Furthermore, we found that, even when the same selection criteria of SPRINT trial are applied, a different risk profile does exist, thus confirming the caution suggested for the adoption of SPRINT results to CKD populations followed in nephrology setting [15].

A similar low generalizability of the whole SPRINT results has been disclosed for the U.S. and Canadian general population. In NHANES 2007–2012, in fact, only 16.8% of patients with treated hypertension met the SPRINT eligibility criteria [24]. This estimate was very close to that derived from the Canadian Health Measures Survey 2007–2013, reporting that only 18.7% of patients with treated hypertension were eligible for SPRINT [25].

Discrepancies in cardio-renal risk profile and adverse events, particularly ESRD, between our cohort and SPRINT-CKD control group may be related to several reasons. First if low GFR is the only criterion to define CKD in general population, as in SPRINT patients, confounding may arise due to the renal dysfunction related to physiological aging, which is often different from true kidney disease. In SPRINT-CKD, 66% of patients had an eGFR 45–59 mL/min/1.73 m^2 [4] as compared with 25% in our cohort. If one considers that in SPRINT-CKD mean age was 72 years and 44% of patients were > 75 years old, it is possible that these subjects may not have true CKD unless other features, high albuminuria in primis, are present [7–10]. Both these characteristics were exclusion criteria in SPRINT trial. Conversely, patients with low GFR under nephrology care more likely have "true" CKD even if the proteinuria is not elevated (< 1 g/day according to SPRINT criteria); indeed, in nephrology setting, proteinuria is regarded as main therapeutic target and intensive anti-proteinuric strategies, including dual RAS blockade, low sodium diet and analogs of vitamin D are usually used by nephrologists to delay ESRD onset. The presence of clinically meaningful CKD in our patients is further testified by the incidence rate of ESRD that is sixfold higher than that

reported in SPRINT trial, indirectly supporting a larger prevalence of progressive kidney disease among patients followed in renal clinics.

Second, the higher CV risk reported in referred CKD patients could be partially explained by the lower use of CV preventive agents (statin and aspirin) in our patients. However, these agents are not of proven nephroprotective efficacy, therefore not explaining the higher renal risk.

Third, SPRINT trial was not specifically focused on CKD patients, and we cannot exclude that the participating physicians preferentially enrolled patients with actual risk lower than expected. This contributed to the slower than expected enrolment rate, and eventually prompted to a number of randomized patients (n = 2646) much smaller than that originally planned (n = 4300).

Interestingly, cardiorenal risk was higher in our cohort despite it included only Caucasian patients while in SPRINT-CKD about 24% of patients were non-Hispanic black that per se convey a higher risk of adverse CV and renal events [26–28]. A main difference between our cohort and SPRINT trial is the way BP was measured; we used sphygmomanometer rather than automated devices and unattended measurements [4]. However, a recent post-hoc analysis of SPRINT trial did not find any difference between attended and unattended BP measurements [29]. Conversely, in unselected CKD population, it has been reported that BP levels recorded with latter modality are on average 12 mmHg lower than those recorded by sphygmomanometer [30]. Hence, from a theoretical point of view, adopting SPRINT methodology instead of sphygmomanometer measurement would have produced a shift toward the left side of the BP distribution; however, it would have not changed the prevalence of patients potentially eligible for SPRINT-CKD. Indeed, when considering a 12-mmHg lower SBP with automated devices and unattended measurements, we calculated in our CKD cohort that the number of patients potentially excluded because of a low BP (n = 352 with SBP 130–142 mmHg measured by sphygmomanometer) would have been balanced by those not included because of high BP (n = 350 with SBP > 162–192 mmHg measured by sphygmomanometer). Because SBP value is part of Framingham risk score calculation, this would have produced a more conservative estimate of risk profile among CKD patients followed in renal clinics. We cannot exclude that difference in BP measurement would have a different impact on outcomes [31]. This is particularly true for renal events when considering that a J curve in the relationship between BP reduction and changes in GFR is present in CKD patients [32].

Cardiorenal risk was higher in our cohort despite it included only Caucasian patients while in SPRINT-CKD about 24% of patients were non-Hispanic black that per se convey a higher risk of adverse CV and renal events.

Of note, we are also well aware that reproducibility of our findings to other countries should be assessed. Indeed, potential differences in CKD prevalence can produce different estimates of generalizability of SPRINT results. Furthermore, differences in referral policies as well as in background CV risk profile, as described for CKD patients from northern to southern European countries [33], may lead to incidence rates of adverse outcomes dissimilar from those reported in the present paper [34].

In conclusion, the SPRINT-CKD cohort is poorly representative of the Italian CKD population steadily followed in renal clinics, as testified by the small percentage of eligible subjects (20%) and by a more severe cardiorenal risk profile that led to a higher incidence of adverse events in patients under nephrology care. Therefore, SPRINT-CKD conclusions should be adopted with caution in the nephrology setting. These results call for further trials specifically targeted to the vast majority of high-risk population of CKD patients seen in renal clinics and that are often excluded by large trials, as occurred for SPRINT. Conversely, these trials are mandatory when considering the heterogeneous risk now disclosed even in advanced CKD [35].

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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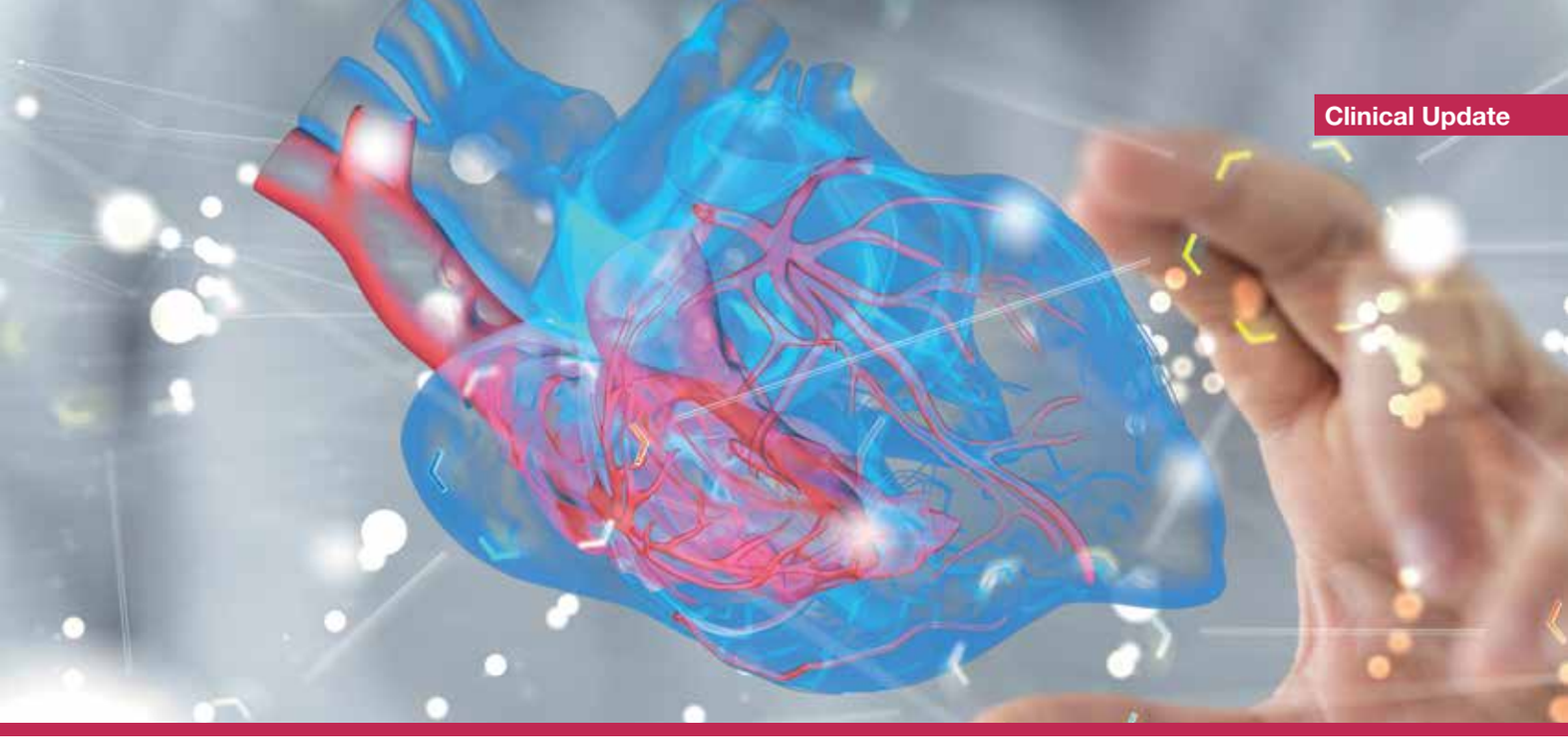

Do Cholesteryl Ester Transfer Protein Inhibitors have a Role in the Treatment of Cardiovascular Disease?

Stephen J. Nicholls[1,2], Adam J. Nelson[1]

Cholesteryl ester transfer protein (CETP) plays an important role in lipid metabolism and has presented an attractive target for drug development, primarily resting on the hope that CETP inhibition would reduce cardiovascular events through its ability to increase levels of high-density lipoprotein cholesterol (HDL-C).

Statins are widely used to reduce cardiovascular risk in a range of clinical settings, but many patients continue to experience clinical events [1]. This residual risk highlights the need to develop novel therapeutic approaches to achieve more effective prevention of cardiovascular disease. According to population [2–4] and animal [5] studies suggesting that high-density lipoproteins (HDLs) are atheroprotective, agents that can increase HDL cholesterol (HDL-C) ought to reduce cardiovascular risk. However, to date, the field has been littered with underwhelming results, from fibrates through to niacin, largely driven by agents with only modest, specific HDL-raising capacity. Over the last decade, interest has increased in developing new therapies that directly target this function. One pharmacological method receiving considerable focus in efforts to substantially raise HDL-C has been the inhibition of cholesteryl ester transfer protein (CETP).

Stephen J. Nicholls(✉)

stephen.nicholls@sahmri.com

[1] South Australian Health and Medical Research Institute, PO Box 11060, Adelaide, SA 5001, Australia

[2] Monash Cardiovascular Research Centre, Monash University, Melbourne, Australia

Cholesteryl Ester Transfer Protein (CETP) and Lipid Metabolism

Cholesteryl ester transfer protein is a plasma-based factor that is synthesized in the liver and adipose tissue. It facilitates the transfer of esterified cholesterol from HDL to apolipoprotein B (ApoB)-containing lipoproteins, mainly very low-density lipoprotein and low-density lipoprotein (LDL), in exchange for triglycerides. The precise mechanism underlying this exchange of lipid species remains uncertain but is likely to involve CETP forming a bridge to link lipoproteins or shuttle lipid species between particles [6]. The fundamental reason for the presence of CETP in humans is unknown; several species (e.g., mice) do not endogenously express CETP. Moreover, humans with homozygous CETP deficiency, despite elevated HDL, appear otherwise physiologically normal [7]. While CETP activity theoretically results in cholesterol depletion of LDL particles, the fact that

LDL is taken up by the liver suggests that CETP-mediated transfer may play an additional role in reverse cholesterol transport. With their capacity to enrich HDL particles, agents that inhibit CETP have been shown to raise HDL to a much greater degree than any other lipid-modifying agent currently used in clinical practice [8].

Evidence Supporting Development of CETP Inhibitors

A number of lines of evidence have suggested that low levels of CETP activity are associated with cardiovascular protection. Population studies have demonstrated that low CETP activity, when associated with elevated HDL-C levels, are associated with less prospective cardiovascular events [9]. Large genome-wide association studies have also reported that polymorphisms associated with low CETP activity similarly had a lower prevalence of cardiovascular disease [10]. Inhibiting CETP via small molecules, vaccines, or antisense oligonucleotides had favorable effects on atherosclerotic plaque burden in rabbit models [11–13]. On the basis of these findings, a number of programs have evaluated the impact of small-molecule CETP inhibitors.

Cholesteryl Ester Transfer Protein Inhibitors

Torcetrapib

Torcetrapib was the first CETP inhibitor to reach an advanced stage of clinical development [14]. Early studies demonstrated dose-dependent elevation of HDL-C > 70% and lowering of LDL cholesterol (LDL-C) by 20%, when administered as monotherapy or in combination with statins [15]. Despite these profound lipid changes, development of torcetrapib was stopped prematurely after adverse clinical effects were observed in a large outcomes trial [16]. When administered in patients at high cardiovascular risk, torcetrapib increased the primary cardiovascular endpoint by 25% and all-cause mortality by 58%. This increase in mortality involved both cardiovascular and non-cardiovascular (cancer, sepsis) events (Table 1). In parallel, three imaging studies failed to demonstrate any benefit of torcetrapib administration on progression of either carotid intima-medial thickness [17, 18] or coronary atherosclerosis [19].

This surprising result provided support for critics of CETP inhibition, suggesting that this strategy would have an adverse effect on HDL function and reverse cholesterol transport. A number of studies provided evidence to suggest that HDL function remained intact in the setting of CETP inhibition. HDL isolated from the plasma of individuals with either CETP deficiency or receiving torcetrapib treatment demonstrated retained capacity to promote cellular cholesterol efflux. In fact, cholesterol efflux activity increased with higher torcetrapib doses [20]. This was supported by observations that torcetrapib was associated with regression of coronary atherosclerosis in a further analysis of patients with the highest HDL-C levels [21]. Parallel studies demonstrated that torcetrapib possessed off-target effects, including blood pressure (BP) elevations (mean 5 mmHg) [22], stimulated adrenal synthesis of cortisol and aldosterone [23], and increased artery wall expression of endothelin [24] and was associated with a modest but statistically significant increase in C-reactive protein (+0.04 mg/dL; $P = 0.01$). Given that patients with aldosterone and bicarbonate levels above the median appeared to have greater mortality, these off-target effects may have contributed to the harm observed with torcetrapib.

Dalcetrapib

Dalcetrapib is a modest CETP inhibitor, raising HDL-C by up to 30% but with no effect on LDL-C levels [8]. Clinical development of this agent progressed in the post-torcetrapib era on the basis of reassuring findings that demonstrated no adverse effects of dalcetrapib on either endothelial function [25] or plaque inflammation [26]. However, a large clinical outcomes trial in patients with a recent acute coronary syndrome was stopped because of clinical futility, with no evidence of an association between on-treatment HDL-C levels and cardiovascular events [27]. Post hoc pharmacogenomic analyses demonstrated that patients harboring the AA genotype of the ADCY9 gene on chromosome 16 treated with dalcetrapib had a 39% reduction in cardiovascular events and regressed atheroma in their carotids [28]. Conversely, those with the GG phenotype, and particularly GG homozygotes, experienced a 27% increase in cardiovascular events (hazard ratio [HR] 1.27; 95% confidence interval [CI] 1.02–1.58), which was directionally supported by the imaging substudies with either an absence of regression or mild progression. This observation led to the initiation of a new trial to compare the effects of dalcetrapib or placebo on cardiovascular outcomes exclusively in high-risk patients with the ADCY9 AA phenotype.

Evacetrapib

Evacetrapib is a more potent CETP inhibitor with dose-dependent increases in HDL-C by up to 125% and lowering of LDL-C by 25–30% [29]. While this agent similarly lacked any such torcetrapib off-target effects in early studies, the lipid effects did not translate to clinical benefit, with the large cardiovascular outcomes trial terminated early because of futility [30]. Pharmacogenomic analyses of this trial failed to demonstrate a clear relationship between ADCY9 genotypes and cardiovascular benefit with evacetrapib [31]. Whether this reflects a dalcetrapib-specific effect or the play of chance is unknown. Of note, evaluation of the Kaplan–Meier event curves of the anacetrapib trial (Sect. Anacetrapib) revealed divergence of the curves at 2 years. When applying this late effect to the evacetrapib trial, it is conceivable that any potential benefits, even if modest, from this agent were yet to emerge given the trial was terminated for futility at a mean follow-up of only 2 years.

Table 1: Features of large phase III cardiovascular outcome trials of CETP inhibitors.

Drug	Date	Sample	Lipid effects	Duration	Safety endpoints	Efficacy endpoint
Torcetrapib (ILLUMINATE)	2007	$n = 15{,}067$; established CVD (MI, stroke, ACS, angina, PVD) within 5 years; LDL < 100 ng/dL	↑ HDL 72% ↓ LDL 25% ↓ TG 9%	Median 1.5 years; event driven; stopped by DS&MB for safety	SBP: ↑ 5.4 vs. 0.9 mmHg ($P < 0.001$) CRP: median ↑0.04 mg/DL ($P = 0.01$) K^+: ↓ 0.1 ± 0.4 mmol/L ($P < 0.001$) Na^+: ↑ 1.4 ± 3.1 mmol/L ($P < 0.001$) HCO_3: ↑ 2.3 ± 3.5 mmol/L ($P < 0.001$) Aldosterone: ↑ 10% ($P < 0.001$)	Primary composite: HR 1.25 (95% CI 1.09–1.44, $P = 0.001$) Death (any cause): HR 1.58 (95% CI 1.14–2.19, $P = 0.006$) CV death: NS
Dalcetrapib (Dal-OUTCOMES)	2012	$n = 15{,}871$; post ACS; LDL < 100 ng/dL (most)	↑ HDL 25–30% ↓ LDL 30% ↓ TG 9%	2.3 years; event driven; stopped by DS&MB for futility	SBP: ↑ 0.6 mmHg ($P < 0.001$) CRP: ↑ 0.2 mg/dL ($P < 0.001$) K^+: NS Na^+: NS HCO_3: NS Aldosterone: NS	Primary (CAD death, MI, stroke, CV hospitalization): NS Death (any cause): NS CV death: NS
Evacetrapib (ACCELERATE)	2017	$n = 12{,}092$; high vascular risk (ACS, CVD, PVD, DM + CAD); HDL < 80 ng/dL	↑ HDL 132% ↓ LDL 37% ↓ TG 6%	Mean 2 years, event driven; stopped for futility	SBP: ↑ 1.2 mmHg ($P < 0.001$) CRP: median ↑ 8% ($P < 0.001$) K^+: NS Na^+: NS HCO_3: NS Aldosterone: NS	Primary (CV death, MI, stroke, CV hospitalization, revascularization): NS Death (any cause): HR 0.84 (95% CI 0.70–1.00; $P = 0.04$) CV death: NS
Anacetrapib (REVEAL)	2017	$n = 30{,}449$; high vascular risk (MI, CVD, PAD, DM + CAD)	↑ HDL 104% ↓ LDL 41% ↓ TG 7%	4.1 years; pre-determined duration; completed protocol	SBP: ↑ 0.7 mmHg ($P = 0.002$) New diabetes: ↓ 11% ($P = 0.0496$) CRP: NR K^+: NR Na+: NR HCO_3: NR Aldosterone: NR	Major coronary event: HR 0.91 (95% CI 0.85–0.97; $P = 0.004$) Death (any cause): NS CV death: NS

ACS acute coronary syndrome, *CAD* coronary artery disease, *CI* confidence interval, *CRP* C-reactive protein, *CV* cardiovascular, *CVD* cardiovascular disease, *DM* diabetes mellitus, *DS&MB* data safety and monitoring board, *HDL* high-density lipoprotein, *HR* hazard ratio, *LDL* low-density lipoprotein, *MI* myocardial infarction, *NR* not reported, *NS* not significant, *PVD* peripheral vascular disease, *SBP* systolic blood pressure, *TG* triglycerides

Anacetrapib

Anacetrapib is also a potent CETP inhibitor, with dose-dependent HDL-C increasing by up to 138% and LDL-C lowering by 30–40% [32]. A large safety study provided reassuring data, again failing to demonstrate any torcetrapib-like off-target effects [33]. Importantly, it ruled out with 94% certainty that a torcetrapib-like clinical effect would be observed. In fact, a reduction in need for coronary revascularization was observed in this relatively small study. This ultimately translated to demonstration of a modest yet significant reduction in cardiovascular events in a larger trial in which patients were treated for longer than in other CETP-inhibitor programs [34]. The degree of benefit was associated with reductions in levels of non-HDL-C (but not LDL) and had no relationship with HDL-C raising; a finding that is at least partially explained by mendelian randomization data (Sect. Evidence from Mendelian Randomization). In parallel, it became increasingly apparent that, as a lipophilic molecule, anacetrapib demonstrated considerable adipose tissue accumulation, with subsequent slow release back into the circulation [35]. This ultimately resulted in a very long terminal half-life of the drug. When combined with the relatively modest clinical benefit observed in the large outcomes trial, the decision was taken to not pursue regulatory approval, and therefore anacetrapib will not come to clinical practice.

TA-8995

A third potent CETP inhibitor, TA-8995, underwent early clinical evaluation [36]. At much smaller doses than studied with the other agents, TA-8995 produced dose-dependent increases in HDL-C by up to 179% and LDL-C-lowering by up to 45%, complemented by a lack of apparent torcetrapib-associated safety signals [37]. To date, the agent has not been further developed, but these results give some sense that robust lipid changes can be observed with very small doses.

Safety

After the termination of the torcetrapib program, preclinical studies attempted to delineate the cause for harm, not only for clarity of the ILLUMINATE result but also for the entire CETP-inhibitor field. The aldosterone and hypertension effect appeared to be largely CETP independent: not only did rodents lacking CETP become hypertensive

when exposed to torcetrapib [23], but also torcetrapib placed in the tissue culture of adrenal cells stimulated the synthesis of aldosterone and cortisol [38]; findings that were not replicated with the chemically dissimilar dalcetrapib or anacetrapib [39]. Nonetheless, the subsequent trials of the remaining agents found a consistent but very modest increase in BP (~ 1 mmHg; one-fifth of the effect seen with torcetrapib). Similarly, the two trials that reported C-reactive protein found a small but statistically significant increase in those treated with CETP inhibitors (~ 0.2 ng/dL). Class effect or not, it seems unlikely these individual phenomena will independently lead to harm (e.g., no signal for intracranial hemorrhage or infection, etc.) but may instead be mitigating potential additional efficacy. If further agents come to trial, these effects may be an ongoing challenge, and, if consistent, the degree of net clinical benefit may dictate whether the drug goes to market.

Evidence from Mendelian Randomization

Genome-wide association studies consistently demonstrated a relationship between polymorphisms associated with low CETP activity and lower rates of incident cardiovascular disease [40–42]. Mendelian randomization subsequently permitted more extensive investigation of this relationship. This approach uses genotype as a natural randomization tool and demonstrated that polymorphisms associated with low CETP activity resulted in lower rates of cardiovascular disease [10, 42], with the degree of protection correlating with lower levels of ApoB [43]. This provided further evidence to suggest that it is the reduction in atherogenic lipoproteins, not HDL raising, that is likely to underscore any potential benefits of this therapeutic strategy. Further analysis demonstrated that the protection associated with genetically low CETP activity was observed in the presence of functional HMG-CoA reductase, but not in the setting of less HMG-CoA reductase activity; a phenomenon that appears proportional to ApoB rather than LDL levels. Although levels of LDL-C and ApoB tend to be highly correlated, reduction of LDL by CETP inhibition in the setting of a statin produces a discordant, attenuated reduction in ApoB level for a given LDL reduction. While this provides some plausibility to the lack of correlation between LDL reduction and events in both ACCELERATE and REVEAL, it also poses the provocative concept that CETP inhibition may be far more effective when administered as monotherapy and less effective when used in combination with statins [44]. Given that all large trials performed to date have been conducted in patients at high cardiovascular risk, background statin therapy has been expected. Whether this approach would be useful as monotherapy in lower-risk primary prevention or in patients with documented statin intolerance remains to be tested.

Cholesteryl Ester Transfer Protein Inhibition, Diabetes, and Lipoprotein(a)

The era of clinical development of CETP inhibitors has witnessed a transition of focus from increasing HDL-C to reducing atherogenic lipoprotein levels. Additional factors should also be considered with regard to their potential clinical utility. Potent CETP inhibitors have been demonstrated to lower levels of Lp(a) and therefore provide a novel approach to reducing levels of these difficult-to-treat lipid parameters [33]. No studies have evaluated the impact of CETP inhibitors specifically in patients with elevated Lp(a) levels. The trials have also consistently demonstrated that administration of CETP inhibitors appears to have a favorable impact on glycemic control. This was evidenced by reports of lower rates of new-onset diabetes [45] and improved glycemic control in patients with established diabetes at baseline [46]. It is uncertain whether this reflects a specific antidiabetic effect of CETP inhibition or the documented beneficial effect of HDL on a variety of diabetes-relevant pathways, including protection from beta-cell apoptosis, stimulation of beta-cell function, and increasing cellular glucose uptake (thereby reducing insulin resistance) [47, 48]. Whether this suggests that administration in patients with prediabetes or other settings of dysglycemia before the development of fulminant diabetes would be a more optimal cohort for future clinical trials remains to be tested.

Summary

After nearly two decades of clinical development, the early failures and subsequent lessons from both outcomes trials and genetic studies suggest that CETP inhibition may still present an alternative approach to reducing cardiovascular risk. Over the course of this era, the likely factor that may produce any clinical benefit has transitioned from the ability to raise HDL-C to lowering a range of atherogenic lipid parameters and potential benefits on glycemic control. Whether this will result in another large clinical outcomes trial, learning from the lessons provided by prior studies, is unknown. For now, the door for CETP inhibition remains slightly open; the question remains, will we walk through one more time?

Compliance with Ethical Standards

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What's New in Cardiorenal Syndrome?

Michael Darmon[1,2,3]*, Miet Schetz[4]

Cardiorenal syndrome (CRS) is a bidirectional disorder in which heart and kidney may induce or perpetuate disease in the other organ. Five subtypes reflecting the primary dysfunction and its chronicity have been described.

*Correspondence: michael.darmon@aphp.fr

[1] Medical ICU, Saint-Louis University Hospital, AP-HP, 1 Av. Claude Vellefaux, 75010 Paris, France

[2] Faculté de Médecine, Université Paris-Diderot, Sorbonne-Paris-Cité, Paris, France

[3] ECSTRA Team, Biostatistics and Clinical Epidemiology, UMR 1153 (Center of Epidemiology and Biostatistic Sorbonne Paris Cité, CRESS), INSERM, Paris, France

[4] Clinical Department and Laboratory of Intensive Care Medicine, Division of Cellular and Molecular Medicine, KU Leuven University, Herestraat 49, 3000 Louvain, Belgium

Cardiorenal syndrome (CRS) is a bidirectional disorder in which heart and kidney may induce or perpetuate disease in the other organ [1, 2]. Five subtypes reflecting the primary dysfunction and its chronicity have been described. This "what's new" paper will focus on CRS type 1 in which acute heart failure (AHF) (mostly in the setting of cardiogenic shock or acute decompensated heart failure) induces renal dysfunction and/or injury. CRS type 1 is common, may affect 25–33% of patients with AHF, and is associated with a grim prognosis [2, 3].

Definition and Pathophysiology

The pathophysiological mechanisms underlying CRS type 1 include renal hypoperfusion due to hypotension and low cardiac output, renal congestion, maladaptive activation of the renin–angiotensin–aldosterone and the sympathetic nervous system, and inflammation [1, 2]. Recent literature has shifted from low cardiac output to venous congestion (causing increased renal backpressure and compartment syndrome) as the major pathophysiological mechanism [1, 4].

Renal congestion remains difficult to identify. Hence, although unadjusted risk of AKI increases steadily with increasing central venous pressure, this relationship is linear without clear threshold [5]. Besides hemodynamic parameters of congestion, novel imaging techniques such as renal vein Doppler patterns might be useful [6]. ST2, an interleukin-1 (IL-1) receptor family member, is a new biomarker of congestion, less affected by kidney function than NT-ProBNP and may add to its diagnostic and prognostic information [7].

An important impediment that hampers the interpretation of the literature on type 1 CRS is the absence of a consensus definition. In the cardiologic literature, it is mostly described as worsening renal function (WRF) during hospitalization and treatment of AHF. The most commonly used criterion for WRF is an increase of serum creatinine of at least 0.3 mg/dL or at least 25% over the first 5 days of hospitalization which differs from the current KDIGO definition for acute kidney injury (AKI) [1]. In addition, the definition of WRF does not include AKI on admission, which is associated with mortality and cardiovascular events [8].

Significance of Worsening Renal Function and Role of Biomarkers

Since congestion is the major pathophysiological mechanism of CRS type 1, a beneficial effect of diuretics is to be expected. Benefits and feasibility of decongestion is, however, heterogeneous. In the same line, impact of decongestion on outcome is inconstant. A post hoc analysis of the DOSE trial, evaluating diuretic dosing in AHF, showed that improved renal function during decongestion therapy, rather than stable or WRF, was associated with worse outcome [9]. Similarly, others studies have shown that in the situation of successful decongestion with hemoconcentration (a surrogate of intravascular volume status), WRF has less prognostic impact than in patients with persistent congestion and absence of hemoconcentration [10]. This apparently surprising finding is partly due to confounders in serum creatinine evaluation. In the context of decongestion, serum creatinine elevation may result from mechanisms independent from decreased glomerular filtration rate (GFR) such as hemoconcentration (reducing the distribution volume of creatinine) (Fig. 1). This harmless and mostly transient renal dysfunction in the context of clinical improvement has also been called pseudo-WRF. The concept of pseudo-WRF may explain why biomarkers of tubular injury were found to be poor predictors of WRF in the setting of AHF, previous studies being liable to mix true AKI and pseudo-WRF [11, 12]. A recent study showed that during aggressive decongestion increased serum creatinine occurred in 22% of the AHF patients without increase in damage markers, further suggesting a potentially high proportion of pseudo-WRF or transient AKI due to excessive decongestion [11]. However, in the setting of WRF, damage markers may probably help in predicting outcome of renal dysfunction (Fig. 1) [13, 14].

Treatment of CRS Type 1

The search for effective treatment in CRS type 1 has been largely unsuccessful and current guidelines for AHF do not provide specific guidance for this subgroup [15]. Effective decongestion with diuretics and vasodilators remains the mainstay of the initial treatment of AHF. Signs of reduced cardiac output should trigger inotropes. Observational data suggest that vasodilators and inotropes provide similar hemodynamic decongestion and have no short-term (24 h) effect on renal function [16]. Preliminary data suggest direct renal benefit for levosimendan in heart failure, but this requires confirmation in a large randomized controlled trial (RCT) [17].

Intensifying standard therapy targeting urine output may increase the success rate without deleterious effect on kidney function [18]. However,

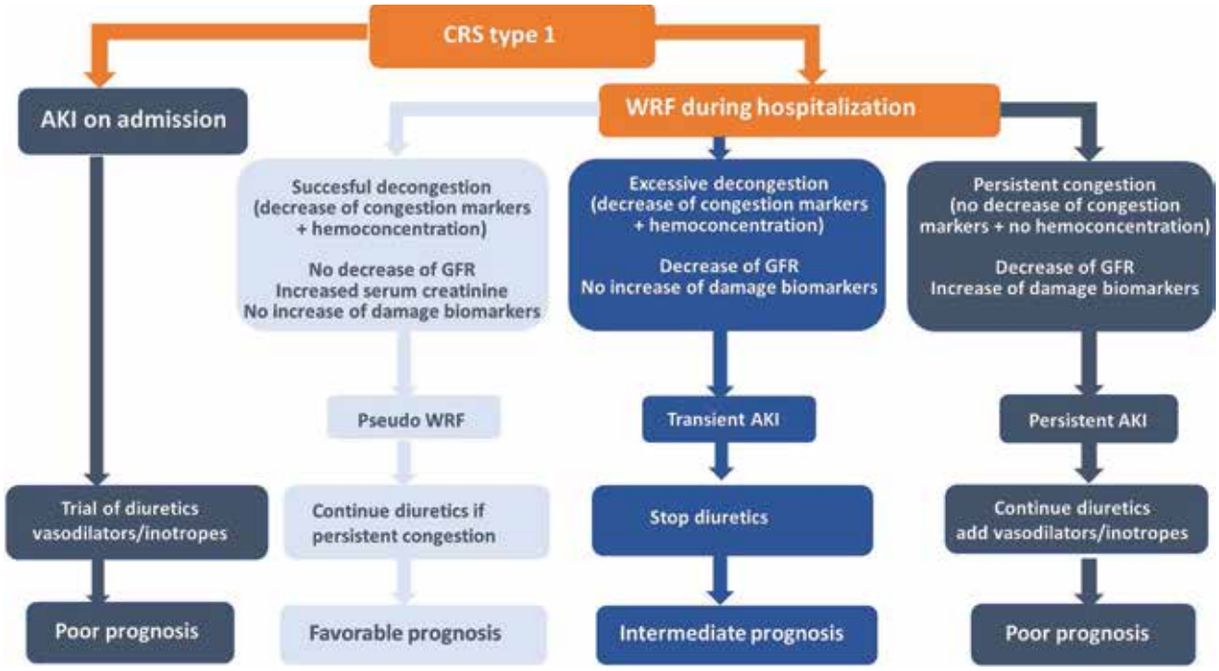

Fig. 1: Pathophysiology of different presentations of CRS type 1 with suggested treatment and prognosis. AKI on admission has poor prognosis—the prognosis of WRF during hospitalization depends on whether it concurs with successful, excessive, or unsuccessful decongestion. Treatment suggestions are provided by authors on the basis of currently perceived pathophysiology. Validity of this theoretical frame requires validation by prospective studies. AKI acute kidney injury, CRS cardiorenal syndrome, GFR glomerular filtration rate, WRF worsening of renal function

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Patient with Isolated Nocturnal Hypertension

Julian Segura

A 71-year-old, Caucasian female, diagnosed of hypertension at 52 years of age, was followed up in our centre from the age of 65 years. She was diagnosed as true resistant hypertensive and treated with four drugs, including spironolactone. A 24-h ambulatory blood pressure monitoring (ABPM) was performed, and the final diagnosis was nocturnal hypertension.

Julian Segura

Hypertension Unit, Department of Nephrology, Hospital Universitario 12 de Octubre, Madrid, Spain

Clinical Case Presentation

A 71-year-old, Caucasian female, diagnosed of hypertension at 52 years of age, was followed up in our centre from the age of 65 years. She was classified as having true resistant hypertension and treated with olmesartan 40 mg once daily (in the morning), amlodipine 10 mg once daily (in the morning), furosemide 40 mg once daily (in the morning) and spironolactone 25 mg once daily (in the morning). She attends her scheduled visits.

Family History

Her mother was hypertensive.

Clinical History

Type 2 diabetes mellitus from the age of 62 years treated with insulin and metformin.

Hypercholesterolemia treated with statin.

Physical Examination

- Weight: 87 kg
- Height: 158 cm
- Body mass index (BMI): 34.85 kg/m^2
- Waist circumference: 107 cm
- Normal cardiopulmonary auscultation
- Abdomen without findings
- Extremities with palpable distal pulses, with minimal oedema

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

Haematological Profile

- Haematocrit: 39.8%
- Haemoglobin: 12.6 g/dL
- White blood cells: 5400/mm^3
- Platelets: 210,000/mm^3

Blood Biochemistry

- Fasting plasma glucose: 180 mg/dL
- Fasting lipids: Total cholesterol: 131 mg/dL, HDL-cholesterol: 39 mg/dL, LDL-cholesterol: 62 mg/dL, triglycerides: 247 mg/dL
- Renal function: Creatinine 0.73 mg/dL, estimated glomerular filtration rate (MDRD formula) 85.6 mL/min/1.73 m^2
- Serum uric acid 6 mg/dL
- Electrolytes: Sodium 147 mEq/L, potassium 4.17 mEq/L
- Urine analysis: Albumin/creatinine ratio 25.2 mg/g
- Liver function tests: Normal
- Thyroid function tests: Normal

This case is an example of several phenotypes of hypertensive patients. Our patient shows elevated clinic BP values (Table 1) and 24-h ABPM values below 130/80 mmHg (Table 2). According to these BP values, she could be diagnosed as white-coat uncontrolled hypertension. Moreover, albeit 24-h and daytime BP are below 130/80 and 135/85 mmHg, respectively; nighttime BP is over 120/70 mmHg (Table 2 and Fig. 1). In consequence, our patient could be diagnosed as masked uncontrolled hypertension, limited to nighttime period.

Diagnosis

White-coat uncontrolled hypertension and nocturnal hypertension.

Prescriptions

Taking into account that the average of 24-h ABPM is normal, the patient does not need to increase the doses of antihypertensive medications. In reviewing the treatment regimen, we confirmed that the four drugs were administered in the morning. We recommend the patient to keep the same doses of drugs but to take the amlodipine at night. We decided to perform a second ABPM 2 months later.

Table 1: Repeated clinic BP and HR.

Systolic BP (mmHg)	Diastolic BP (mmHg)	HR (bpm)
165	77	65
162	87	72
161	80	65

Table 2: A 24-h ambulatory blood pressure monitoring.

	24-h period	Daytime period	Nighttime period
Systolic BP (mmHg)	127	124	133
Diastolic BP (mmHg)	67	66	70
HR (bpm)	69	70	65

Follow-up (2 Months)

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

The new therapeutic scheme shows an effective and sustained BP control over the 24-h period, both during daytime and nighttime periods (Table 4 and Fig. 2).

Discussion

Ambulatory blood pressure monitoring has become important in determining the total BP elevation and to distinguish between patients with both clinic and ambulatory elevated BP from those with isolated office hypertension and masked hypertension [1]. In addition to the prognostic values obtained by average 24-h BP, the relative importance of several additional ABPM-derived parameters has been addressed in clinical trials. According to these trials, absolute values of BP during activity (or daytime), sleep (or nighttime) and the night-to-day BP ratio have all been reported as important predictors of cardiovascular risk.

Threshold for nocturnal hypertension diagnosis based on ambulatory blood pressure monitoring is a nighttime average:

1. ≥120/70 mmHg
2. ≥125/75 mmHg
3. ≥130/80 mmHg
4. ≥135/85 mmHg

Threshold for the diagnosis of nocturnal hypertension based on ABPM is a nighttime average BP ≥120/70 mmHg

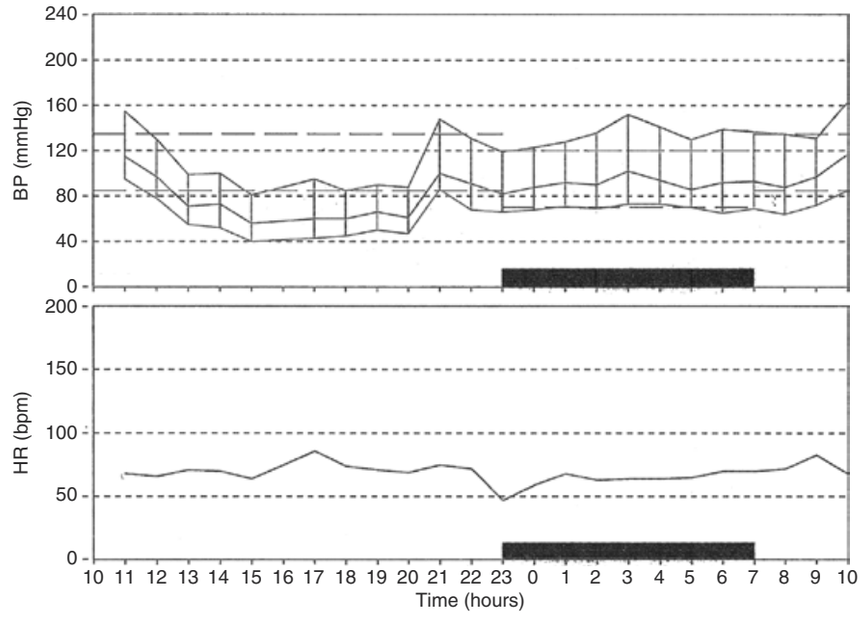

Fig. 1: A 24-h ambulatory blood pressure monitoring. *BP* arterial blood pressure, *HR* heart rate, *bpm* beats per minute, *Time (hours)*.

Table 3: Repeated clinic BP and HR.		
Systolic BP (mmHg)	**Diastolic BP (mmHg)**	**HR (bpm)**
157	83	65
144	84	66
140	81	61

Table 4: A 24-h ambulatory blood pressure monitoring.			
	24-h period	**Daytime period**	**Nighttime period**
Systolic BP (mmHg)	117	118	115
Diastolic BP (mmHg)	60	62	55
HR (bpm)	68	67	69

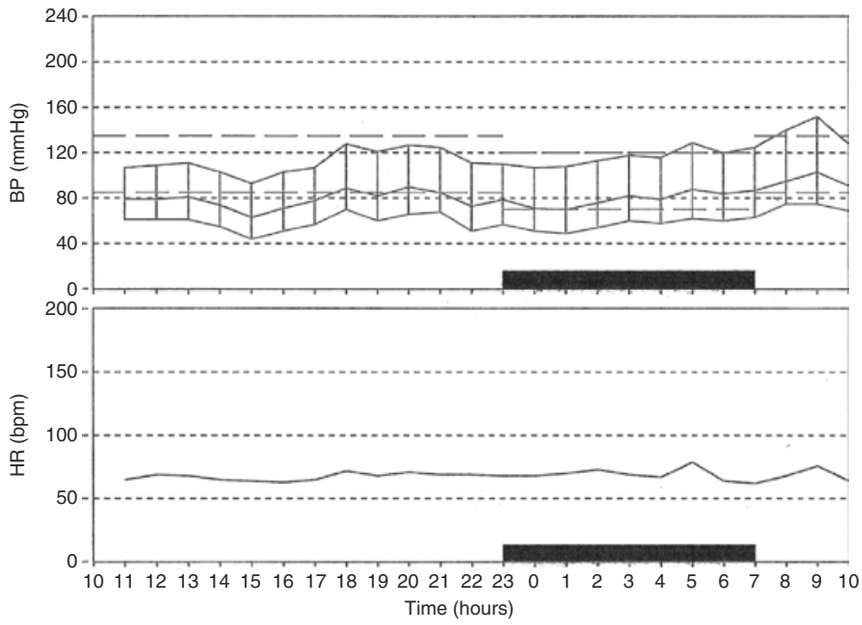

Fig. 2: A 24-h ambulatory blood pressure monitoring. *BP* arterial blood pressure, *HR* heart rate, *bpm* beats per minute, *Time (hours).*

[1]. It is generally agreed that a nocturnal BP falls more than 10% of daytime values, which correspond to a night-to-day ratio of more than 0.9 which is acceptable as an arbitrary cut-off to define patients as 'dippers' [1].

Select the correct sentence:

1. Nighttime BP is the most potent predictor of outcome.
2. Daytime BP is the most potent predictor of outcome.
3. Office BP and ABPM are similar predictors of outcome.
4. Nighttime BP is not a good predictor of outcome.

Nighttime BP is the most potent predictor of outcome. Dolan *et al.* analysed 5292 untreated hypertensive patients in a prospective study on mortality outcome. There were 646 deaths (of which 389 were due to cardiovascular events) during a median follow-up period of 8.4 years. With adjustment for gender, age, risk indices and clinic BP, higher mean values of ABPM were independent predictors for cardiovascular mortality. The relative hazard ratio for each 10 mmHg increase in systolic BP was 1.12 (1.06–1.18; $P < 0.001$) for daytime and 1.21 (1.15–1.27; $P < 0.001$) for nighttime systolic BP. The hazard ratios for each 5 mmHg increase in diastolic BP were 1.02 (0.99–1.07; P = NS) for daytime and 1.09 (1.04–1.13; $P < 0.01$) for nighttime diastolic pressures. The hazard ratios for nighttime ambulatory BP remained significant after adjustment for daytime ABPM [2]. Kikuya *et al.* described similar results in general population of a rural Japanese community, showing that nighttime BP has better prognostic value than daytime BP [3].

De la Sierra *et al.* explore the prognostic value of ABPM in real-life conditions in treated hypertensive patients, included in the Spanish ABPM Registry. A total of 2115 treated hypertensive patients with high or very high added risk were evaluated by means of office and 24-h ABPM. Cardiovascular events and mortality were assessed after a median follow-up of 4 years. Two hundred and sixty-eight patients (12.7%) experienced a primary event (nonfatal coronary or cerebrovascular event, heart failure hospitalization or cardiovascular death) and 114 died (45 from cardiovascular causes). In a multiple Cox regression model and after adjusting for baseline cardiovascular risk and office BP, nighttime systolic BP predicted cardiovascular events [hazard ratio for each SD increase, 1.45; 95% confidence interval (CI) 1.29–1.59] [4].

More recently, Banegas *et al.* analysed the associations of BP measured in the clinic and ABPM with all-cause and cardiovascular mortality in a cohort of 63,910 patients included in the Spanish ABPM Registry. During a median follow-up of 4.7 years, 3808 patients died from any cause, and 1295 of these patients died from cardiovascular causes. The association of 24-h systolic BP with all-cause and cardiovascular mortality was similar to that seen for daytime systolic pressure and nighttime systolic pressure and remained significant in multivariate adjustment that included clinic BP. These findings were consistent in subgroups defined according to age, sex, the presence or absence of obesity and status with respect to diabetes, previous cardiovascular disease and antihypertensive drug treatment. In addition, they calculated rate advancement periods to estimate the number of additional years of chronologic age that would be required to yield the equivalent mortality rate per 1-SD increase in BP as compared with

normotension. Nighttime systolic BP showed the highest rate advancement period in comparison with other BP components (10.2 and 8.4 years for all-cause and cardiovascular mortality, respectively) [5].

The cut-off to define a patient as dipper is a nocturnal fall:

1. More than 10% of daytime values
2. More than 10% of 24-h values
3. Less than 10% of daytime values
4. Less than 10% of 24-h values

Non-dipping status has also been associated with poor prognosis. Several studies have also reported an increased mortality of those with a non-dipping or a riser (higher BP during the night than during the day) patterns [6–8]. Data from the Spanish ABPM Registry showed that in untreated patients, 59.1% had nocturnal systolic BP <120 mmHg, whereas the remaining 40.9% had nocturnal hypertension (SBP ≥120 mmHg). A normal dipping pattern (nocturnal systolic BP decline >10%) was observed in 55.5% untreated patients, whereas the remaining 44.5% were considered non-dippers (nocturnal systolic BP decline ≤10%). Among treated patients, prevalence of nocturnal hypertension was 49.8%, and non-dipping was present in 57.2% [9].

There has been relatively little study into the benefits of therapeutic modification of nocturnal patterns. However, there is overall agreement that the reduction of nocturnal hypertension should be a therapeutic objective, in order to achieve effective BP control over the entire 24-h period [1].

Take-home Messages

- Nighttime BP is the most potent predictor of cardiovascular outcome.
- Prevalence of nocturnal hypertension is around 40% in untreated patients and close to 50% in treated hypertensive.
- There is overall agreement that the reduction of nocturnal hypertension should be a therapeutic objective, in order to achieve BP control over the entire 24-h period.

References available on request Healthcare.India@springer.com

Source: Segura J. (2019) Patient with Isolated Nocturnal Hypertension. In: Hypertension and 24-hour Ambulatory Blood Pressure Monitoring. Practical Case Studies in Hypertension Management. Springer, Cham. https://doi.org/10.1007/978-3-030-02741-4_4.

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determining the efficacy of decongestion may be difficult and pseudo-WRF is likely to trigger potentially inappropriate discontinuation of treatment. Promising parameters that may guide decongestion therapy are numerous but poorly studied and include kidney damage markers [13], clinical and biochemical markers of congestion, such as BNP or the previously mentioned ST-2 [7], clinical signs of hypoperfusion, urine output or diuretic responsiveness, weight loss, and hemoconcentration. In this line, decongestion along with real-time monitoring of glomerular filtration, not yet available in clinical practice, might avoid unnecessary and potentially deleterious therapeutic changes. Although multimodal evaluation using these parameters seems promising in optimizing decongestive therapy, prospective validation of this concept is lacking [10].

In case of diuretic resistance ultrafiltration should be considered, although the most recent trial failed to show renal benefit and even suggested harm in comparison with standard treatment.

New treatments targeting congestion and neurohormonal activation in AHF such as nesiritide, tolvaptan, rolofylline, ularitide, and serelaxin did not pass the test of the large RCT (references in supplement). Valsartan/sacubitril, a combination of an angiotensin receptor blocker (ARB) and a neprilysin inhibitor, has shown decreased mortality and improved kidney outcomes compared with enalapril and is likely to revolutionize the treatment of chronic heart failure with reduced ejection fraction [19]. Its place in the management of AHF is, however, unclear, 20% of the patients in the run-in phase being unable to tolerate the drug because of hypotension.

In the absence of a clear panacea for the management of CRS type 1, timely introduction and optimization of treatments according to recent guidelines remains the best available option [15]. Future developments should include uniform criteria for the diagnosis of CRS, along with implementation and validation of strategies based on reliable parameters allowing distinction of pseudo-WRF from renal dysfunction.

Abbreviations: AHF: Acute heart failure; AKI: Acute kidney injury; CRS: Cardiorenal syndrome; GFR: Glomerular filtration rate; WRF: Worsening renal function

Compliance with ethical standards

Conflicts of interest: None to declare.

Source: Darmon, M. & Schetz, M. Intensive Care Med (2018) 44: 908. https://doi.org/10.1007/s00134-018-5190-0.

What's New in the ESC 2018 Guidelines for Arterial Hypertension

The ten most important messages

Jutta Bergler-Klein

The new guidelines on hypertension of the European Society of Cardiology (ESC) 2018 have refined the treatment cut-offs and therapy decisions in adults. This review highlights important recommendations of the guidelines and also on the situation of hypertension in Austria. The general treatment targets of blood pressure have been lowered to at least 130/80 mmHg for most patients.

Univ. Prof. J. Bergler-Klein, MD, FESC(✉)

Department of Cardiology, Medical University of Vienna, Waehringer Guertel 19–20, 1090 Vienna, Austria

jutta.bergler-klein@meduniwien.ac.at

The new 2018 guidelines on hypertension of the European Society of Cardiology (ESC) have refined the treatment cut-offs and therapy decision-making in adults [1]. This review focuses on the most important messages and also on the situation in Austria.

Ten Most Important Messages

1. What is defined as hypertension?

The definition of hypertension is now specified as a constant, repeated systolic blood pressure (SBP) in the office of ≥140 mm Hg and or diastolic BP (DBP) ≥90 mm Hg. Before office determination patients should be seated quietly for 5 min.

A 24-h ambulatory BP (ABPM) is strongly encouraged in all patients for screening and diagnosis of hypertension. It is important to note that in ABPM a lower value with an average of ≥130/80 mm Hg is already defined as hypertension. For home BP monitoring, an average value of ≥135/85 mm Hg is now defined. These values enable patients and physicians to choose from the available diagnostic tools; however, the different cut-offs for the definitions should be considered. It also empowers patients and their own responsibility by home measurements to detect and monitor hypertension.

2. Target range for blood pressure treatment

The general treatment targets of BP have been lowered to at least 130/80 mmHg for almost all patients. This is in line with the recommendations of the American ACC/AHA guidelines for hypertension [2]. In all patients that can tolerate treatment, the office SBP should be lowered to <140 mm Hg. Office diastolic BP should in general be lowered to <80 mm Hg. In patients younger than 65 years old, office systolic BP lower than 130 mm Hg should be aimed for, but not below 120 mm Hg. In older patients over 65 years, and in old patients up to age 80 years who are capable of an independent lifestyle and are not frail, a target SBP of 130 mm Hg but not below 130 mm Hg is recommended. In old patients over 80 years, treatment should generally be initiated in an office SBP ≥160 mm Hg. In frail patients individual decisions with gentle reductions are advised according to the benefit expectations of treatment. Importantly, the lower thresholds for BP treatment are now also clearly defined. Systolic BP should not be lowered to below 120 mm Hg. Diastolic BP should not be lowered to below 70 mm Hg. Therefore, clear target ranges have now been defined with lower BP cut-offs where antihypertensive treatment should not go beyond these values. When starting antihypertensive drugs, the first objective should be to lower BP to <140/90 mm Hg in all patients. If the treatment is then well-tolerated, BP should be targeted to 130/80 mm Hg or lower in most patients; however, treated SBP should not be targeted to <120 mm Hg as stated above and DBP not below 70 mm Hg.

3. Grading of degree of hypertension

The degree of hypertension (grades 1–3) determines the initiation of treatment and the individual cardiovascular risk of the patient. Fig. 1 depicts the grades according to BP levels.

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

Fig. 1: Staging of hypertension according to blood pressure and cardiovascular risk by the SCORE system [1]. *CKD* chronic kidney disease, *CV* cardiovascular, *DBP* diastolic blood pressure, *HMOD* hypertension-mediated organ damage, *SBP* systolic blood pressure, *SCORE* Systematic COronary Risk Evaluation. Source and © [3]. Reproduced by permission of Oxford University Press on behalf of the European Society of Cardiology. www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Arterial-Hypertension-Management-of. This figure is not included under the Creative Commons CC BY license of this publication.

4. Treatment initiation: cut-offs revisited in high or low risk

Whether pharmaceutical treatment should be initiated immediately or after a delay with lifestyle interventions is focused on high or low cardiovascular risk of the patients (Fig. 2).

In lower risk patients with grade 1 hypertension (defined as office BP 140–159/90–99 mmHg, see Fig. 1) and without end organ damage aged up to 80 years, treatment should be started after a trial of lifestyle changes, eg for 3–6 months. On the other hand, for high risk patients with grade 1 hypertension (140–159/90–99 mmHg) medical drug therapy should be initiated immediately without delay. Patients with grade 2 (160–179/100–109 mm Hg) or grade 3 hypertension (≥180/≥110 mm Hg) should receive immediate antihypertensive drug treatment along with lifestyle intervention. Lifestyle changes are enforced in the current guidelines,

The degree of hypertension (grades 1–3) determines the initiation of treatment and the individual cardiovascular risk of the patient.

whether before begin as well as always during ongoing medical treatment. They include smoking cessation, weight loss, sodium restriction, moderation of alcohol, exercising, and healthy food with high amounts of vegetables and fruits.

5. Sodium restriction, alcohol

A maximum sodium intake of 2.0 g per day (about 5.0 g salt, one small teaspoon) in the general population and in all hypertensive patients is now recommended. Adding salt and processed foods with hidden salt should be avoided, as they involve 80% of salt consumption. The BP lowering effect of sodium restriction is endorsed as greater in black patients and in older patients and concomitant diabetes or chronic kidney disease. Importantly, sodium restriction may reduce the necessary number or dose of antihypertensive drugs. For cardiovascular event reduction, a controversial J-shaped curve for sodium intake has been suggested in meta-analyses [4]. Overall, lowering the sodium intake is targeted at patients with manifested hypertension. In hypertensive men, alcoholic drinks should be limited to 14 units per week, in women to 8 units per week (1 unit corresponds to 1/8 l of wine or 1/4 l of beer). Alcohol-free days

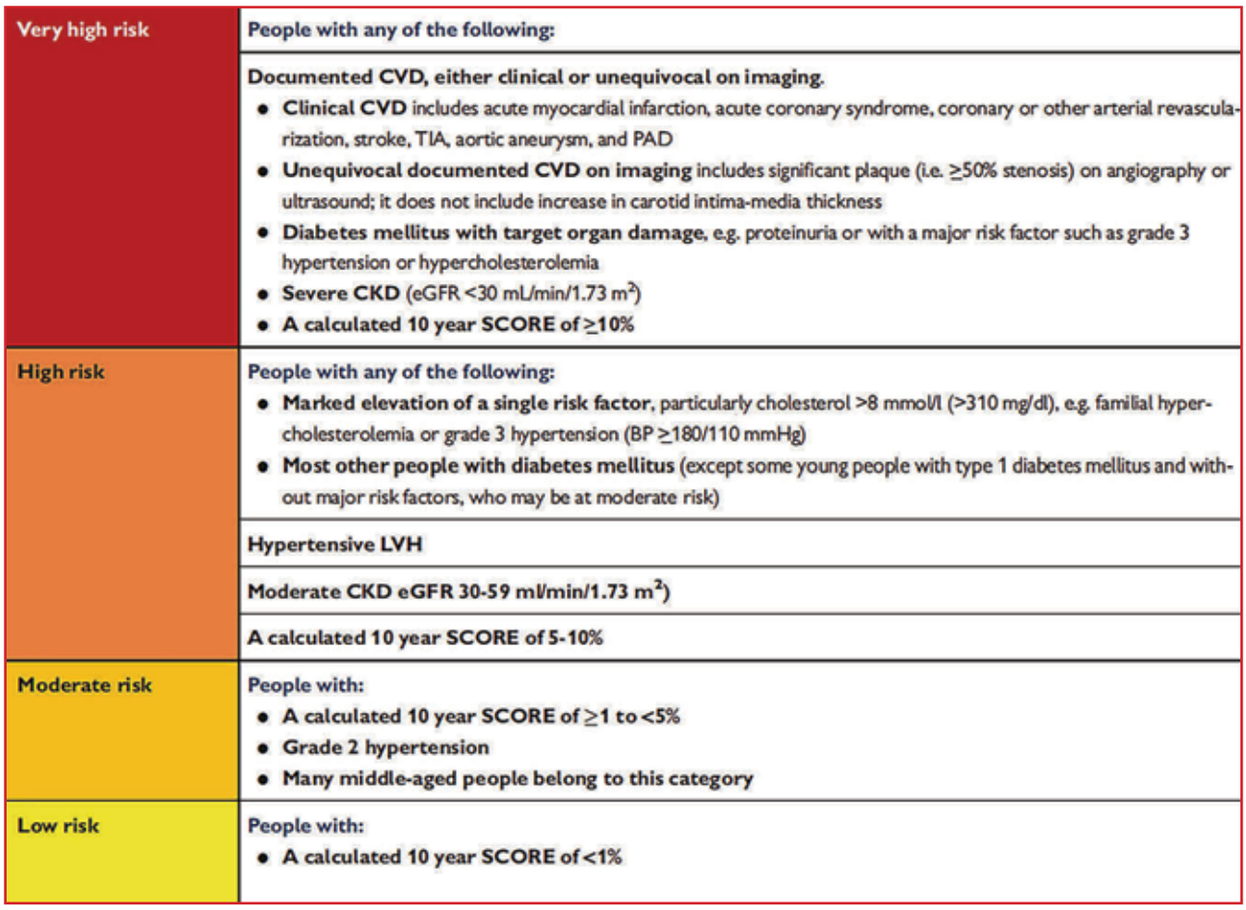

Fig. 2: The 10-year cardiovascular risk categories by the European Systematic COronary Risk Evaluation system (SCORE) [1]. Source and © [3]. Reproduced by permission of Oxford University Press on behalf of the European Society of Cardiology. www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Arterial-Hypertension-Management-of. This figure is not included under the Creative Commons CC BY license of this publication.

during the week and avoidance of binge drinking are advised.

6. Two in one approach: single pill dual drug from the start

The new guidelines emphasize that medical treatment should in general be started straight away with a combination pill of two drugs as usual care. In most patients the currently recommended lower BP targets will not be reached without modern dual therapy. Furthermore, a single pill approach with optimal retardation drug formulation for a long plasma half-life will increase the medical adherence of the patients. If BP targets are not reached, augmenting to a single pill with 3 drugs is preferred.

7. Simplified drug algorithm

For most patients, a combination of a renin-angiotensin system (RAS) blocker, either an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), with a calcium channel blocker (CCB) or thiazide/thiazide-like diuretic (TH) such as chlorthalidone and indapamide is preferred as initial therapy. If three drugs are required to lower BP to targets, a combination of an ACEI or ARB with a CCB and a TH-diuretic are the right choice, again in a single pill combination. Beta-blockers are only recommended in specific indications such as angina, after myocardial infarction, heart failure with reduced ejection fraction or heart rate control in arrhythmias. Beta-blockers should be combined with any of the other major antihypertensive drug classes (RAS blockers, CCB, diuretics). A combination of two RAS blockers (ACEI and ARB) is not recommended. In resistant hypertension, especially the addition of spironolactone (25–50 mg o.d.) is recommended. Also, another diuretic, an alpha-blocker or beta-blocker can be added. Hypertension is defined as resistant when the recommended treatment fails to lower office SBP and DBP to <140 mm Hg and/or <90 mm Hg, respectively and is confirmed by 24-h ABPM or home BP measurements despite confirmed drug adherence. Optimal doses of tolerated drugs and three or more drugs are recommended along with lifestyle changes. Secondary causes of hypertension should be excluded. BP resistance can be mimicked by severe brachial artery calcification, white coat hypertension, wrong measurements, eg with too small cuffs, and of course a lack of patient therapy compliance.

8. Special considerations in special groups

Treatment thresholds of office BP are defined as ≥140/≥90 mm Hg and are the same in hypertensive patients with additional diabetes, coronary artery disease (CAD), chronic kidney disease (CKD), stroke or transient ischemic attack (TIA); however, in very high-risk patients with CAD, previous stroke or TIA, treatment may be considered already

in high-normal SBP of 130–<140 mm Hg. In patients older than 80 years, a threshold of ≥160/≥90 mm Hg is advised for all groups, equally in diabetes, CAD, CKD or stroke.

Coronary disease

In CAD, diastolic BP should not be lowered <70 mm Hg as myocardial perfusion may be impaired in lower values [5]. In CAD, treatment is already recommended at the threshold of high-normal BP of 130–139/85–89 mm Hg, as these patients are considered to be at very high risk.

Diabetes

For patients with diabetes, the same treatment targets are recommended for an office SBP target of 130 mm Hg or lower. SBP should not be lowered to <120 mm Hg. DBP target should be <80 mm Hg. In older patients ≥65 years the SBP target range is 130–140 mm Hg if tolerated. A variable visit to visit BP should be noted due to associated increased cardiovascular and renal risk. Caution is emphasized in autonomic polyneuropathy concerning postural or orthostatic hypotension. Nocturnal BP should be assessed by 24-h ABPM or in order to detect hypertension in apparently normotensive diabetic patients.

Chronic kidney disease

The RAS blockers (ACEI or ARB) are endorsed as more effective in reducing albuminuria than other antihypertensive drugs. The guidelines recommend a RAS blocker and CCB as the initial regimen drugs. In both diabetic or non-diabetic CKD, the SBP target is 130–139 mm Hg. Individualized treatment is advocated according to electrolytes. The use of loop diuretics is recommended when the estimated glomerular filtration rate (eGFR) is <30 ml/min/1.72 m^2, as thiazide/thiazide-like diuretics are less effective or ineffective at this level. There is risk of hyperkalemia with spironolactone, especially when eGFR is <45 ml/min/1.72 m^2 or baseline K^+ ≥4.5 mmol/l.

Heart failure

In hypertensive patients with preserved or reduced ejection fraction (EF), antihypertensive treatment should be considered if BP ≥140/≥90 mm Hg. If antihypertensive treatment is not needed, the treatment of heart failure (HF) should follow the current ESC HF guidelines [6]. In HF with reduced EF the initial antihypertensive regimen advocates an ACEI or ARB (or angiotensin receptor/neprilysin inhibitor as indicated by guidelines) plus a TH-diuretic (or loop diuretic in edema), plus a beta-blocker. The second step adds the mineralocorticoid receptor antagonists spironolactone or eplerenone. It is emphasized not to use non-dihydropyridine CCBs, such as verapamil or diltiazem. Although in general, actively lowering the BP below 120/70 mm Hg should be avoided, patients may achieve lower values due to HF guideline-directed medications, which if tolerated should be continued.

A single pill prescription with two or more drug ingredients is now confirmed as usual care when initiating antihypertensive treatment right from the start.

Pregnancy

For pregnant women the special considerations are outlined in the new pregnancy guidelines in cardiovascular disease [7]. It is important to follow the compelling contraindications of specific antihypertensive drugs, especially ACEI and ARBs in pregnancy. Beta-blockers may be considered alternatively in women planning pregnancy or already pregnant, although fetal and neonatal bradycardia have been described.

Hypertension is defined as office values of SBP ≥140 mm Hg and/or DBP ≥90 mm Hg. The classification of hypertension in pregnancy is mild if BP is 140–159/90–109 mm Hg, and severe if ≥160/110 mm Hg [1, 7]. The different entities include pre-existing hypertension, gestational hypertension, pre-existing plus superimposed gestational hypertension with proteinuria, pre-eclampsia and antenatally unclassifiable hypertension. All pregnant women should be screened for proteinuria early to detect renal disease and in the second half of pregnancy for diagnosis of pre-eclampsia.

9. What else for risk reduction?

Statins should in general be prescribed in hypertensive patients with established coronary disease or in moderate to high cardiovascular risk by SCORE evaluation (Fig. 2) but are also recommended already in low to moderate risk. Low dose aspirin is not recommended for primary prevention in patients without cardiovascular disease. Antiplatelet therapy is indicated in hypertensive patients for secondary prevention, eg after myocardial infarction or stent intervention.

10. Renal denervation not recommended

The use of device-based interventions such as carotid baroreceptor stimulation with pulse generator or baroreflex amplification stent device implantation, as well as catheter-based renal denervation for reduction of sympathetic tone is not recommended for the routine treatment of hypertension. Currently, not enough evidence for efficacy and safety is considered to be available.

Discussion

The new ESC guidelines have lowered the treatment target to a BP of 130/80 mm Hg. The definition of hypertension is set at systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg. This has caused some

discussion, although the guidelines clearly aim at especially lowering the high-risk profiles of patients with concomitant cardiovascular diseases, eg coronary disease or diabetes [8].

Importantly, the new guidelines have also introduced lower BP thresholds, below which treatment should not be continued, in general SBP 120 mm Hg as lower systolic threshold. Therefore, the current ESC guidelines have defined clear BP target ranges: SBP of 120–130 mm Hg in patients younger than 65 years old and 130–139 mm Hg in those older than 65 years and even over age 80 years if tolerated. Diastolic BP should not be lowered below 70 mm Hg. Therefore, the diastolic target range is now 70–79 mm Hg in all patients. It has been realized that excessive BP lowering causes more adverse events and higher discontinuation rates by patients [9]. A dilemma in hypertension treatment remains in discrepancy of systolic or diastolic hypertensive BP values, as both components cannot be regulated independently in some patients [8].

A single pill prescription with two or more drug ingredients is now confirmed as usual care when initiating antihypertensive treatment right from the start. This regimen will increase patient compliance and reduce side effects, as a relatively lower dosage of individual drugs may be applied with better galenics. Beta-blockers are now only recommended in special situations, eg after myocardial infarction, reduced ejection fraction heart failure and arrhythmias.

Austrian Perspective

A wider use of out of office measurements is now recommended. Ambulatory 24-h BP measurement is useful to demask nocturnal hypertension and lack of adequate dipping. In Austria, ABPM is not reimbursed by all public healthcare systems so far and will need to be established further. The salt consumption should be reduced in the majority of patients. The usual consumption of sodium is 3.5–5.5 g per day (9–12 g of salt), depending on country or region. In Austria, half of the adults consume more than 2 teaspoons of salt per day [10]. There is a causal relationship between the pressor effect of excessive sodium intake >5 g per day and an increased prevalence of hypertension and SBP rise with age [11]. In Austria as in other European countries the food industry must be involved in the future in the attempt to decrease hidden sodium consumption.

High altitudes above 3000 m and possibly 2000 m may contribute to aggravation of hypertension, which must be considered especially in the alpine regions of Austria [1, 12]. Frequent BP measurements and intensified antihypertensive medication adaptation are recommended, eg during holidays in mountain areas.

Conclusion

The new ESC guidelines have clearly defined therapeutic targets with lower thresholds. In most patients a BP goal of at least 130/80 mm Hg is recommended, but not below 120/70 mm Hg. Lifestyle interventions are enforced in all stages of hypertension.

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References available on request
Healthcare.India@springer.com

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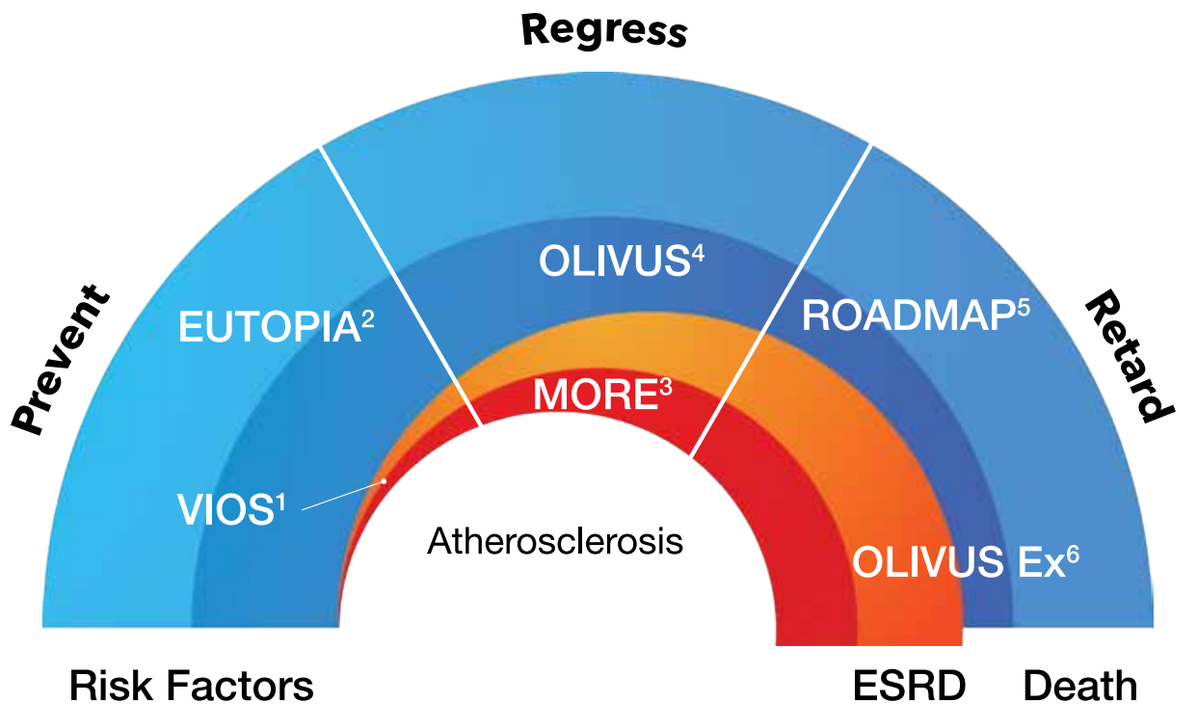

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