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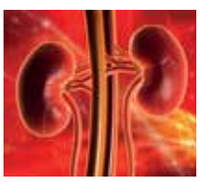

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Mobile Health Technologies for Older Adults with Cardiovascular Disease: Current Evidence and Future Directions

Advances in digital health and mobile technologies may help clinicians and patients prevent and treat cardiovascular disease. The current study documents the most promising areas of mobile health (mHealth) use in cardiovascular disease, current barriers to mHealth adoption in older adults, and future directions of mHealth utilization that may increase engagement in this population.

Mobile health technologies are being rapidly adopted as smartphones and wearable biometric devices enable increasingly sophisticated health monitoring. Cardiovascular disease management is particularly conducive to mobile health utilization, as many mobile platforms currently support software capable of sophisticated cardiovascular

data collection. While cardiovascular disease most commonly affects older adults, these individuals also have the greatest barriers to mHealth adoption, limiting the potential for current technologies to achieve benefit.

Recent studies investigating mHealth interventions for older adults with cardiovascular disease have yielded mixed results. More work is needed to create engaging mHealth platforms that provide the necessary level of support to create sustained behavioral change. Addressing specific motivational, physical, and cognitive barriers to mHealth adoption among older adults may increase utilization of future interventions.

Source: Searcy R.P., Summapund J., Estrin D., et al. Mobile health technologies for older adults with cardiovascular disease: current evidence and future directions. Curr Geri Rep. 2019;8(1):31–42. DOI 10.1007/s13670-019-0270-8. © Springer Science+Business Media, LLC, part of Springer Nature 2019.

The Predictive Value of the Renal Resistive Index for Contrast-induced Nephropathy in Patients with Acute Coronary Syndrome

Percutaneous coronary intervention (PCI) has been associated with contrast-induced nephropathy (CIN) at a rate that varies depending on the patient's risk factors. The researchers conducted a study to evaluate the predictive value of the renal resistive index (RRI) for CIN in patients with acute coronary syndrome (ACS) undergoing PCI.

The team enrolled 146 consecutive patients with ACS in this study. Renal Doppler ultrasound examinations to measure RRI were performed pre-PCI and at 1 h and 24 h after PCI. The primary endpoint was CIN, defined as a relative (≥25%) or absolute (≥0.5 mg/dL; 44 µmol/L) increase in serum creatinine from baseline within 48 h after contrast exposure.

Contrast-induced nephropathy was identified in 31 patients (21.2%); however, none of the patients required

haemodialysis. Compared to patients without CIN, higher RRIs were observed at 1 h (0.71 ± 0.05 vs. 0.65 ± 0.06, $p < 0.05$) and 24 h (0.70 ± 0.05 vs. 0.66 ± 0.06, $p < 0.05$) post-procedure in patients with CIN. The RRI rose transiently from baseline (0.68 ± 0.05) to 1 h (0.71 ± 0.05) and then tended to decline at 24 h (0.70 ± 0.05). A receiver operating characteristic curve analysis showed that the pre-procedure RRI was a powerful predictive indicator of CIN (area under the curve = 0.661, $p = 0.006$). The best cutoff value was 0.69 with 67.7% sensitivity and 67% specificity. Besides hyperuricemia and chronic kidney disease, the multivariate logistic regression analysis revealed that a high baseline RRI (≥0.69) was a significant predictor of CIN (odds ratio = 4.445; 95% confidence interval: 1.806–10.937; $p = 0.001$).

A high pre-procedural RRI appears to be independently predictive of CIN in patients with ACS undergoing PCI.

Source: Zheng-rong Xu, Jun Chen, Yuan-hui Liu, Yong Liu, Ning Tan. The predictive value of the renal resistive index for contrast-induced nephropathy in patients with acute coronary syndrome. BMC Cardiovasc Disord. 2019;19:36. DOI 10.1186/s12872-019-1017-3. © The Author(s). 2019.

Congenital Heart Disease in India: A Status Report

Anita Saxena

Considering a birth prevalence of congenital heart disease as 9/1000, the estimated number of children born with congenital heart disease in India is more than 200,000 per year. Of these, about one-fifth are likely to have serious defect, requiring an intervention in the first year of life. Currently advanced cardiac care is available to only a minority of such children.

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Congenital heart disease (CHD) is the most frequently occurring congenital disorder, responsible for 28% of all congenital birth defects [1]. The birth prevalence of CHD is reported to be 8-12/1000 live births [2,3]. Considering a rate of 9/1000, about 1.35 million babies are born with CHD each year globally [4].

With rapid advances in diagnosis and treatment of CHD, vast majority of children born with CHD in high-income countries reach adulthood. However, this is not the case for children born in low- and middle-income countries (LMIC) as such advanced care is not available for all children. Considering a birth prevalence as 9/1000, the estimated number of children born with CHD every year in India approximates 240,000, posing a tremendous challenge for the families, society and health care system. This article discusses the current state of cardiac care available to children with CHD and how it has changed over last decade [5].

Epidemiology

The birth prevalence of severe CHD has been consistently reported as 1.5-1.7/1000 live births [3, 6, 7]. Use of echocardiography is associated with higher birth prevalence as many milder cases are also detected [6-8]. Similarly, hospital-based data is unlikely to be representative of community prevalence in LMIC where a substantial proportion of births occur at home. Critical CHD, especially those dependent on patency of ductus arteriosus, may go undiagnosed in these settings.

Most studies reported from India are on prevalence at a given point of time, and not on prevalence at birth. Many reported studies are based on data from pediatric patients reporting to hospitals leading to a possible sampling bias [9-14]. The profile of patients with CHD that present to health care facilities in LMIC is largely determined by the natural history of individual conditions. A high attrition of patients with serious CHD results in low frequency of these lesions encountered in hospital settings, and may contribute to the prevailing perceptions on their rarity.

The true incidence or birth prevalence has been reported only in few studies from India, which also include only babies born in the hospital (Table I) [15-18]. In two of these studies, echocardiography was performed for all newborns. The birth prevalence of CHD in these studies was higher in comparison to data available from other countries. Several other studies have reported the prevalence of CHD during childhood, and, it varies from to 9.2/1000 population (Table II) [19-27]. The wide variation is partly explained by population studied and the diagnostic method used for evaluation.

Current Status of Care in India

The issue of pediatric cardiac care in India has been discussed earlier [28,29]. Gross disparity exists between high-income countries and LMIC as far as care of children with CHD is concerned. Whereas one cardiac center caters to a population of 120,000 in North America, 16 million population is served by one center in Asia [30]. Similarly, the number of cardiac surgeons is also much more in North America and Europe (one cardiac surgeon per 3.5 million population) as compared to Asia (one cardiac surgeon per 25 million population) [3]. Of the 240,000 children born with CHD each year in India, about one fifth would need early intervention to survive the first year of life. A large pool of older infants and children who may have survived despite no intervention add to the burden of CHD.

Most studies reported from India are on prevalence at a given point of time, and not on prevalence at birth. Many reported studies are based on data from pediatric patients reporting to hospitals leading to a possible sampling bias.

Status of Care for Serious CHD

A number of cardiac care centers have come up in India over the last decade. The total number approximates to 63; ten of these can be considered high volume centers (more than 500 cardiac surgeries per year). As per data provided by all large and medium volume centers and a majority of small volume centers, a total of approximately 27,000 patients with CHD underwent cardiac surgery over a one-year period (2016-2017). Of this, about 9,700 patients were infants (<1 year), and about 1700 were neonates (<1 month). Considering the birth prevalence of serious CHD (requiring intervention in first year of life) as 1.6/1000 live births, about 43,000 babies are born in India every year with serious CHD, of which only about one-fourth seem to be receiving optimal cardiac care. This proportion, though still very low, is much better when compared with similar projections from India a decade ago [5,31]. These data suggest that pediatric cardiac care is gradually improving in India; although, we still have a long way to go.

Regional Variations

There is marked regional variations in the population and crude birth rates in various parts of India. The total number of births are much higher in Northern and Eastern parts of India (Delhi, Jammu and Kashmir, Punjab, Haryana, Himachal Pradesh, Rajasthan, Uttar Pradesh, Uttarakhand, Bihar, Jharkhand, Orissa and West Bengal) as compared to rest of four regions (Southern, Western, Central and North-East). Consequently, the total number of babies born with CHD are likely to be much more in regions with high birth rates (Fig. 1).

Based on the information provided by 47 centers in India, there is a clear

Table I: Birth prevalence of congenital heart disease in India.

Author [Ref.]	No. screened	Screening method	No. with CHD	Prevalence/1000 live births
Khalil, *et al*. [15]	10964	Clinical examination only	43	3.9
Vaidyanathan, *et al*. [16]	5487	Clinical, pulse oximetry,	Minor*:	Minor CHD*: 74.4 at
		echocardiography in all cases	408 at birth 119 at	birth 21.7 at 6 weeks
			6 weeks Major**: 17	Major CHD**: 3.1
Sawant, *et al*. [17]	2636	Clinical; echocardiography in	35	13.3
		suspected cases only		
Saxena, *et al*. [18]	20307	Clinical, pulse oximetry, echocardiography in all cases	Significant#: 164 Major##: 71 Major##: 4.5/1000	Significant#: 8.1 (95% CI 6.94; 9.40)

CHD: congenital heart disease; *Those which are likely to normalize by 6 weeks and include; atrial septal defect >5 mm, patent ductus arteriosus >2 mm with left ventricular volume overload, ventricular septal defect with gradient of >30 mmHg, aortic stenosis/pulmonic stenosis with gradients of <25 mmHg and pulmonary artery branch stenosis with gradients of <20 mmHg; **CHD that is likely to require early intervention; #atrial septal defect >5 mm, patent ductus arteriosus >2 mm with left ventricle volume overload, restrictive VSD, and valvular aortic/pulmonary stenosis with gradients <25 mmHg (in addition to Major CHD); ##any CHD that is likely to require intervention within the first year, including newborns with critical CHD that require intervention within the first 4 weeks of life.

Table II: Prevalence of congenital heart disease in children beyond neonatal age.

Author [Ref.]	Age group (y)	Setting	Place of study	Total no.	Screening method	No. with CHD	Prevalence per 1000
Gupta, *et al*. 1992 [19]	6-16	Community	Jammu	10263	Clinical	8	0.8
Vashishtha, *et al*. 1993 [20]	5-15	School	Agra	8449	Clinical	44	5.2
Thakur, *et al*. 1995 [21]	5-16	School	Shimla	15080	Clinical	30	2.25
Chadha, *et al*. 2001 [22]	<15	Community	Delhi	11833	Clinical	50	4.2
Misra, *et al*. 2009 [23]	4-18	School	Eastern Uttar Pradesh	118212	Clinical echo for suspected cases only	42	1.3
Kumari, *et al*. 2013 [24]	5-16	School	Dist. Prakasam, Andhra Pradesh	4213	Clinical and echo in all	39	9.2
Saxena, *et al*. 2013 [25]	5-15	School	Ballabgarh, Haryana	14716	Clinical clinical and echo	3577	2.37 5.23
Bhardwaj, *et al*. 2016 [26]	All age groups 19.5 y	Community	Himachal Pradesh	1882 (<18 y: 660)	Clinical echo for suspected cases only	12	6.312.95 (in <18 y)
Nisale, *et al*. 2016 [27]	1st to 10th class	School	Latur, Maharashtra	3,53,761	Clinical echo for suspected cases only	143	0.4

paradox as many centers are located in regions with lower burden of CHD. When considering the critical CHD (requiring intervention in first year of life), the Southern and Western states of India have fared much better than other regions (Fig. 2). On the contrary, states such as Uttar Pradesh, Bihar, Jharkhand and Madhya Pradesh, which presumably have much higher CHD burden as compared to the rest of states, have fared much worse. The data suggest that children born with serious CHD in Southern India have a 70% chance of receiving good cardiac care even if we consider that some of the children operated in these centers are from other parts of India. In contrast, babies born in Eastern and Central parts of India have a much lower chance of receiving an intervention. This status may soon change as the pediatric cardiac care centers start within the campuses of newly opened government institutes (All India Institute of Medical Sciences). These institutes are already operational in various states, including those in Eastern, Central and Northern parts of India. Currently, the number of congenital heart surgeries is less in these institutes, especially for neonates and infants.

Obstacles to Pediatric Cardiac Care in India

Lack of awareness and delay in diagnosis: A substantial proportion of births in India occur at home, and the infant is likely to die before the critical, ductus-dependent CHD is diagnosed. Fortunately, the rate of hospital deliveries have significantly increased due to several incentivized schemes by the Government of India. Ductus-dependent CHD may still escape detection as babies are often discharged earlier. Pre-discharge screening of newborns by pulse oximetry, which may pick up these CHDs, is often not practiced, especially in rural and semi-urban centers. Frontline health workers and primary caregivers are not sensitized to the problem of CHD and a number of them believe that a child with CHD is doomed and will never be able to lead a fruitful life, even if intervened. Delay in referral results in poor outcomes as complications and co-morbidities (such as under-nutrition) may have already set in.

Maldistribution of resources: The resources for treatment of CHD are not only inadequate but also seriously mal-distributed. As mentioned earlier, the

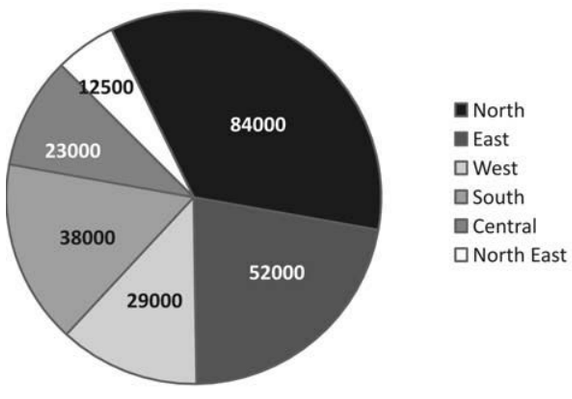


Fig. 1: Regional distribution of infants born with CHD in India every year (see color figure at website).

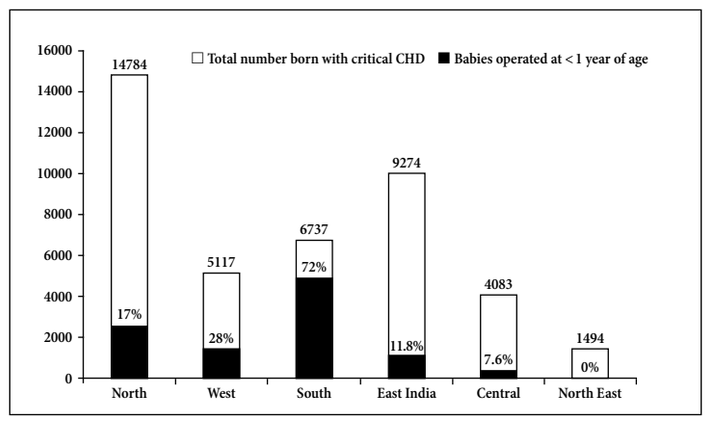


Fig. 2: Regional distribution of infants with critical heart disease accessing surgery as compared to total number born with critical heart disease.

geographical distribution of these centers is very uneven. Poverty, which is the greatest barrier to successful treatment of CHD is more common in states with little or no cardiac care facilities. Transport of newborns and infants with CHD is another neglected issue in India. There is practically no organized system for safe transport of newborns and infants with CHD. The risks of developing hypothermia and hypoglycemia during long, unsupervised transport further adds to the already serious condition of the infants with CHD [32]. Limited resources and inefficient governance further compromise a fair distribution.

Financial constraints: Medical insurance is practically nonexistent in India, especially for birth defects. In most instances, families are expected to pay for the treatment out of their pocket, which they can barely afford. In a study from Kerala [33], surgery for CHD resulted in significant financial burden for majority of families. Approximately half of the families borrowed money during the follow-up period after surgery [33]. Many families lose their wages as they are away from work during care of these children. Though several state government level programs, microfinance schemes, charitable and philanthropic organizations exist for the benefit of economically weaker sections of the society, awareness amongst community about such programs is very low. The number of public hospitals which provide care at a low cost are very few. Most cardiac centers, especially those set-up more recently, are in the private sector and may not be affordable for the majority. Public hospitals are faced with a very large number of patients and have waiting lists ranging from months to years. Children undergoing surgery are often in advanced stages of disease with associated malnutrition [34]. The results of intervention in such settings are expected to be less than ideal.

According to data collected from 47 centers in India, about 35% of cardiac surgeries are funded by families themselves. Government schemes, mostly at state level, cover about 40% of all surgeries for CHD patients. Many hospitals partner with charitable non-government organizations and multinational companies to assist economically weaker families. About 20% of cardiac surgeries are funded by such organizations. Other less common (<5%) funding sources include parents' employer and donations. Some of the charitable cardiac centers are providing completely free treatments; however, such centers generally have long waiting lists.

To make meaningful reductions in mortality and morbidity from CHD, it is imperative to focus on comprehensive newborn and infant cardiac care.

Health seeking behavior of the community: Often the parents seek medical care only when child develops significant symptoms. This may not be only due to financial constraints. Local religious and socio-cultural practices in India affect the level of care received by children with CHD. Illiteracy may be partly contributing to such behavior. Gender bias, as prevalent in some societies, may put girls at a disadvantage compared to boys. In a study from a referral tertiary care center, girls were less likely to undergo cardiac surgery for CHD than boys [35].

Lack of follow-up care: Most children with CHD, including those who have undergone an intervention, require long-term care for a good outcome. Unfortunately, a large number of children in India, especially those from middle or lower socioeconomic strata, are lost to follow-up. The onus of follow-up is totally on the family of the affected child as our health system is not proactive despite having a network of primary health care units.

Other factors: Investment on health care is one of the lowest in India when compared with several other countries, including many LMIC. There is no national policy for CHD. Rapid population growth, competing priorities, inefficient and inadequately equipped infrastructure, and a deficit of trained staff at all levels of health care are some of the other major roadblocks to cardiac care of children with CHD.

Strategies for Improvement of Cardiac Care

To make meaningful reductions in mortality and morbidity from CHD, it is imperative to focus on comprehensive newborn and infant cardiac care. However, improvements in maternal and child health services must occur simultaneously. Health is a state subject and the various states of India differ vastly in their economy, literacy levels, population, languages, cultural beliefs and human development indices. This regional diversity makes the task more difficult as 'one size fits all' approach is not tenable [36].

Increasing awareness: Community needs to be sensitized to the problem of congenital defects, through electronic and print media. Targeting pediatricians and educating them not just about diagnosing CHD in a newborn, but also about the advancements that have occurred in the care of children with CHD should also be helpful.

Preventive measures and screening: So far, little emphasis has been placed on preventive measures for CHD. This needs to be stressed as the investment required is much smaller. Mass immunization against Rubella should be the starting point at the national level. Although one can have a specific preventive program for children with CHD, a more comprehensive program which caters to the well-being of children in general, and incorporates a number of other common disorders is more likely to be sustainable.

A flagship scheme of Government of India (Rashtriya Bal Swasthya Karyakram [RBSK]) has been launched in February 2013 with a mandate to screen all children, aged 0-18 years for early detection and management of birth defects and other diseases. Under this initiative, comprehensive health care is expected to be provided for all diagnosed cases of birth defects. Periodic education programs to sensitize the practicing physicians and pediatricians are necessary. The frontline health workers as well community in general should be made aware of the availability of advanced care in India for children with CHD. Screening newborns with pulse oximetry to diagnose critical CHD should become a part of newborn care [37].

Geographic distribution of centers of excellence: Establishing more centers for cardiac care would be ideal, but this is a very challenging task. One not only needs sophisticated technology and infrastructure, but also a motivated team of health professionals. Pediatric cardiac care is a team effort involving cardiologists, surgeons, anaesthesiologists and intensive care specialists. There should be at least one center in each state unit, may be more in populous states, so that families do not have to travel long distances to new cities with different local environments and languages. Ideally, these centers should be supported by the government, either directly or through welfare schemes, so that families belonging to middle and lower strata on socioeconomic scale can also reap the benefits. This would also maintain a high volume of cases, leading to professional satisfaction and motivation of the employed staff.

Optimal utilization of resources: The model of piggybacking pediatric cardiac program on a successful ongoing adult cardiac program is useful for optimizing resource utilization, and has been successfully used in several hospitals. The cardiac catheterization laboratory, operating rooms, staff and other services are shared for both pediatric and adult patients. In such 'adult-program first' models, the pediatric cardiac program is gradually expanded. However, this model is not without problems as adult care may get preference over pediatric care as adult program are much less resource-intense. Collection of outcome data to assess the quality of program is very important for self-sustainability.

A flagship scheme of Government of India (Rashtriya Bal Swasthya Karyakram [RBSK]) has been launched in February 2013 with a mandate to screen all children, aged 0-18 years for early detection and management of birth defects and other diseases.

In-country training of staff: Currently India has approximately 130 pediatric cardiologists and 110 pediatric cardiac surgeons. These numbers are grossly inadequate, but are much better than what it was a decade ago. Given a choice, very few specialists choose pediatric cardiology and cardiac surgery as these specialities are much more demanding, less glamorous and provide lower monetary return. Hand-holding of new recruits by senior staff/expatriates on short-term deputation from established cardiac centers, is likely to improve skills and morale of junior surgeons. With ever increasing numbers of centers, in-country structured training programs for pediatric cardiac care specialists are necessary as has been successfully done in some countries [38]. In the last five years or so, some good quality training programs have started in India, including a three year courses in pediatric cardiology. Incorporating research into a training program is also very important, and helps in its sustainability.

Indigenization and innovation: For cardiac surgery and interventions to be affordable, cost-containment is necessary. Currently, majority of equipment and disposable items required for cardiac surgery are being imported. Encouraging home grown technology will reduce the cost of equipment considerably. Few LMIC, such as Brazil and Mexico, are manufacturing products locally, reducing the costs significantly. However, high standards have to be prescribed for local manufacturers and a strict quality control is necessary.

Prioritization of care: A contentious issue is prioritizing CHD care for those cases which are 'one time fixes' with good long-term outcome over those with complex CHD requiring multistage, often palliative surgeries with suboptimal long-term survival. This issue gains importance because of the enormous burden of CHD in India and availability of limited facilities for their management. The denial of cardiac surgery to children with complex CHD and single ventricle physiology (eg, heterotaxy syndromes) and to those associated with significant extra-cardiac malformations is for efficient resource utilization in a resource-constrained setting. Such decisions can be challenged and are best taken in consultation with parents.

Providing financial support for treatment: A number of financial models are supporting health care in India. Many of them cater to children and cover for CHDs. Some of the private hospitals support patients utilizing funding from corporate social responsibility programs. Payment is sometimes linked to the patient's capacity to pay, helping to subsidize services for poorer patients. Charitable hospitals often depend on donations. Insurance is another way to provide high quality care. One of the successful schemes adopted by Karnataka, called Yeshashwini, is a microfinance scheme where each member of a cooperative group pays a nominal amount to create a corpus which is used to fund surgeries [39]. Several other states have similar schemes under different

Key Messages

- Over 200,000 children are estimated to be born with congenital heart disease in India every year.
- About one-fifth of these suffer from critical heart disease requiring early intervention.
- The currently available care for these children is grossly inadequate.
- There are over 60 centers that cater to children with congenital heart disease; majority are in southern states of India.
- Most of babies born with congenital heart disease in most populous states of India, such as Uttar Pradesh and Bihar, do not receive the care they deserve.
- Improving care of children with congenital heart disease is an uphill task, but needs to be addressed.

names. A number of initiatives by the central government are directed at health of children. Provision is also provided for free treatment of children from families which are below poverty line. In addition, poor patients can get financial help from Prime Minister's Relief Fund and Chief Minister's Relief Fund. The policy makers and others in the government are taking note of pediatric health, and in future, we may see more schemes for the benefit of children with CHD. However, we must have the infrastructure to take care of this increasing demand.

Recently government of India has launched a National Health Protection Scheme, which is a flagship program under Ayushman Bharat [40]. This scheme is expected to cover over 10 crore poor and vulnerable families (approximately 50 crore people). Under this scheme, a coverage of up to Rs. 500,000 per family per year will be provided, for secondary and tertiary care hospitalization. Whether this scheme would significantly impact the cardiac care of children with CHD is to be seen, considering the mismatch between the high load of cases and number of cardiac care centers in India.

Conclusion

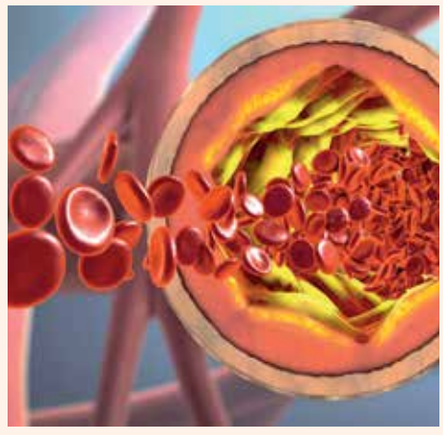
The care available for children with CHD is vastly different in MIC, including India, from that in high-income countries. A large proportion of children with CHD go undiagnosed and untreated in India due to the large numbers and limited resources. A significant amount of progress has been made in India for the management of children with CHD over the last three decades, but it still remains grossly inadequate. Interactions with pediatricians and other front line health staff are necessary to improve the overall outlook for children with CHD. Advocacy with health policy makers is very important so that more resources are allocated to care of children with CHD – at primary, secondary and tertiary levels. Potential solutions to improve access to cardiac care must consider the local social, economic and political systems for each region. A locally relevant research must be a part of this endeavor.

References available on request Healthcare.India@springer.com

Source: Anita Saxena. Congenital heart disease in India: a status report. Indian Pediatr. 2018;55(12):1075–1082. DOI 10.1007/s13312-018-1445-7. © Indian Academy of Pediatrics 2018.

Arterial stiffness and hypertension

Measures of the functional and structural properties of blood vessels can be used to assess preclinical stage of vascular disorders. Recent experimental and population studies show that arterial stiffening precedes development of high blood pressure, and can be used to predict future cardiovascular events. Arterial stiffness was also shown to be reversible in several experimental models of various conditions. Since reversing arterial stiffness could prevent development of hypertension and other clinical conditions, understanding the biological mechanisms of arterial stiffening and investigating potential therapeutic interventions to modulate arterial stiffness are important research topics. For research and application in general clinical settings, it is an important step to develop reliable devices and a standardized arterial stiffness measurement protocol.



Source: Young S. Oh. Arterial stiffness and hypertension. Clin Hypertens. 2018;24:17. DOI 10.1186/s40885-018-0102-8. © The Author(s). 2018.

Preventing Heart Failure by Treating Systolic Hypertension: What Does the SPRINT Add?

Bharathi Upadhya[1], Richard B. Stacey[1], Dalane W. Kitzman[1]

Previous trials definitively established that lowering systolic blood pressure (BP) to 140 mmHg prevented heart failure (HF) exacerbations, but the potential benefits and risks of further BP reduction remain unclear due to a paucity of trial-based data.

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Introduction

Hypertension (HTN) remains a major public health problem associated with considerable morbidity and mortality. HTN continues to be the most prevalent risk factor for heart failure (HF) and precedes the diagnosis of HF in 75–85% of persons who develop HF [1, 2]. Higher systolic blood pressure (SBP) increases the risk of developing HF, and BP reduction prevents incident HF, but the optimal BP target for prevention of HF remains uncertain [3]. Further, in the elderly, aggressive BP-lowering strategies may potentially lead to complications, such as mechanical falls with injury and renal failure, as well as adverse effects associated with polypharmacy. This article aims to review current BP targets to prevent HF among older patients with HTN.

Case Histories

Patient 1: an 84-year-old African American man (body mass index [BMI] of 34) who is followed routinely at his cardiologist's clinic subsequent to a coronary revascularization performed 5 years ago. He remains asymptomatic without diabetes mellitus (DM), but continues to smoke half-a-pack of cigarettes per day. His last echocardiogram showed a normal left ventricular ejection fraction (LVEF) 1 year ago. His routine laboratory tests showed an estimated creatinine clearance of 35 ml/min. His BP was 140/90 mmHg after 5 min in a seated position.

Patient 2: an 84-year-old Caucasian woman (BMI, 24) was examined at a routine annual visit with her primary care physician. She was asymptomatic. Her BP was 140/90 mmHg after 5 min

in a seated position. She did not have DM or history of cardiovascular disease (CVD). Her routine laboratory tests were unremarkable, including normal renal function.

To reduce the risk of HF, should both patients be treated to a BP reduction target of < 120/80 mmHg?

Hypertension and HF Risk—Pathophysiology

The progression from HTN to structural cardiac changes and eventually systolic and diastolic left ventricular (LV) dysfunction is demonstrated in Fig. 1. Although LV hypertrophy (LVH) can precede the development of HTN, the progression from HTN to concentric LVH is an important step in the pathway toward HF. Along with mechanical stress resulting from pressure overload, neurohormonal abnormalities also play an important role in LVH. Neurohormones can directly promote myocyte hypertrophy and matrix deposition independently of their effects on BP [4]. There is a considerable inter-individual variability in how the LV hypertrophies in response to HTN. For example, compared to Caucasians, African Americans have higher LV mass, are more likely to develop concentric hypertrophy, and experience more severe diastolic dysfunction [5–7]. Similarly, those with higher SBP develop concentric hypertrophy much more frequently than eccentric hypertrophy [8]. Women with isolated systolic HTN also develop concentric LVH [9]. Increasing age has also been associated with a concentric as opposed to an eccentric hypertrophic response [1]. Along with afterload excess and LVH with its associated cardiac fibrosis and increased arterial stiffness, HTN also induces inflammation, oxidative stress, and endothelial dysfunction—all predispositions to HF [10]. Further, HTN may progress directly to HF in the absence of LVH or myocardial ischemia or infarction. However, contrary to conventional belief, BP may account for only 25% of the variability of LV mass in a population [11]. Indeed, the majority of patients with HF with preserved EF did not have significant LVH at baseline [12]. A recent report by Soliman *et al.* showed that changes in electrocardiographic LVH explained only 1% of the reduction in CVD events in the Systolic Blood Pressure Intervention Trial (SPRINT) [13]. Thus, there is uncertainty regarding the relationships between BP lowering, LV mass reduction, and improved CVD outcomes in hypertensive patients, particularly at the lower ranges of target BP.

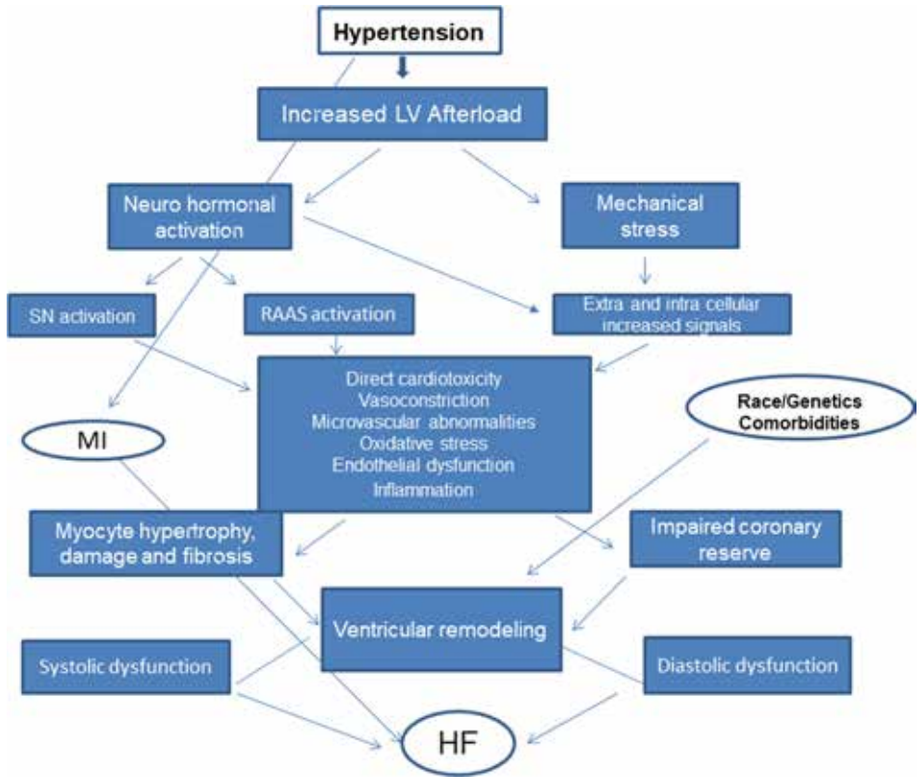

Fig. 1: Hypertension and heart failure risk—pathophysiology. LV, left ventricle; SN, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; HF, heart failure; MI, myocardial infarction

Systolic Blood Pressure Target and HF Risk

Risk for HF rises continuously with increasing BP [3]. The lifetime risk for HF doubles in those with BP > 160/100 versus < 140/90 mmHg [14]. Several prior trials in older patients with systolic HTN showed large reductions in new HF events resulting from SBP reductions to 140–145 mmHg [15–18] (Table 1). The particularly large reduction in HF events in the Hypertension in the Very Elderly Trial (HYVET) likely reflects the older age of the participants compared to the other three trials [15]. Similarly, a larger benefit was also observed in participants aged > 80 years in the Systolic Hypertension in the Elderly Program (SHEP) trial [16]. Although the benefit of lowering SBP to 140 mmHg for preventing HF events was well established by previous trials [15–18], there has been a paucity of information regarding the potential benefit and risk of lowering BP further. To address this uncertainty, a propensity score analysis of 7785 patients with mild to moderate HF with reduced or preserved EF followed for 5 years was carried out. The study found that a baseline SBP ≤ 120 mmHg was associated with increased CV and HF mortality and all-cause, CV, and HF hospitalizations, independently of other baseline characteristics [24]. Similarly, BP-lowering therapy among intermediate-risk adults showed a trend for harm among those with baseline SBP levels < 130 mmHg in the Heart Outcomes Prevention Evaluation (HOPE-3) trial [25]. Achieving intensive SBP reductions will inevitably also lower diastolic BP (DBP). Since myocardial

Table 1: Randomized systolic hypertension trials that used heart failure as outcomes.

First author/trial (ref. no.)	Mean basal SBP	Between-group difference in mean SBP at the end of follow-up	Patient type	Relative risk reduction for HF	Average follow-up
HYVET [15] *n* = 3845	173 mmHg	15 mmHg	Mean age, 84 years; women, 61%; h/o CVD, 12%; DM, 7%; h/o stroke, 7%; h/o HF, 3%.	64%	1.8 years
SHEP [16] *n* = 4736	171 mmHg	12 mmHg	Mean age, 72 years; 57%, women; African Americans, 14%; h/o CVD, 5%; h/o HF, 0.3%; h/o stroke, 1.4%; h/o DM, 10%.	50%	4.5 years
Syst-Eur [17] *n* = 4695	174 mmHg	10 mmHg	Mean age, 70 years; women, 67%; CVD, 30%; h/o stroke, 4%	36%	2.0 years
ALLHAT [18] *n* = 33,357	146 mmHg	11 mmHg	Mean age, 67 years; women 47%; African Americans, 35%; DM, 36%; h/o CVD, 52%; h/o HF excluded	26%	4.9 years
ACCORD [19] *n* = 4733	139 mmHg	14 mmHg	Mean age, 62 years; women, 48%; African Americans, 24%; h/o CVD, 34%, h/o HF, 4.3%; all with type II DM	8%	4.7 years
Cardio-Sis [20] *n* = 1111	163 mmHg	4 mmHg	Mean age, 67 years; 59%, women; h/o CVD, 13%; h/o stroke, 9%	62%	2.0 years
SPRINT [21] *n* = 9361	140 mmHg	13 mmHg	Mean age, 68 years (28% were aged 75 years and older); women, 36%; African Americans, 30%; h/o CVD, 20%; h/o CKD, 28%; h/o stroke and HF excluded	38%	3.3 years
Upadhya *et al.* [22] *n* = 9361	140 mmHg	13 mmHg	The same as above	36%	3.3 years
SPRINT SENIOR—Williamson *et al.* [23] *n* = 2636	142 mmHg	11.4 mmHg	Mean age, 80 years; women, 38%; African Americans; 17%, h/o CVD, 24%; h/o stroke and HF excluded	36%	3.1 years

SBP—measured in sitting position
SBP, systolic blood pressure; *HF*, heart failure; *CVD*, cardiovascular disease; *DM*, diabetes mellitus; *CKD*, chronic kidney disease

perfusion requirements are increased in HTN, and myocardial perfusion pressure depends on adequate DBP, a drop in DBP could result in myocardial ischemia and increase LV dilation with subsequent HF with reduced LVEF [26]. A recent study demonstrated that among adults with a systolic BP ≥ 120 mmHg, a low DBP, particularly < 60 mmHg, was associated with subclinical myocardial damage and coronary artery disease events [27].

Intensive Systolic Blood Pressure Target (< 130 mmHg) and HF

Based on data to this point, the outcomes from large clinical trials have not successfully addressed the question of whether lowering SBP < 130 mmHg is an effective strategy to prevent HF. The Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica (Cardio-Sis) trial showed that lowering systolic BP to < 130 mmHg in non-diabetic patients decreased composite CV outcomes compared with a SBP < 140 mmHg [20]. However, HF event reduction was not significantly different between treatment arms (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.11–1.63) (Table 1). The results of the Cardio-Sis trial have to be interpreted within the context of its potential limitations. First of all, they powered their study on LVH as the primary outcome. Few clinical events, short clinical follow-up time with a fairly small sample size might have affected the power to examine HF outcomes. Cardio-Sis excluded people with DM and chronic kidney disease (CKD). In addition, the study included only Caucasian patients, so extrapolation to other racial/ethnic groups might not be justified. The study was not double-blind; thus, awareness of the randomization code could have affected the clinical decisions related to admission for HF events [20].

In Action to Control Cardiovascular Risk in Diabetes (ACCORD), a large randomized trial that specifically addressed the potential benefit of lowering SBP to < 130 mmHg (the target was 120 mmHg) in patients with DM, the HF event reduction was smaller and not statistically significant (HR, 0.94; 95% CI, 0.70–1.26) [19] (Table 1). This lower event rate in ACCORD was likely because of several factors. ACCORD recruited patients with DM and excluded people with CKD and those aged > 79 years. In addition, inclusion criteria directed participants with dyslipidemia into the ACCORD lipid trial, leaving participants who were at lower risk for CV events to be enrolled into the BP trial. ACCORD also used a factorial design that included comparisons of standard and intensive glycemic and lipid treatment targets in the same trial. Furthermore, the event rate in the standard therapy group in ACCORD was almost 50% lower than expected; thus, the trial may not have been adequately powered to examine HF events. In a recent meta-analysis, every 10-mmHg reduction in SBP reduced the risk of HF by an average of 28% (HR, 0.72; 95% CI, 0.67–0.78; $p < 0.001$). The

proportional reductions per 10-mmHg decrease in SBP were greater for stroke and HF than for coronary heart disease, and there was a trend toward decreased HF events even with baseline SBP < 130 mmHg [28]. Similarly, meta-analysis of 35 HTN treatment trials with HF events showed a strong, significant correlation between the extent of SBP and DBP reduction and the reduction in HF events [29].

A secondary analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), a large multicenter (102 sites), racially diverse randomized open-label trial, showed that treatment that targets a SBP of < 120 mmHg, compared with < 140 mmHg, resulted in a 36% lower rate of acute decompensated HF events [22] (Table 1). Persons with DM, those with a history of stroke, and institutionalized people were excluded from the study. Symptomatic HF within the past 6 months, a LVEF of less than 35%, and an estimated glomerular filtration rate less than 20 ml/min/1.73 were also

The benefit of intensive BP control was consistent among elderly persons (≥ 75 years) who were frail or had reduced gait speed. An analysis of the HYVET population showed similar treatment benefits, even in the frailest participants

exclusions [21]. All HF events were new (incident) events and were adjudicated based on a manual of operations that had been validated in the Atherosclerosis Risk in Communities (ARIC) study [30]. The beneficial effect of the intervention on the HF event rate became apparent early, at 6-month follow-up, and increased with duration of follow-up [22]. The beneficial effect was consistent across all the key pre-specified subgroups, including age > 75 years or < 75 years, with or without prior CVD, with or without CKD, women or men, black race or non-black race, and the tertiles of baseline SBP

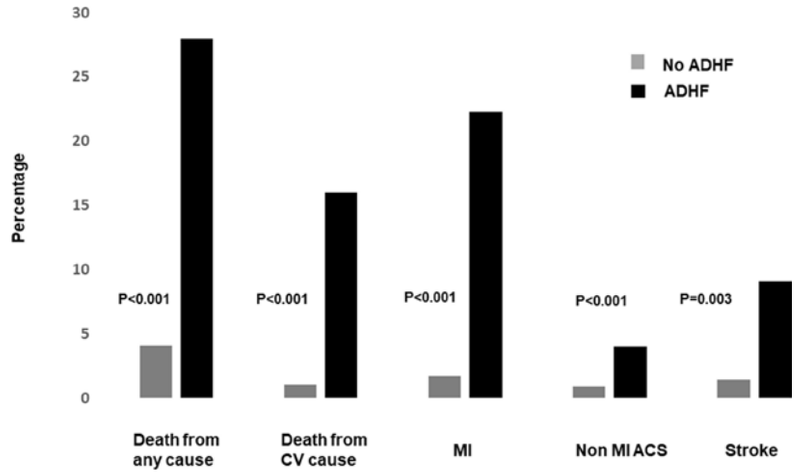

Fig. 2: Subsequent clinical outcomes based on initial acute decompensated heart failure events occurrence. ADHF, acute decompensated heart failure; CV, cardiovascular; MI, myocardial infarction; ACS, acute coronary syndrome

[22]. Participants who had an initial HF event had markedly increased risk of subsequent events, including recurrent HF (Fig. 2) [22]. Similar results were also seen in the SPRINT SENIORS cohort (participants' age ≥ 75 years) [23].

Clinical Implications of Lowering SBP to < 130 mmHg: Feasibility, Safety, and Patient Burden

While the efficacy of the SPRINT strategy is clear, given that the trial was stopped early due to benefit, some have questioned the feasibility, safety, and patient burden of lowering SBP to < 130 mmHg, particularly in older, frail patients. However, in both the main SPRINT and in the SPRINT SENIORS cohort, HF events were lower in the intensive arm compared with those of the standard arm, despite significantly lower DBPs (SPRINT, 69 versus 76 mmHg; SPRINT SENIORS, 62 versus 67 mmHg) [21, 23]. The benefit of intensive BP control was consistent among elderly persons (≥ 75 years) who were frail or had reduced gait speed [23]. An analysis of the HYVET population showed similar treatment benefits, even in the frailest participants [31]. Furthermore, the overall serious adverse event rate was comparable in both treatment groups, including among the frailest participants in the SPRINT SENIORS cohort [23]. There were no differences between treatment groups in injurious falls or orthostatic hypotension [23].

Similarly, the ACCORD trial showed that intensive treatment (mean SBP < 120 mmHg) was not associated with an increased risk of falls or non-spine fractures in patients with type II DM [32]. Further, the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston (MOBILIZE Boston Study) showed that improved BP control (< 140/90 mmHg) reduces risk for orthostatic hypotension in older community-dwelling adults (mean age of 78 years; female, 65%) and has no effect on risk for injurious falls [33]. A recent meta-analysis of existing randomized trials suggested that in patients with HTN, an on-treatment SBP target of < 130 mmHg achieved optimal balance between efficacy and safety [34]. Although there is no evidence of permanent kidney injury associated with the lower BP goal in SPRINT SENIORS, mild acute kidney injury occurred more frequently in the intensive treatment group [23]. Similarly, hypotension, electrolyte abnormalities, and syncope were more frequent in the intensive group, though infrequent in the study overall [21]. In the SPRINT intensive treatment group, an average of 2.8 antihypertensive drugs was required to reach SBP goal. Some health care providers have expressed reluctance to prescribe more than two antihypertensive drugs to a given patient, and adherence is generally lower with increasing complexity of clinical regimens. However, these disadvantages must be balanced

with the clear benefit of substantially reduced mortality and CVD events from adopting the SPRINT intensive BP treatment strategy.

What Does the SPRINT Add?

The SPRINT results have substantial implications for the future of intensive BP therapy in older adults because of this condition's high prevalence, the high absolute risk for CVD complications from elevated BP, and the devastating consequences of such events on the independent function of older people. However, the public health implications are dependent on the generalizability of the SPRINT outcomes to the U.S. population, especially populations excluded from the trial, eg, younger and lower-risk persons; those with DM, severe kidney disease, prior HF, and stroke; and subgroups of elderly adults (nursing home residents, extremely frail or demented individuals). Using data from the National Health and Nutrition Examination Survey (NHANES), Bress *et al*. found that 8.2 million adults with treated HTN (17% of the hypertensive population) meet the SPRINT eligibility criteria and thus may benefit from intensive BP treatment [35]. They also predicted that in patients who fit SPRINT eligibility criteria, intensive BP treatment would prevent approximately 46,100 cases of incident HF per year but would cause 56,100 episodes of hypotension, 88,700 cases of AKI, 34,400 episodes of syncope, and 43,400 cases of electrolyte disorders (hyponatremia and hypokalemia) compared to standard care [36].

The results of SPRINT are likely to have a major impact on the treatment of HTN. SPRINT results are reflected in changes in recent HTN guidelines regarding treatment goals and BP measurement techniques.

Blood Pressure Measurement in SPRINT

Knowing how BP is measured is important for guiding clinicians in appropriate management of HTN [37]. Although numerous HTN experts have argued that the BP measurement technique in SPRINT makes it an outlier, SPRINT BP measurements were conducted using methods that were commonly recommended by professional societies and BP guideline committees [38, 39]. The SPRINT used programmable automated oscillometric devices (Omron Digital BP Monitor) to measure BP [40]. This device could be programed to incorporate the 5-min rest and then initiate the three BP measurements automatically after the 5 min had elapsed. Coordinators were instructed how to program the Omron device during training [40]. The coordinators could have been in or out of the room during the 5-min rest period and/or during the time the Omron was automatically taking the BP measurements. Recent publications have stated that the BP measurement technique used in SPRINT was unattended, and was not comparable with BP readings in other trials where the measurement was attended and that the intensive treatment goal of < 120 mmHg in SPRINT would actually correspond to higher SBP values in other trials [41]. Notably, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not comment on the presence or absence of an observer during BP measurement. The recent post hoc SPRINT analysis suggested that there was no compelling evidence in SPRINT that unattended BP measurements led to lower SBP at baseline or during follow-up compared to the attended BP measurements [40]. Importantly, similar BP levels and CVD risk reduction were observed in the intensive treatment group of SPRINT participants whether the measurement technique used was primarily attended or unattended [40]. Similarly, data from the SPRINT Ambulatory BP Ancillary Study also showed that the BP values obtained at the SPRINT study clinic visit, whether attended or unattended, are similar to values obtained during 24-h ambulatory BP monitoring [42].

Impact of SPRINT on Guidelines

In 2017, the ACC/AHA HTN guideline changed the definition of HTN to incorporate the former "pre-hypertension" as stage 1 hypertension. Thus, normal BP is considered < 120/80 mmHg, elevated BP is 120–129/80 mmHg, and hypertension is > 130/80 mmHg [38]. Similarly, they recommended that in adults with HTN and increased risk of HF, the optimal BP should be < 130/80 mmHg [38]. The guideline committee concluded that the available randomized controlled trials that provided evidence for their recommendation were efficacy studies in which BP measurements were more consistent with guideline recommendations than is common in clinical practice, resulting in lower absolute values for SBP. However, the Eighth Joint National Committee determined that SBP targets should be below 140 mmHg or below 150 mmHg in those 60 years of age or older [39]. The 2016 Canadian HTN Education Program guidelines recommend intensive BP treatment with target SBP ≤ 120 mmHg (grade B) for high-risk patients based on automated office BP measurements (grade D) [43]. Importantly, the 2016 Canadian HTN Education Program guidelines recommend that BP be measured as in the SPRINT. The 2016 Australian guidelines recommend an SBP target < 120 mmHg (strong recommendation, class II) for high-CV-risk patients without DM, including CKD patients and those aging > 75 years [44]. Finally, the 2017 ACC/AHA HF guideline is one of the first to recommend the lower SBP target of 130 mmHg to prevent HF, based in part on the results of the SPRINT [21–23, 45].

Case Resolution

Based on this, considering that the risk for future development of HF differs considerably among these individuals, should their therapeutic targets be different? Would a lower SBP target for patient 1 than current recommendation further decrease the risk of HF? It is self-evident that patient 1 is at significantly higher risk of development of HF compared with patient 2. The former patient has a history of CVD and renal dysfunction. Patient 1 definitely needs a SBP target of 130 mmHg. If we implement the guideline-recommended BP measurement technique as in SPRINT, patient 1 needs a SBP target of 120 mmHg. However, for patient 2, the SBP target to reduce HF risk remains uncertain. On the basis of the available data, we recommend the SBP target of 2 to 130 mmHg for patient 2 to reduce the risk of HF.

In summary, using the SPRINT intensive treatment algorithm and a SBP goal of < 120 mmHg, along with the BP measurement techniques recommended by HTN guideline committees (staff training to allow for a quiet rest period, proper positioning of the arm and body, use of proper cuff size, and multiple measurements using a validated automated BP device), will reduce the risks of HF in non-diabetic patients at medium–high CVD risk.

Conclusion

Uncontrolled SBP continues to be a highly prevalent and highly modifiable HF risk factor. Targeting only those at the highest end of the BP spectrum does not address most individuals at risk for developing HF. Therefore, treatment decisions should be based on a person's absolute risk. The results of SPRINT are likely to have a major impact on the treatment of HTN. SPRINT results are reflected in changes in recent HTN guidelines regarding treatment goals and BP measurement techniques. SPRINT revisits BP target goals and challenges us to improve BP measurement and management to prevent HF events. In addition, these results suggest that translation of the SPRINT results will require measurement of BP as performed in that trial. After all, BP is a vital sign and should be measured as in the clinical trials so that we can provide evidence-based care to our patients.

Compliance with Ethical Standards

Conflict of Interest: Dr. Kitzman declares the following relationships: consultant for Abbvie, Bayer, Merck, Medtronic, GSK, Relypsa, Regeneron, Merck, Corvia Medical, DCRI, and Actavis, research grant funding from Novartis, St. Luke's Medical Center, and stock ownership in Gilead Sciences. Dr. Upadhya has received research funding from Novartis and Corvia.

Human and Animal Rights and Informed Consent: This article does not contain any studies with human or animal subjects performed by any of the authors.

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References available on request Healthcare.India@springer.com

Source: Upadhya B., Stacey R.B., Kitzman D.W. Preventing heart failure by treating systolic hypertension: what does the SPRINT add? Curr Hypertens Rep. 2019;21:9. DOI 10.1007/s11906-019-0913-3.

Quality Measures in Heart Failure: the Past, the Present, and the Future

Quality measurement in healthcare is the process of applying data to evaluate the performance of healthcare delivered, usually compared with recognized high-quality standards. The researchers evaluate performance measure in health, their importance, and methodologic issues, focusing on metrics for health failure patients. Quality measures are instruments to assess structural aspects or processes of care aiming to guarantee that optimal patient outcomes are achieved. As heart failure is a chronic condition in which established therapies reduce mortality and hospital admissions, there are quite a lot of initiatives that aim to monitor for quality of care and to coordinate the disease management.

Several performance measures were validated for these patients, from process of care (left ventricular function assessment and use of ACEi/ARBs and beta-blockers) to health outcomes (hospital mortality and readmissions). In the early years, studies demonstrated a relationship between quality measurements and health outcomes. Nonetheless, more recent ones based on large databases of patients' medical records have shown that traditional indicators explain only a small fraction of health and patient reported and perceived outcomes. Public reporting of quality measures and payment conditioned to the quality of care provided were not able to show benefit in terms of hard outcomes. Data science and big data methods are promising in providing actionable knowledge for quality improvement, with real-time data that could support decision-making.

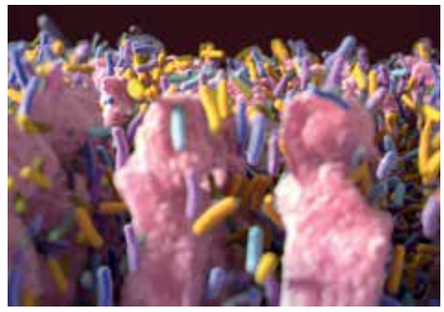
Heart failure is a chronic condition that has proven to be useful for measuring medical and health care quality. Evidence-based indicators have already reached high rates of adherence and are currently poorly correlated with outcomes. Using real-life data and based on the patient's perspective can be useful tools to improve these indicators.

Source: Carisi A. Polanczyk, Karen B. Ruschel, Fabio Morato Castilho, Antonio L. Ribeiro. Quality measures in heart failure: the past, the present, and the future. Curr Heart Fail Rep. 2019;1–6. DOI 10.1007/s11897-019-0417-0.

Towards an Individualized Nutrition Treatment: Role of the Gastrointestinal Microbiome in the Interplay Between Diet and Obesity

Dietary treatments for obesity have relatively low long-term success. Recent studies have identified the gastrointestinal microbiome as a factor of high relevance. The current knowledge on the interplay between diet, obesity, and the gastrointestinal microbiome and the potential for individualized dietary treatment will be discussed.

Studies indicate that each individual digests and metabolizes identical food substances differently depending on their gastrointestinal microbiome composition. Factors related to this crosstalk may improve our understanding of weight homeostasis and treatment of obesity.



Long-time dietary intake is the key in the composition of the gastrointestinal microbiome which seems to be an important factor for energy balance, resulting in emerging opportunities for increasingly varied obesity treatment. Compliance to dietary treatment is critical for long-term success as enduring changes in gastrointestinal microbiome seem to slow over time. More research is urgently needed to investigate this missing link in our understanding of obesity.

Source: Solveig A. Adalsteinsdottir, Ola K. Magnusdottir, Thorhallur I. Halldorsson, Bryndis E. Birgisdottir. Towards an individualized nutrition treatment: role of the gastrointestinal microbiome in the interplay between diet and obesity. Curr Obes Rep. 2018;7(4):289–293. DOI 10.1007/s13679-018-0321-z.

Risk Factors for Medication Non-Adherence Among Atrial Fibrillation Patients

Atrial fibrillation (AF) patients are routinely prescribed medications to prevent and treat complications, including those from common co-occurring comorbidities. However, adherence to such medications may be suboptimal. Therefore, Stephanie R. Reading and colleagues sought to determine risk factors for general medication nonadherence in a population of patients with atrial fibrillation.

Data were collected from a large, ethnically-diverse cohort of Kaiser Permanente Northern and Southern California adult members with incident diagnosed AF between January 1, 2006 and June 30, 2009. Self-reported questionnaires were completed between May 1, 2010 and September 30, 2010, assessing patient socio-demographics, health behaviors, health status, medical history and medication adherence. Medication adherence was assessed using a previously validated 3-item questionnaire. Medication non-adherence was defined as either taking medication(s) as the doctor prescribed 75% of the time or less, or forgetting or choosing to skip one or more medication(s) once per week or more. Electronic health records were used to obtain additional data on medical history. Multivariable logistic regression analyses examined the associations between patient characteristics and self-reported general medication adherence among patients with complete questionnaire data.

Among 12,159 patients with complete questionnaire data, 6.3% ($n = 771$) reported medication non-adherence. Minority race/ethnicity versus non-Hispanic white, not married/with partner versus married/with partner, physical inactivity versus physically active, alcohol use versus no alcohol use, any days of self-reported poor physical health, mental health and/or sleep quality in the past 30 days versus 0 days, memory decline versus no memory decline, inadequate versus adequate health literacy, low-dose aspirin use versus no low-dose aspirin use, and diabetes mellitus were associated with higher adjusted odds of non-adherence, whereas, ages 65–84 years versus < 65 years of age, a Charlson Comorbidity Index score ≥ 3 versus 0, and hypertension were associated with lower adjusted odds of non-adherence.

Several potentially preventable and/or modifiable risk factors related to medication non-adherence and a few non-modifiable risk factors were identified. These risk factors should be considered when assessing medication adherence among patients diagnosed with AF.

Source: Stephanie R. Reading, Mary Helen Black, Daniel E. Singer, et al. Risk factors for medication non-adherence among atrial fibrillation patients. BMC Cardiovasc Disord. 2019;19:38. DOI 10.1186/s12872-019-1019-1.

Management of "Hypertension" Based on Blood Pressure Level Versus an Absolute Cardiovascular Risk Approach

Mark Nelson[1,2]

To address the tension between guideline recommendations and the evidence from clinical trials supporting them and clinician concerns of overtreatment of elevated blood pressure.

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Introduction

The recognition of elevated blood pressure as a risk factor for early death belongs not to clinicians or epidemiologists but the more hardnosed actuaries employed by life insurance companies in the first half of the twentieth century. Physicians of the day were want to say "there is some truth in the saying that the greatest danger to a man with a high blood pressure lies in its discovery, because then some fool is certain to try and reduce it" [1] and "hypertension may be an important compensatory mechanism which should not be tampered with, even if we were certain that we could control it" [2] and "people with 'mild benign' hypertension ... [defined as blood pressures up to levels of 210/100 mm Hg] ... need not be treated" [3]. When treatment did became available, which included open surgical renal sympathectomy, it was limited and laced with patient risk and intolerance.

From the days of the Framingham study and the availability of efficacious and safe medications such as thiazide diuretics from the late 1950s and beta-blockers from the 1960s, these earlier physician biases were turned on their head. When levels were very high and high blood pressure effects on target organs such as the retina and kidneys and major cardiovascular disease events were prevalent, the need for treatment was obvious. The evidence supporting lower treatment thresholds has been amassed by clinical trialists by their recognition

that those with more modestly elevated blood pressure needed a cluster of other risk factors to ensure sufficient cardiovascular disease events, most trials are event driven to ensure adequate power, for example conducting such trials in older populations. However, as blood pressure medications have been given to persons with lower and lower thresholds for treatment, physicians' concerns have started rising again as such thresholds are approaching near universal medication recommendation in adults. The publication of the National Institutes of Health sponsored Systolic Blood Pressure Intervention Trial (SPRINT) has brought this to a head as treatment targets reach down to "normal" blood pressure levels [4]. The benefits seen in this study are not trivial with an all-cause mortality reduction of one third in the lower target, intensive treatment group compared with the less aggressively managed comparator. Thomas Kuhn famously spoke of a scientific idea holding sway until accumulating evidence meant an alternate explanation was needed, the so-called paradigm shift [5]. We have long ago reached this juncture with the concept of "hypertension" for the therapeutic reduction of blood pressure based on blood pressure alone.

A Brief History of Absolute Cardiovascular Disease Risk

An alternative approach to primary prevention of CVD is a more recent phenomenon. Critical cohort studies such as the Framingham study identified the multiple risk factors for the condition beyond just raised blood pressure. Risk algorithms that better predicted who was likely to have a myocardial infarction or stroke were developed from these observations and operationalised in New Zealand through their risk charts and inclusive guidelines [6].

Absolute risk is calculated as the probability of a stroke, transient ischaemic attack, heart attack, angina, peripheral arterial disease or heart failure occurring over a specified period of time, usually 5 or 10 years. Five years has been adopted in Australia and New Zealand due to patient preference, discounting means that they are more likely to change behaviour or accept drug therapy if they are at immediate rather than long-term risk, but elsewhere 10 years is utilised. The rationale behind this strategy is outlined in Table 1.

Is There Evidence for the Absolute Risk Approach in Deciding Who Needs Therapy?

Using the absolute risk approach younger patients and those with elevated blood pressure and no other risk factors will not be treated with blood pressure lowering agents. This approach does not mean that such patients are left unmanaged. Attention to risk factors for elevated blood pressure such as alcohol intake and other cardiovascular disease risk factors such as smoking and sedentariness are indicated through behavioural modification and other strategies. Such a strategy, rather than just writing a script, will have benefits for other prevalent diseases such as cancer. However, many clinicians will be uncomfortable with this approach as they fear that delayed drug treatment will lead to inferior outcomes in the long-term, a so-called legacy effect. They will therefore need to be reassured about the intermediate and long-term safety of such an approach.

It is very unlikely that there will be a randomised controlled trial of the absolute risk versus the individual risk factor approach to provide the highest level of evidence because of the enormous sample size and the time required to accumulate cardiovascular endpoints in a low-risk population. However, individual patient data (IPD) meta-analyses of blood pressure lowering trials have shown that the relative risk reduction of cardiovascular events is consistent regardless of baseline blood pressure levels. An IPD meta-analysis of blood pressure trials showed that the relative risk reduction was constant down to the lowest levels observed in the trials (110 mmHg systolic and 70 mmHg diastolic) and results were consistent in trials of patients with a prior history of coronary heart disease, stroke and no prior history of vascular disease [7]. The same result has been observed in cohort studies [8].

What Do the Guidelines Say?

Guideline writers who maintain a "hypertension" approach to the management of elevated blood pressure, have like the clinicians they serve, been placed in a quandary. How do they respond to the evidence of indisputable hard outcome benefits of blood pressure lowering at any level in high risk patients but dealing with clinician concerns that treatment goals are unobtainable and the results are not generalisable to my "real" patients and that we are medicalising the whole general population? All guidelines have some form of recommendation to conduct risk stratification but usually

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Table 1: Rational for absolute risk stratification for thresholds for drug therapy of elevated blood pressure.

Medication is best given to those most likely to have covert cardiovascular disease that will become evident in the intermediate future
Those at highest risk have a most favourable risk to benefit ratio
It is more cost effective than intervention on single risk factors
It avoids medicalisation of the low risk population
It identifies those most likely to have covert CVD avoiding costly additional investigations
Therapeutic agents can be initiated at a level above the ideal rather than at an arbitrary threshold
Individuals at high CVD risk can be identified and treated in circumstances where other chronic disease management may lead them to be neglected (e.g. in the setting of diabetes or a mental health problem)

Practice Guide

Highlights of ESC/ESH 2018 Guidelines on the Management of Hypertension: What Every Doctor Should Know

Massimo Volpe[1,2], Giovanna Gallo[1], Allegra Battistoni[1], Giuliano Tocci[1,2]

This is a review article aiming to make focus on the changes made in the most recent sets of clinical recommendations and indications from European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines for the management of arterial hypertension.

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Introduction

From the end of August 2018, the most recent guidelines issued jointly by the European Society of Cardiology (ESC) and European Society of Hypertension (ESH) [1] are available online for all physicians involved in the management of hypertension. These guidelines reflect solid scientific achievements as well as evidence from clinical trials and large meta-analyses, and tackle in an extensive and detailed way, multiple aspects of the daily clinical management of patients affected by arterial hypertension. Therefore, they appear too extensive when a physician is looking for solutions to face everyday problems in clinical practice. This longstanding problem, which is typical for most guidelines, can be partially overcome with executive documents. However, this has not worked out in past editions. Therefore, in this article we attempted to focus on the new elements introduced in order to meet the need of doctors to adhere to guidelines and to provide their patients with the most updated recommendations for the clinical management of hypertension.

Definition of Hypertension: European Guidelines Stand Still

According to 2018 ESC/ESH guidelines, hypertension is defined as office systolic blood pressure (SBP) ≥ 140 mmHg

Table 1: Blood pressure categories according to 2018 ESC/ESH guidelines. Derived from 2018 ESC/ESH guidelines [1].

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	< 120	and	< 80
Normal	120–129	and/or	80–84
High-normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	180	and/or	110
Isolated systolic hypertension	140	and	< 90

and/or diastolic blood pressure (DBP) ≥ 90 mmHg, independently of age, sex and comorbidities. This definition and the category classification reported in Table 1 are the same as was reported in the previous 2013 European guidelines [2] and strikingly differ from the classification adopted in November 2017 in North American guidelines [3] which consider hypertensive those individuals with BP levels > 130/80 mmHg and define subjects with SBP between 120 and 129 mmHg and DBP between 80 and 84 mmHg as having elevated BP. We respectfully disagree with the United States (U.S.) approach and support the classification of European guidelines. In fact, while the American guidelines classification recognizes their roots in authoritative epidemiological data [3], the evidence derived by randomized clinical trials does not univocally support these definitions.

Which is the BP Measurement to Rely on Office or Out-of-Office?

According to European guidelines, office BP should be preferably measured with auscultatory or oscillometric semiautomatic or automatic sphygmomanometers. To confirm the diagnosis of hypertension, repeated office BP measurement in at least two different visits in a quiet room and with appropriate tools should be performed. Thus, the diagnosis of hypertension remains finally and mostly based on office BP. However, 2018 ESC/ESH guidelines also encourage a wider use of out-of-office BP measurements, either home BP monitoring (HBPM) or ambulatory BP monitoring (ABPM) or both, if logistically and economically feasible, as a strategy to support diagnosis and follow up of patients [1]. ABPM consists in repeated and automated BP measurements, every 15 min during the day and every 30 min over the night, providing the average of BP readings over a predefined period, usually 24 h. HBPM is the average of BP readings, taken twice in a quiet room with a semiautomatic, validated BP monitor, every morning and evening for at least 3 consecutive days before each clinic visit. Both ABPM and HBPM are essential tools for the diagnosis of white-coat and masked-hypertension. However, these two out-of-office BP measurement approaches present substantial differences, which are reported in Table 2.

Table 2: Advantages and disadvantages of HBPM and ABPM. Modified from 2018 ESC/ESH guidelines [1].

ABPM	HBPM
Advantages Identification of white-coat and masked hypertension Better predictive value for hypertension mediated organ damage and major cardiovascular events Night-time measurement and evaluation of nocturnal blood pressure dipping Measurement during routine daily activities Abundant information from a single measurement session, including short-term BP variability	*Advantages* Identification of white-coat and masked-hypertension Cheap and easily available Recording in a relaxed home setting Patient engagement in BP measurement Repeated measurements over longer periods Day-to-day BP variability assessment
Disadvantages Expensive and not simply available Uncomfortable due to close measurements	*Disadvantages* Unavailability of dynamic measurements Potential errors in measurement methods Unavailability of information about night-time BP trend

Since hypertension is predominantly an asymptomatic condition, BP recordings should be performed at regular intervals whose frequency depends on BP levels detected (Fig. 1).

The new guidelines, for the first time, provided recommendations for the minimal follow up to be respected according to the levels of BP or grade of hypertension. The recommended intervals for monitoring BP especially in the general population may appear too loose, but it is a mandatory rule to follow in the clinical practice. Moreover, physicians should also tailor the intervals of follow up on the basis of the age and individual total cardiovascular risk of the patients.

Estimation of Cardiovascular Risk

An adequate assessment of estimated total cardiovascular (CV) risk, not only limited to a static observation brief, but extended to a lifelong projection, is a milestone for improper management of hypertensive patients, because elevated BP levels often concur with other risk factors such as dyslipidemia, overweight, diabetes. This latest edition of European guidelines recommends, as in the previous one, the use of the SCORE system [4], which estimates the 10-year risk of a fatal atherothrombotic event considering systolic BP, total cholesterol level, age, sex, smoking habit. Even if the SCORE system has recently been adapted for elderly

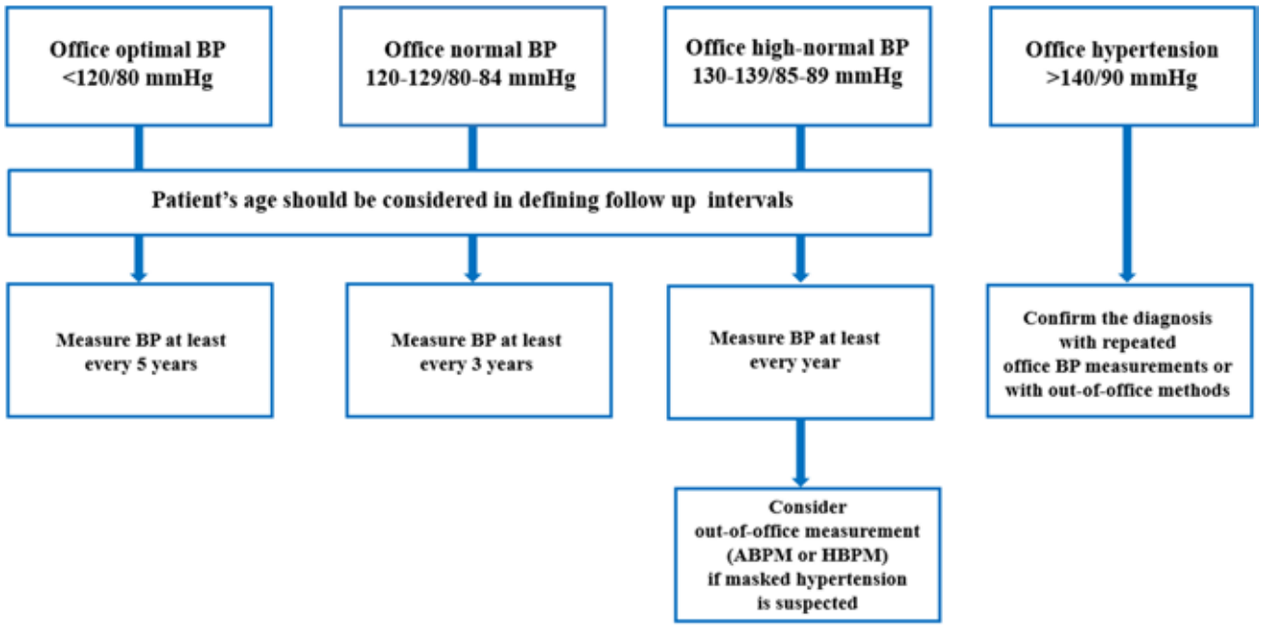

Fig. 1 : Screening and diagnosis of hypertension. Modified from 2018 ESC/ESH guidelines [1]. *BP* blood pressure

patients aged more than 65 years old [5], it still presents remarkable limitations, such as the exclusion of non-fatal major CV events and the limited period of time taken into account. To perform a better estimation of total CV risk, also including non-fatal events, a document from the ESC Working Group on Thrombosis has proposed to threefold multiply the calculated risk of fatal events [6–8].

For the first time, the evaluation of new components of risk, such as socioeconomic deprivation, but also atrial fibrillation, appears formally listed among CV risk modifying factors.

For a more complete and comprehensive CV risk assessment in hypertensive patients, physicians should always consider the presence of hypertension mediated organ damage (HMOD), which has replaced the concept of target organ damage (TOD) by including the presence of structural and functional abnormalities in major organs, such as heart, brain, kidney, vasculature and retina, induced and sustained by hypertension [9]. The screening tests that should be performed for the clinical evaluation of HMOD are described in Table 3. Based on the presence of HMOD, hypertension is now classified as uncomplicated (stage 1), asymptomatic (stage 2) or with established disease (stage 3).

In addition, physicians should always investigate history of comorbidities or experienced previous events, such as

Staging	Previous CV events, Associated risk factors, Asymptomatic HMOD	Classification of BP			
		High normal SBP 130-140 mmHg DBP 85-90 mmHg	Grade 1 SBP 140-159 mmHg DBP 90-99 mmHg	Grade 2 SBP 160-179 mmHg DBP 100-109 mmHg	Grade 3 SBP ≥180 mmHg DBP ≥ 110 mmHg
Stage 1 Uncomplicated	No concomitant risk factors		Low risk	Moderate risk	High risk
	1-2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2 Asymptomatic disease	eGFR 30-49 ml/min/mq, Diabetes of recent diagnosis Organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 Symptomatic disease	CV/cerebrovascular disease, eGFR < 30/ml/min/mq, Long-standing diabetes	Very high risk	Very high risk	Very high risk	Very high risk

Fig. 2: Stages of hypertension. Modified from 2018 ESC/ESH guidelines [1]. *BP* blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *CV* cardiovascular, *HMOD* hypertension mediated organ damage

Table 3: Assessment of hypertension mediated organ damage (HMOD). Modified from 2018 ESC/ESH guidelines.

Basic screening tests for HMOD	**Indication and interpretation**
12-lead ECG	Screen for LVH and other abnormalities, evaluate heart rate and cardiac rhythm
Urine albumin:creatinine ratio	To investigate elevations in albumin excretion as a sign of renal disease
Blood creatinine and eGFR	To detect possible renal disease
Fundoscopy	To assess hypertensive retinopathy in grade 2 or 3 hypertensives
More detailed screening tests for HMOD	**Indication and interpretation**
Echocardiography	Evaluation of cardiac structure and function
Carotid ultrasound	To investigate the presence of carotid plaque or stenosis particularly in patients with cerebrovascular disease
Abdominal ultrasound and Doppler studies	To examine renal size and structure, abdominal aorta for evidence of aneurysmal dilatation and vascular disease, adrenal glands for evidence of adenoma or phaeochromocytoma, renal artery Doppler studies to screen for the presence of renovascular disease
Pulse wave velocity	To evaluate aortic stiffness and underlying arteriosclerosis
Ankle-brachial index	Screening for lower extremity artery disease
Brain imaging	To evaluate the presence of ischaemic or haemorrhagic brain injury, especially in patients with a history of cerebrovascular disease or cognitive decline

established renal disease, cerebrovascular disease (ischemic or hemorrhagic stroke, transient ischemic attack), coronary artery disease (myocardial infarction, angina, myocardial revascularization), heart failure both at reduced and preserved ejection fraction, detection of atheromatous plaque with imaging, peripheral artery disease, atrial fibrillation.

Based on BP levels, presence of concomitant CV risk factors, HMOD or comorbidities, hypertension is today classified in stages as shown in Fig. 2.

Blood Pressure Thresholds for Treatment

This 2018 edition of guidelines does not break with the previous recommendations as routine work up of hypertensive patients remains the same. In hypertensive patients aged between 18 and 65 years, lifestyle and/or pharmacological interventions should be prescribed for SBP levels ≥ 140 mmHg. For fit older patients aged > 65 years but not > 80 year, the SBP threshold for starting a treatment is in the grade 1 range (140–159 mmHg). In fit older patients aged > 80 years, BP-lowering drug treatment and lifestyle intervention are recommended when SBP is ≥ 160 mmHg. For all these age categories, DBP threshold for treatment is ≥ 90 mmHg (Table 4).

Interestingly, in spite of the evident differences in the classification, the European and American guidelines share the same thresholds for considering initiation of drug treatment in hypertension.

Lifestyle modification, consisting in salt restriction, reduction of alcohol consumption, high consumption of vegetables and fruits, weight loss and maintaining an ideal body weight,

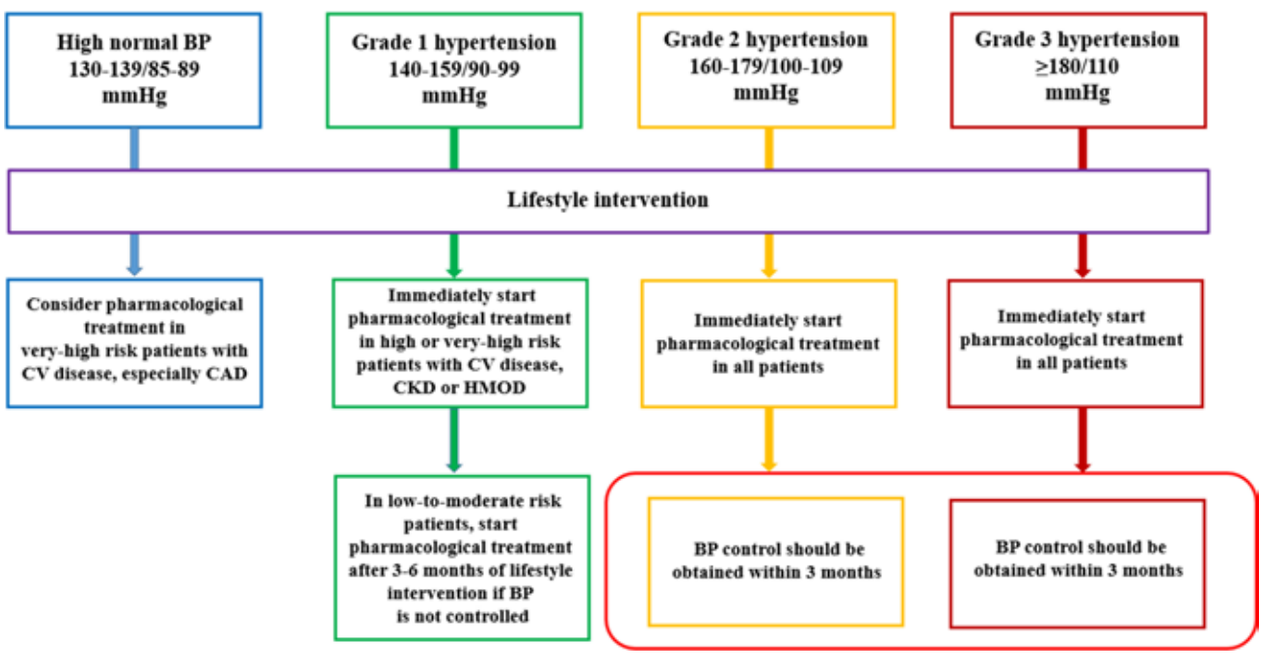

Fig. 3: Management of pharmacological treatment according to the grade of hypertension. Modified from 2018 ESC/ESH guidelines [1]. *BP* blood pressure, *CV* cardiovascular, *CAD* coronary artery disease, *CKD* chronic kidney disease, *HMOD* hypertension mediated organ damage

Table 4: Initiation of hypertension treatment according to 2018 ESC/ESH guidelines. Derived from 2018 ESC/ESH guidelines [1].

Recommendations	Class	Level
BP-lowering drug treatment should be started promptly in patients with grade 2 or 3 hypertension at any level of CV risk, simultaneously with lifestyle intervention	I	A
In patients with grade 1 hypertension: Lifestyle interventions are recommended to try to normalize BP	IIa	B
In patients at low–moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if lifestyle intervention is insufficient to normalize BP	I	A
In patients at high risk or with evidence of HMOD, prompt initiation of drug treatment is recommended simultaneously with lifestyle interventions.	I	A
In fit older patients (even if aged >80 years), pharmacological treatment and lifestyle intervention are recommended when SBP is ≥ 160 mmHg	I	A
Antihypertensive treatment and lifestyle intervention are recommended for fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated	I	A
BP lowering treatment may also be considered in frail older patients if tolerated	IIb	B
If treatment is well tolerated, it should not be withdrawn only on the basis of age, even for patients aged ≥ 80 years	III	A
In patients with high–normal BP (130–139/85–89 mmHg): Lifestyle changes are recommended	I	A
Drug treatment may be considered when their CV risk is very high due to previous cardiovascular events, especially coronary artery disease	IIb	A

and regular physical activity, must be advised to all the hypertensive patients, independently from baseline BP levels.

Blood pressure-lowering drug treatment should be promptly started in patients with grade 2 or 3 hypertension, whatever their estimated CV risk, with the aim of obtaining an adequate BP control within 3 months. The achievement of BP goal preferentially within 3 months in grade 2 and 3 hypertensives and within 3–6 months in patients with grade 1 hypertension represents another novel and challenging recommendation of the 2018 ESC/ESH guidelines. This is in line with growing evidence from literature suggesting that "the earlier the better" in term of BP control and CV outcomes [10–12].

In grade 1 hypertensives at high risk or with evidence of HMOD, drug treatment is recommended simultaneously with the diagnosis of hypertension. Pharmacological treatment may be delayed by 3–6 months in low-to-moderate risk grade 1 hypertensive without HMOD, providing that lifestyle measurements have not been sufficient to normalize BP levels. BP-lowering drugs may be also prescribed to patients with high–normal BP levels at very-high CV risk, especially to those with history of coronary artery disease (Fig. 3).

Blood Pressure Therapeutic Targets

The 2018 ESC/ESH guidelines recommend BP levels < 140/90 mmHg

Table 5: BP treatment targets according to 2018 ESC/ESH guidelines. Derived from 2018 ESC/ESH guidelines [1].

Age group (years)	Office SBP therapeutic target range (mmHg)					Office DBP therapeutic target range (mmHg)
	Hypertension	+ CAD	+ Stroke/TIA	+ Diabetes	+ CKD	
18–65	130 or lower, not < 120	130 or lower, not < 120	130 or lower, not < 120	130 or lower, not < 120	130–139	70–79 For all the patients
65–79	130–139	130–139	130–139	130–139	130–139	
≥ 80	130–139	130–139	130–139	130–139	130–139	

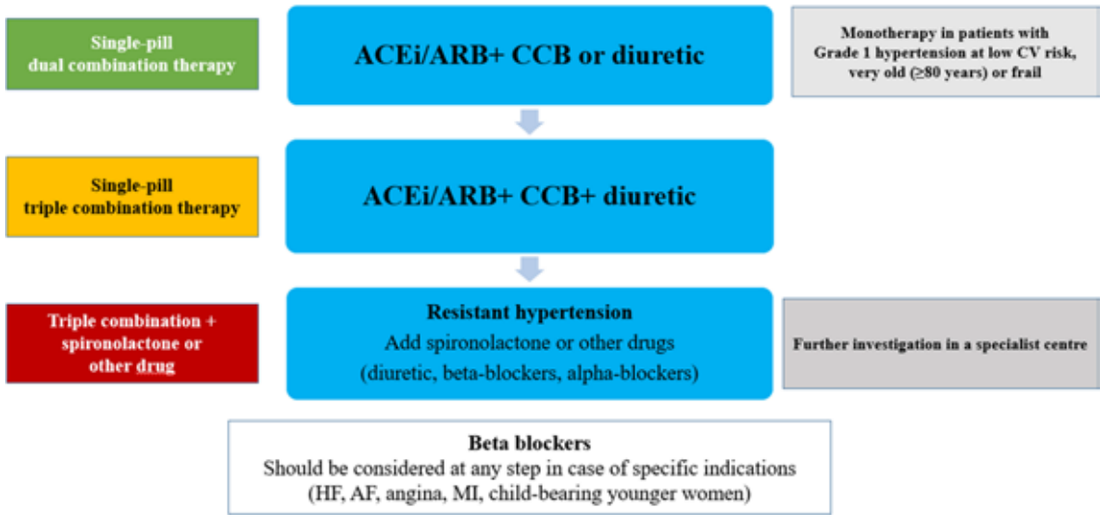

Fig. 4: Therapeutic algorithm for treating hypertension. Modified from 2018 ESC/ESH guidelines [1]. *ACEi* angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *HF* heart failure, *AF* atrial fibrillation, *MI* myocardial infarction

as the first objective of pharmacological treatment in all hypertensives aged between 18 and 65 years [1]. If the treatment is well tolerated, BP values should be further lowered with a suggested SBP target between 130 and 120 mmHg and a DBP target between 80 and 70 mmHg. This BP target is also suggested in patients with left ventricular hypertrophy. In some way these new targets also incorporate the debated results of the SPRINT trial [13, 14]. In fit older patients aged > 65 years, including those aged > 80 years, SBP should be targeted between 140 and 130 mmHg, carefully checking for the occurrence of adverse events [1]. These therapeutic goals (BP < 130/80 mmHg) should be also applied to categories of patients of special interest, such as those with previous coronary and cerebral events or affected by diabetes. Patients affected by chronic kidney disease, considering their often coexisting frail status, should instead reach SBP levels between 140 and 130 mmHg (Table 5).

Therapeutic Strategies

The 2018 ESC/ESH guidelines still recommend as first choice five major drug classes for the treatment of hypertension: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and diuretics (thiazides and thiazide-like diuretics such as chlortalidone and indapamide), due to their established efficacy in reducing BP and CV events [1].

Most of hypertensive patients do not reach therapeutic targets with monotherapy, even after the increasing of the dosages or switching from one monotherapy to another one. This strategy is often ineffective and time consuming, providing only little additional BP lowering and increasing the risk of adverse effects.

For this reason, current European guidelines adopt an historical paradigm shift, which will largely modify medical management of hypertensive patients. In fact, they recommend the use of initial combination treatment as first line strategy in most patients, especially adopting the single-pill fixed combinations. Low dose two-drug combinations as initial therapy have been demonstrated to be safe and well tolerated, with a small incidence of adverse events. Moreover, patients seem to tolerate better the treatment and to be more adherent with the use of single-pill fixed dose combinations.

Combinations of all five major drug classes except for ACE inhibitors and ARBs, are suitable but 2018 ESC/ESH guidelines suggest starting with an ACE inhibitor or ARB with a CCB and/or a thiazide/thiazide-like diuretic, due to their complementary and synergistic effect, also in limiting potential adverse events, and their large availability in a single pill and in a range of doses [1].

A beta-blocker in combination with a diuretic or any drug from the other major classes is suggested when there is a specific indication, such as in patients with coronary artery disease, heart failure, or high rate atrial fibrillation.

A three drug single pill combination, preferably with an ACE inhibitor/ARB, a CCB, and a diuretic is indicated as second step strategy if BP is not adequately controlled with two drugs. Monotherapy may be prescribed in low risk grade 1 hypertensives, very high-risk patients with high–normal BP, or frail older patients (Fig. 4).

Monotherapy is recommended in a minority of patients including grade 1 hypertensives at low CV risk, subjects with high-normal BP at very-high CV risk, especially those with history of coronary events, and frail elderlies.

Resistant Hypertension

According to the ESC/ESH 2018 guidelines hypertension is considered resistant to treatment when a strategy consisting in appropriate lifestyle measures and treatment with optimal or best-tolerated doses of three or more drugs, which should include a diuretic, is ineffective in lowering office SBP and DBP values to < 140 mmHg

and/or < 90 mmHg, respectively. The diagnosis of resistant hypertension must be confirmed by ABPM or HBPM. Undetected secondary forms and pseudo-resistant hypertension must be excluded: poor adherence to prescribed medicines, errors in office BP measurement techniques, marked brachial artery calcification, use of inadequate doses or irrational combinations of BP-lowering drugs as a consequence of clinician inertia. In addition, other causes of resistant hypertension, such as drugs prescribed for other conditions, lifestyle factors such as obesity or excessive alcohol consumption, obstructive sleep apnea, should be detected and promptly corrected.

Guidelines recommend the addition to the current treatment of a low-dose of spironolactone, or other diuretic in case of intolerance, such as eplerenone, amiloride, a higher dose thiazide/thiazide-like diuretic, or a loop diuretic. Alternative suggested strategies consist in the use of bisoprolol or doxazosin. The judgement on the use of device-based non pharmacological treatment of hypertension (such as renal denervation) is suspended in guidelines, looking forward to the results of ongoing clinical trials.

Improvement of Adherence

Poor adherence to the treatment, mainly related to the number of prescribed pills, is the principal cause of inadequate BP control in real world hypertension managament, with a significant increased risk of CV events. Physicians should always investigate this phenomenon, encourage patients' cooperation and prefer strategies consisting in single-pill combinations with long acting drugs and avoiding complex schedules [15].

Conclusions

At first sight the ESC/ESH 2018 guidelines may appear to have moved little from the previous edition, very differently from what happened in the U.S. and Canada. Indeed, in European guidelines the main aspects of definition of hypertension remained quite the same. If we look at BP targets, however, it seems like they may be even more ambitious than those from American Heart Association/American College of Cardiology 2017 Guidelines. In fact, when it is tolerated, a target < 130 mmHg is widely recommended and this is a major novelty of these guidelines. The use of fixed-dose drug combinations, especially in single-pills, is an essential tool to better control BP, consistently improving therapeutic adherence and reaching the suggested targets in a larger number of hypertensive patients.

In our opinion, in the latest edition of ESC/ESH guidelines still some aspects are not fully-covered. For instance, the estimation of CV risk can still be incomplete. Indeed, even though young patients hardly reach a high risk according to SCORE, we cannot weigh the impact of severity or duration of concomitant risk factors, organ damage or diseases, so that the actual absolute or lifetime CV risk might be higher than estimated, supporting a different therapeutic approach.

Compliance with Ethical Standards

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Conflict of interest: Authors have no conflict of interest to disclose.

Ethical approval: This article does not contain data derived by any current studies with human participants performed by any of the authors. The clinical studies mentioned were provided with specific ethical approval.

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such an approach is not preferred over the blood pressure level per se. The U.S. guidelines have taken a hybrid approach recommending treatment in the 130 s based on absolute risk to avoid the general population medicalisation but 140 mmHg and above on the old paradigm [9]. It takes a lot of courage to loosen blood pressure treatment thresholds for low-risk individuals and less so to adopt lower ones for high-risk individuals. Contemporary European guidelines have remained cautious moving from awaiting further evidence for treating those in the 130 s to "Drug treatment may be considered when CV risk is very high due to established CVD, especially CAD" [10]. Thus, the high-risk primary prevention thresholds remain unchanged.

Conclusions

The move to an approach based on absolute risk for the primary prevention of cardiovascular disease is likely to improve the effectiveness and cost-effectiveness of treatment. The absolute risk approach targets the patients who are most likely to benefit and reduces the medicalisation of patients at low risk.

Compliance with Ethical Standards

Conflict of Interest: The author declares no conflicts of interest relevant to this manuscript.

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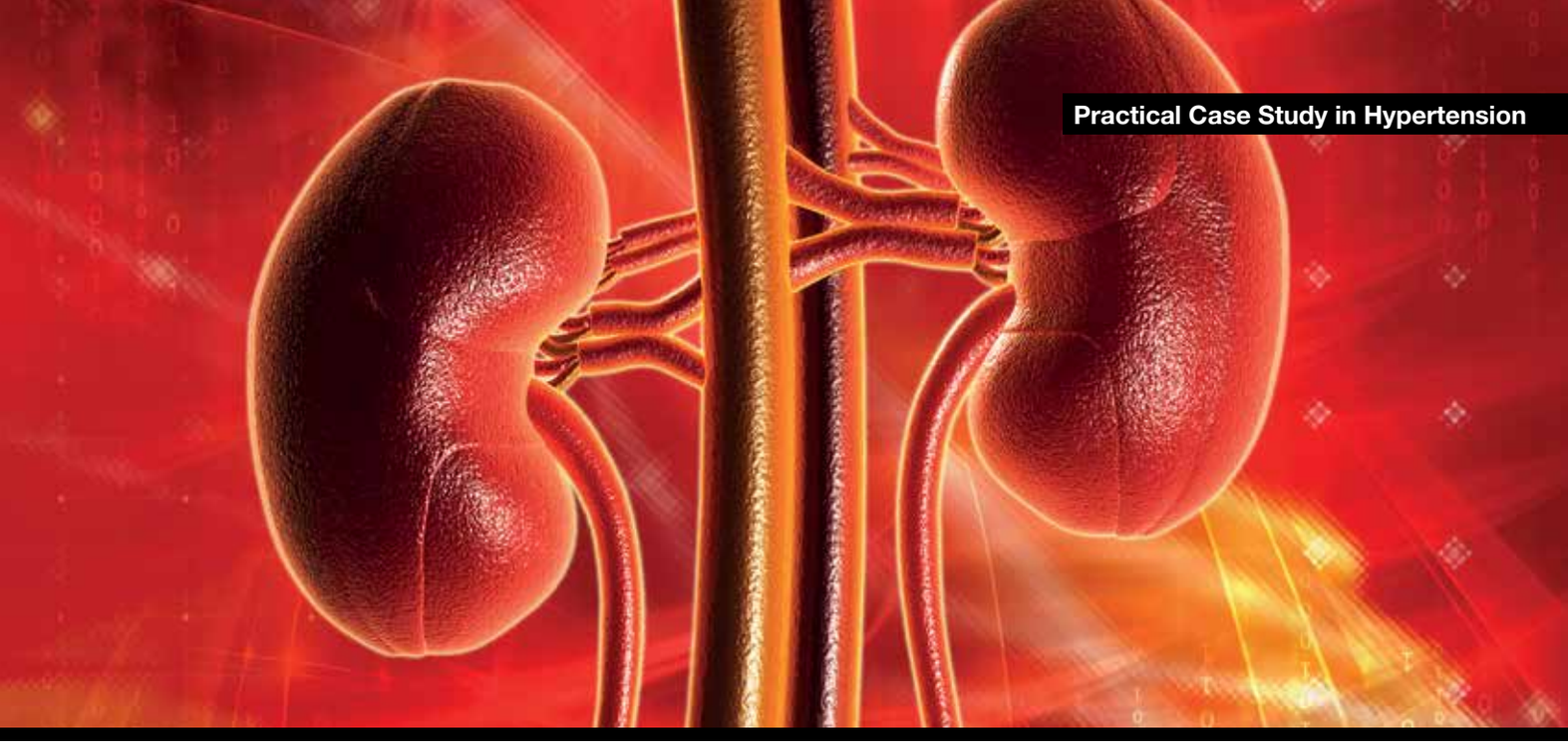


Patient with Hypertension and End-Stage Renal Disease

Roberto Pontremoli

A 48-year-old man, construction worker of North African origins, is taken to our emergency department because of progressive loss of visual acuity over the previous few days accompanied by headache, nausea, vomiting and hyporexia.

Roberto Pontremoli

Roberto Pontremoli University of Genoa, IRCCS Policlinico San Martino, Genoa, Italy

Clinical Case Presentation

A 48-year-old man, construction worker of North African origins, is taken to our emergency department because of progressive loss of visual acuity over the previous few days accompanied by headache, nausea, vomiting and hyporexia.

Family History

He reports no family history for premature cardiovascular disease. He is unable to provide medical information about his several brothers and sisters, who are currently living abroad.

Clinical History

The patient is not aware of previous chronic condition and has not undergone any clinical or lab examination in recent years. He reports general good health over the previous several years. He reports no current medication, nor alcohol or drug abuse. He smokes 20 cigarettes/day.

Physical Examination

- Weight: 93 kg
- Height: 168 cm
- Body mass index (BMI): 33 kg/m^2
- Waist circumference: 116 cm
- Respiration: 16/min, slightly dyspnoeic
- Heart sounds: increased T2, 3/6 systolic murmur
- Resting pulse: 104/min, regular
- Carotid arteries: regular, no bruits
- Femoral and foot arteries: pulses regularly palpable at common anatomic sites
- Physical examination of the abdomen is unremarkable; no palpable masses and no bruits could be detected
- Blood pressure (right and left upper arm): 220/140 mmHg
- Blood pressure (lower limb): 230 mmHg

Biochemical Profile

- Haemoglobin: 12.7 g/dL
- MCV: 89
- PLT: 119,000
- WBC: 13 × 10^9/L

- Fasting plasma glucose: 104 mg/dL
- Fasting lipids: total cholesterol (TOT-C), 167 mg/dL; low-density lipoprotein cholesterol (LDL-C), 103 mg/dL; high-density lipoprotein cholesterol (HDL-C), 32 mg/dL; triglycerides (TG), 160 mg/dL
- LDH: 834 UI
- Haptoglobin: 0.017 g/L
- NT-pro-BNP: 3344 ng/L
- Electrolytes: sodium, 137 mEq/L; potassium, 2.6 mEq/L
- Serum uric acid: 10.2 mg/dL
- Renal function: urea, 134 mg/dL; creatinine, 7.8 mg/dL; estimated glomerular filtration rate (eGFR) (CKD-EPI), 8 mL/min/1.73 m^2
- Urine analysis (dipstick): protein +++ (0.9 g/L); no sediment abnormalities
- ABG: pO_2 92 mmHg, pH 7.42, pCO_2 36.8 mmHg, HCO_3 23.7 mEq/L

12-Lead Electrocardiogram

Sinus rhythm, heart rate 98/min and high-voltage QRS, with abnormal repolarization (strain). Severe left ventricular hypertrophy (LVH) (Fig. 1).

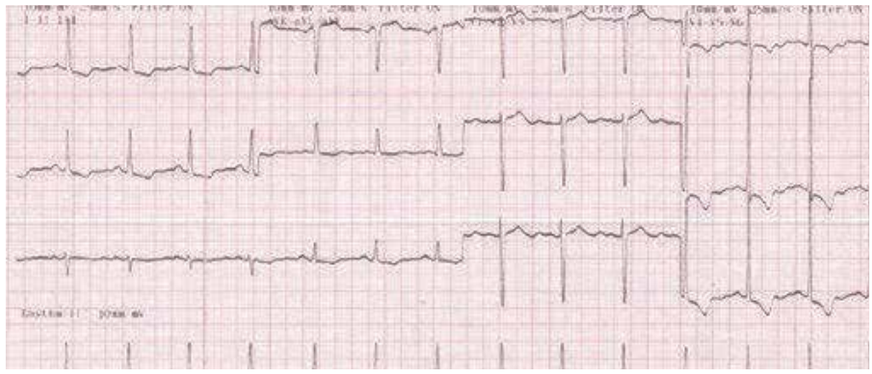


Fig. 1: ECG shows sinus rhythm, heart rate 75/min and high-voltage QRS, with abnormal repolarization (strain), suggesting the presence of severe left ventricular hypertrophy.

Chest Radiogram

Anteroposterior (AP) view. No evidence of pulmonary parenchymal masses or infiltrations. Clear both costophrenic angles. Increased cardiac shape (LVH).

Echocardiogram

Echocardiography showed increased atrial size (49 mm), symmetrical left ventricular hypertrophy (TDD 45 mm, IVSTd 17 mm, PWTd 12 mm, LVMI 143 g/m^2, RWT 0.54). Systolic function was within normal limits. Doppler scan showed signs of abnormal diastolic function. All other findings were unremarkable.

Fundoscopic Examination

Signs of chronic and acute severe hypertensive retinopathy were visible with focal intraretinal periarteriolar transudates and initial optic disc oedema (Fig. 2).

Abdominal US Scan

Both kidneys appear slightly reduced in longitudinal diameter (rx, 10.2 cm; left 9.8 cm) with increased echogenicity and reduced cortical thickness. No Doppler signs compatible with renal artery stenosis; increased renal resistive index (RRI 0.78–0.80).

Diagnosis

Patient is diagnosed with severe hypertension with renal damage, possibly in the context of malignant hypertension.

Emergency Treatment

Fenoldopam i.v. is started at a dose of 0.02 µg/kg/min and later downtitrated to 0.01 µg/kg/in after 2 h for a total of 24 h, together with atenolol 50 mg p.o. and furosemide 20 mg e.v. t.i.d. KCl 30 mEq in 5% glucose 500 mL at 21 mL/h.

Follow-up (Emergency Department)

Blood pressure gradually decreased over the first 3–4 h with remission of symptoms. ECG was unchanged.

Follow-up (Nephrology Ward)

Serum creatinine slightly reduced over the next few days (creatinine 5.5 mg/dL, urea 98 mg/dL along with normalization of serum electrolytes).

Among other tests: no Bence Jones proteinuria, normal or negative immunologic tests (ANA, ANCA, C3, C4 and serum immunoglobulins) including serology for HBV, HCV and HIV.

Also within normal limits, urinary catecholamines, metanephrines and normetanephrines. RM scan and TC confirmed the lack of lesions at the renal arteries as well as at both adrenal glands absence of intra-abdominal masses.

Renal biopsy, performed (Figs. 3 and 4) 4 days after admission, showed diffuse vascular changes compatible with a diagnosis of accelerated hypertension.

Follow-up Evaluation (At Time of Discharge from Hospital)

Three weeks later the patient is discharged from the hospital, and close follow-up is

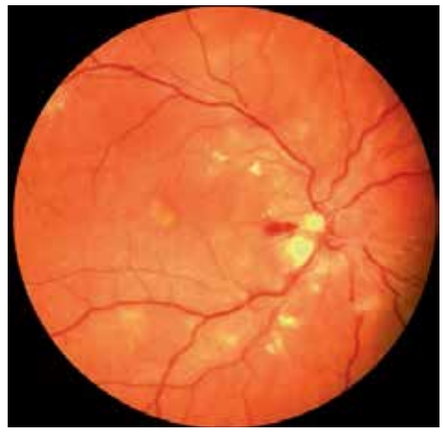


Fig. 2: Funduscopic examination shows a combination of haemorrhages (blot-, dot- or flame-shaped), microaneurysms, cotton wool spots and hard exudates. These lesions are pathognomonic of accelerated hypertension.

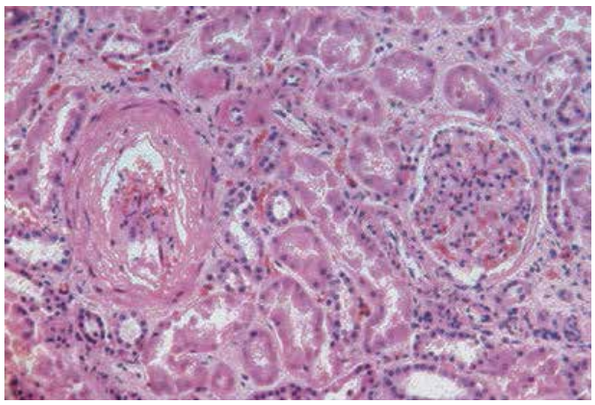


Fig. 3: Renal biopsy: hyperplastic arteriosclerosis and fibrosis with vessel obliteration; diffuse interstitial fibrosis and tubular damage.

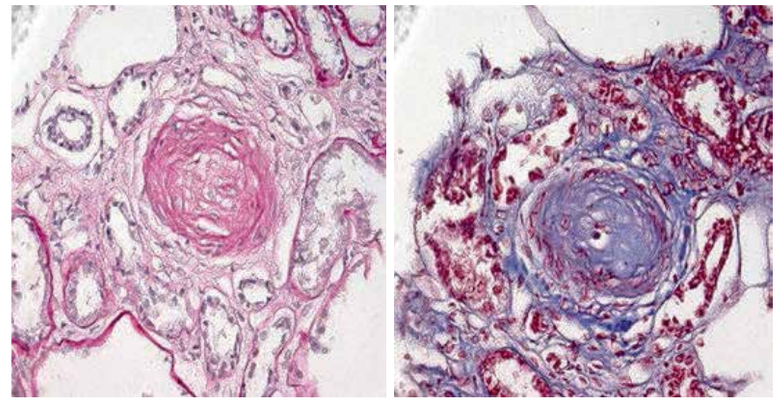


Fig. 4: Immuno Fluorescence (IF), negative; Optic Microscopy (OM) shows four normal glomeruli, diffuse interstitial fibrosis and mild edema; focal tubular thinning and brush border reduction. One medium-sized arteriole shows intimal fibrosis with concentric proliferation and lumen obliteration (periodic acid-Schiff stain [PAS]). Vessel concentric proliferation and lumen obliteration is shown in greater detail at trichrome stain (*right panel*).

planned to evaluate the timing for RRT initiation. His blood pressure is well controlled.

Prescriptions at hospital discharge:

- Atenolol 50 mg 08.00 a.m.
- Valsartan 160 mg 08.00 a.m.
- Furosemide 50 mg b.i.d
- Lisinopril 5 mg 08.00 p.m.
- Nifedipine GITS 60 mg 08.00 a.m. and 08.00 p.m.
- Spironolactone 100 mg 08.00 a.m. every other day
- Clonidine TTS 2, 1transdermic patch/ week
- Allopurinol 150 mg 08.00
- Calcium carbonate 1 g b.i.d. (at meals)
- Sodium bicarbonate 1 g p.o. 08.00 a.m. and 10.00 p.m.

Outpatient Follow-up Visit (3 Months Later)

The patient reports poor treatment adherence. He has been taking prescribed drugs irregularly and did not measure his blood pressure.

Physical Examination

- Weight: 93 kg
- Height: 168 cm
- Body mass index (BMI): 33 kg/m^2
- Waist circumference: 116 cm
- Respiration: 16/min, slightly dyspnoeic
- Heart sounds: increased T2, 3/6 systolic murmur
- Resting pulse: 104/min, regular
- Carotid arteries: regular, no bruits
- Femoral and foot arteries: pulses regularly palpable at common anatomic sites
- Physical examination of the abdomen is unremarkable; no palpable masses and no bruits could be detected
- Blood pressure (right and left upper arm): 220/140 mmHg

Blood tests:

- Hb: 13.8
- Creatinine, 3.7 mg/dL; urea, 125 mg/ dL; uric acid, 8.3 mg/dL; K, 4.2 mEq/L
- PCR: neg
- Ca, 9.4 mg/dL; P, 3 mg/dL
- NaU: 116/die
- Urinalysis: protein +++ (1.1 g/L); albumin to creatinine ratio (spot), 982 mg/g
- vBG: pH, 7.32; CO_2, 59; HCO_3, 30

Blood Pressure (Office)

- 210/130 mmHg (seated)

Ambulatory blood pressure monitoring (ABPM) (Fig. 5).

Follow-up (3 Weeks Later)

Biochemical Profile

- Hb: 16 mg/dL
- Creatinine: 4.6 mg/dL
- Uric acid: 18 mg/dL
- K: 3.9 mEq/L

Daytime (7-23)	Min	Max	Mean
Systolic [mmHg]	103	241	171,32
Diastolic [mmHg]	45	130	80,93
Mean [mmHg]	76	151	110,73
Heart rate [bpm]	53	81	63,41
PP [mmHg]	35	134	90,39

Nighttime (23-7)	Min	Max	Mean
Systolic [mmHg]	160	206	185,42
Diastolic [mmHg]	66	105	88,18
Mean [mmHg]	99	138	120,27
Heart rate [bpm]	55	81	62,88
PP [mmHg]	74	131	97,24

24 hours	Min	Max	Mean
Systolic [mmHg]	103	241	174,60
Diastolic [mmHg]	45	130	82,61
Mean [mmHg]	76	151	112,95
Heart rate [bpm]	53	81	63,29
PP [mmHg]	35	134	91,99

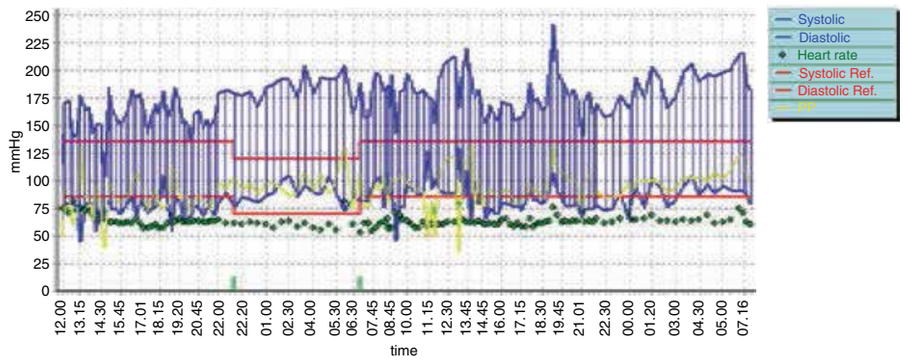


Fig. 5: Ambulatory blood pressure monitoring: the tracing shows markedly elevated blood pressure values through the entire 24 h period, with loss of physiological blood pressure reduction during the night period (non-dipper).

Daytime (8-23)	Min	Max	Mean
Systolic [mmHg]	99	211	145,98
Diastolic [mmHg]	42	138	89,60
Mean [mmHg]	76	142	108,08
Heart rate [bpm]	55	115	88,23
PP [mmHg]	13	145	56,38

Nighttime (23-8)	Min	Max	Mean
Systolic [mmHg]	114	143	129,90
Diastolic [mmHg]	75	103	85,50
Mean [mmHg]	88	116	100,05
Heart rate [bpm]	71	111	81,90
PP [mmHg]	33	54	44,40

24 hours	Min	Max	Mean
Systolic [mmHg]	99	211	141,51
Diastolic [mmHg]	42	138	88,46
Mean [mmHg]	76	142	105,85
Heart rate [bpm]	55	115	86,47
PP [mmHg]	13	145	53,06

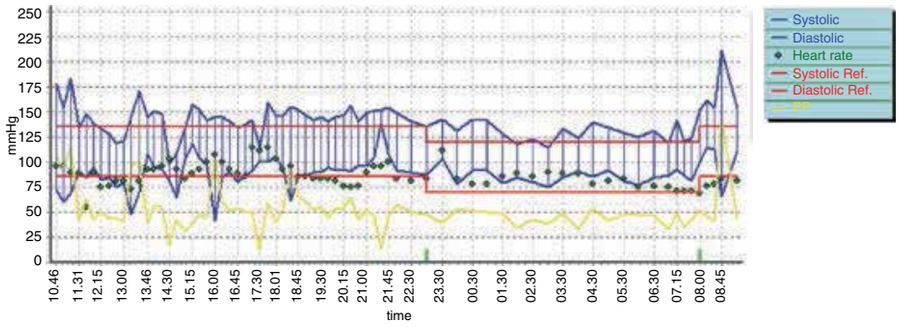


Fig. 6: Ambulatory blood pressure monitoring: the tracing shows improvement of blood pressure control through the 24 h period. Blood pressure values, although not ideal, are considerably lower as compared to previous ABPM.

- Blood pressure (home): 130/90 mmHg
- Blood pressure (office): 140/70 mmHg
- **ABPM** (Fig. 6)

Follow-up (6 Months Later)

The patient reports general well-being and good adherence to treatment.

Physical Examination

- Weight: 92 kg
- Respiration: 12/min, eupnoeic
- Heart sounds: increased T2, 2/6 systolic murmur
- Resting pulse: 84/min, regular
- Physical examination of the abdomen is unremarkable; no palpable masses and no bruits can be detected. Mild peripheral oedema (1+) at the ankles bilaterally

Biochemical Profile

- Hb: 15.1 mg/dL
- Creatinine: 3.9 mg/dL
- Uric acid: 12 mg/dL
- K: 4.1 mEq/L
- Blood pressure (home): 150–160/95–100 mmHg

Prescriptions

- Atenolol 50 mg 08.00 a.m.
- Valsartan 160 mg 08.00 a.m.
- Furosemide 125 mg b.i.d
- Nifedipine GITS 60 mg 08.00 a.m. and 08.00 p.m.
- Spironolactone 25 mg 08.00 a.m. every other day
- Allopurinol 150 mg 08.00
- Clonidine TTS 2, 1transdermic patch/ week
- Calcium carbonate 1 g b.i.d. (at meals)
- Sodium bicarbonate 1 g p.o. 08.00 a.m. and 10.00 p.m.

Discussion

Accelerated hypertension represents a therapeutic challenge. BP control is mandatory to prevent organ damage and major cardiovascular events.

The right amount of diuretic or diuretic combination is key to obtain blood pressure control.

In the case presented here, triple combination of RAAS inhibiting drugs together with appropriate furosemide dose and several other drugs allowed acceptable therapeutic success. In the outpatient setting, however, adherence to treatment as well as side effects are often an issue.

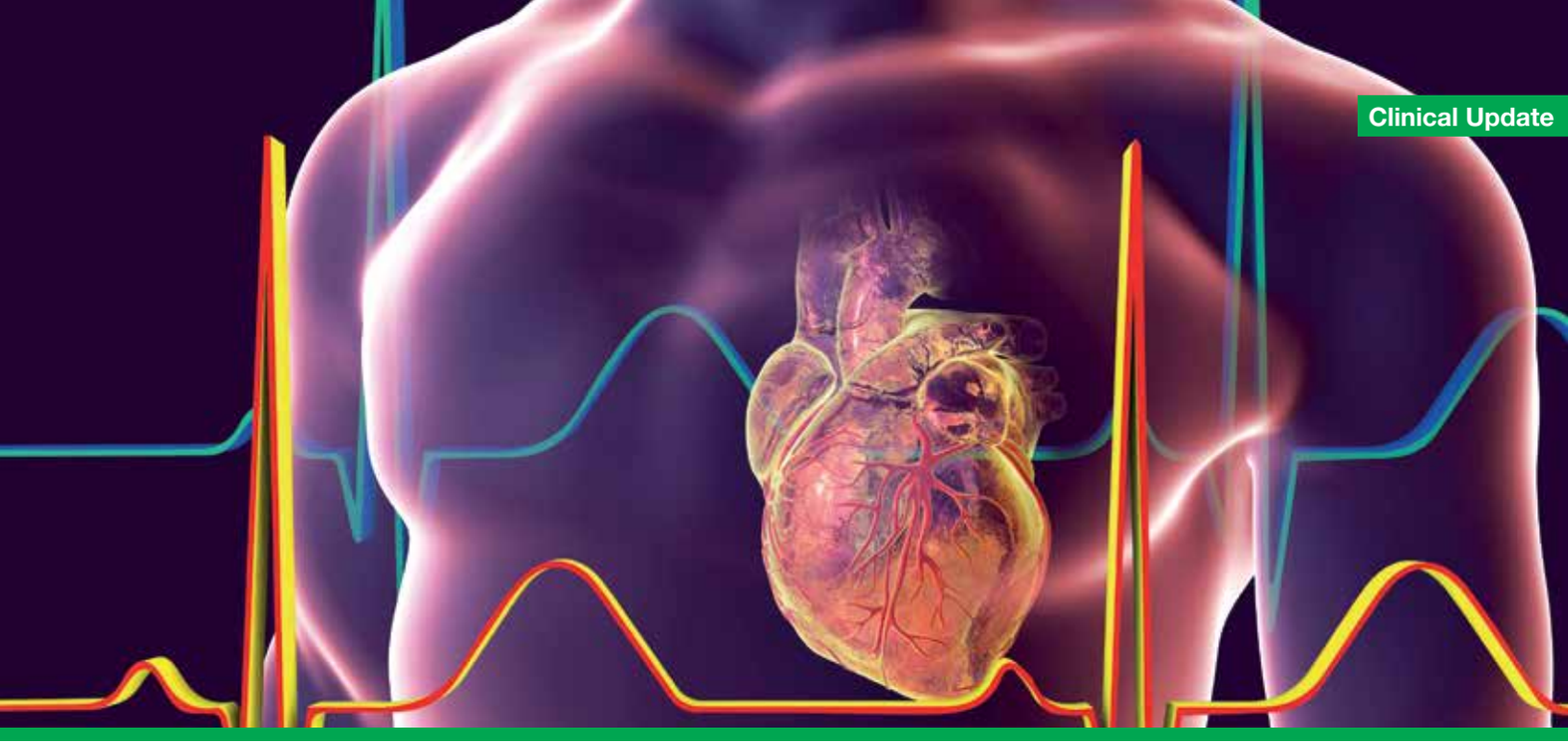
When renal autoregulation is lost, as in the case of CKD and multiple antihypertensive drugs, a paradoxical J curve effect may ensue in the relationship between BP and GFR. As a matter of fact, in the case described here, when adherence to treatment improved and hence BP was better controlled, a parallel reduction in GFR was evident. Antihypertensive treatment should be tailored to each patient's clinical situation to balance side effects between an excess of haemodynamic load and renal worsening due to hypovolemia.

Take-home Messages

- Accelerated or malignant hypertension, although rare in Caucasians, is not uncommon in patients of Afro-American descent. It is characterized by tumultuous clinical course with rapid deterioration of renal function
- Combination treatment and blood pressure control may stabilize renal function and retard progression towards ESRD
- Diuretic combination and sometime RAAS-I combination may be necessary to obtain BP control
- In the presence of CKD and multiple treatment, the relationship between BP and renal function may be described by a paradoxical J curve

References available on request Healthcare.India@springer.com

Source: Pontremoli R. (ed). Patient with hypertension and end-stage renal disease. Hypertension and Renal Organ Damage: Practical Case Studies in Hypertension Management. 1st ed. Switzerland: Springer International Publishing; 2017, pp 55-66. DOI 10.1007/978-3-319-56408-1_5.



Myocardial Infarction with Non-Obstructive Coronary Arteries: A Focus on Vasospastic Angina

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Vasospastic angina (VSA) is considered a broad diagnostic category including documented spontaneous episodes of angina pectoris produced by coronary epicardial vasospasm as well as those induced during provocative coronary vasospasm testing and coronary microvascular dysfunction due to microvascular spasm.

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Introduction

The vast majority of acute myocardial infarction (AMI) patients have obstructive coronary artery disease (CAD) (ie, ≥50% stenosis) at coronary angiography (CAG) and well-established therapeutic guidelines are available, often involving coronary revascularisation. However, 1–14% of AMI occur in the absence of obstructive CAD [1, 2]. Non-obstructive CAD in patients presenting with symptoms and ST-segment deviation suggestive of ischaemia does not preclude an atherothrombotic aetiology, as thrombosis can be a dynamic phenomenon with a non-obstructive atherosclerotic plaque. The diagnosis of myocardial infarction with non-obstructive coronary atherosclerosis (MINOCA) should be considered a 'working diagnosis' and its underlying cause should be investigated (Tab. 1 and 2).

Vasospastic angina (VSA), basically synonymous with the terms Prinzmetal's angina and variant angina, is an important functional cardiac disorder leading to type 2 myocardial infarction [3]. The term VSA is considered a broad diagnostic category including documented spontaneous episodes of angina pectoris produced by coronary epicardial vasospasm (EV) and/or coronary microvascular dysfunction (CMD) due to microvascular spasm as well as angina pectoris induced by provocative coronary vasospasm testing. The diagnostic criteria for VSA as proposed by the Coronary Vasomotion

Table 1: Diagnostic criteria for myocardial infarction with non-obstructive coronary atherosclerosis and vasospastic angina.

MINOCA diagnostic criteria elements	
1	AMI criteria, including:
	(a) Positive cardiac biomarker: defined as a rise and/or fall in serial levels, with at least one value above the 99th percentile upper reference limit and
	(b) Corroborative clinical evidence of infarction, including any of the following:
	– i. Ischaemic symptoms (chest pain and/or dyspnoea)
	– ii. Ischaemic ECG changes (new ST-segment changes or LBBB)
	– iii. New pathological Q waves
	– iv. New loss of viable myocardium on myocardial perfusion imaging or new RWMA
	– v. Intracoronary thrombus evident on angiography or at autopsy
2	Absence of obstructive CAD on angiography (defined as no lesions ≥50%)
3	No clinically apparent cause for the acute presentation
Vasospastic angina diagnostic criteria elements	
1	Nitrate-responsive angina—during spontaneous episode, with at least one of the following:
	(a) Rest angina—especially between night and early morning
	(b) Marked diurnal variation in exercise tolerance—reduced in morning
	(c) Hyperventilation can precipitate an episode
	(d) Calcium channel blockers (but not beta-blockers) suppress episodes
2	Transient ischaemic ECG changes—during spontaneous episode, including any of the following in at least two contiguous leads:
	(a) ST-segment elevation ≥0.1 mV
	(b) ST-segment depression ≥0.1 mV
	(c) New negative U waves
3	Coronary artery spasm—defined as transient total or subtotal coronary artery occlusion (>90% constriction) with angina and ischaemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergonovine or hyperventilation)

AMI acute myocardial infarction, *CAD* coronary artery disease, *ECG* electrocardiogram, *LBBB* left bundle branch block, *RWMA* regional wall motion abnormality

Table 2: Mechanisms of myocardial infarction with non-obstructive coronary atherosclerosis.

Clinical disorder		
1	Epicardiac coronary disorders (MI type 1)	(a) Atherosclerotic plaque rupture
		(b) Ulceration
		(c) Fissuring
		(d) Erosion or coronary dissection with non-obstructive CAD
2	Imbalance between oxygen supply and demand (MI type 2)	(a) Coronary embolism
		(b) Coronary artery vasospasm
3	Coronary endothelial dysfunction (MI type 2)	(a) Coronary microvascular dysfunction
4	Myocardial causes	(a) Cardiomyopathy
		– i. Takotsubo syndrome
		– ii. Dilated
		– iii. Hypertrophic
		(b) (Peri)-myocarditis
		(c) Myocardial trauma or injury
		(d) Tachyarrhythmia-induced infarct
5	Non-cardiac causes	(a) Renal impairment
		(b) Pulmonary embolism

CAD coronary artery disease, *MI* myocardial infarction

Disorders International Study Group (COVADIS) [4] are summarised in Tab. 1. Although VSA may co-exist with coronary microvascular disorders and/or structural CAD (Fig. 1), it is a clinical entity that involves hyperreactivity of the epicardial arteries to vasoconstrictor stimuli [5]. The importance of diagnosing VSA relates to: (1) the major adverse events associated with this disorder including AMI, syncope due to arrhythmia, and sudden cardiac death (SCD) [6–8], and (2) the potential to prevent adverse events by the use of calcium channel blockers and nitrates and avoiding potential vasospasm precipitants (eg, vasoconstrictors). This article aims to provide an overview of the clinical characteristics, diagnostic tests, and treatment for VSA patients. PubMed and Embase were searched for relevant articles focusing on the following terms: 'coronary artery vasospasm', 'vasospastic angina', 'Prinzmetal angina', 'non-obstructive', and 'myocardial infarction'. This article will focus on VSA, either EV or microvascular vasospasm, and will not fully elaborate on CMD in all its subforms.

Clinical Manifestations of Vasospastic Angina

The prevalence of VSA remains largely unknown but ranges between 3 and 95% of all MINOCA patients depending on the stimuli used to trigger vasospasm, definitions of vasospasm, and ethnic background [9]. The hallmark feature of VSA is rest angina, which promptly responds to short-acting nitrates; however, VSA can present with a great variety of symptoms, such as silent myocardial ischaemia, stable angina, acute coronary syndrome or SCD [10, 11]. Patients with VSA typically experience angina at rest, during the night or early in the morning, and this can be precipitated by hyperventilation [10, 12]. A study systematically performing invasive provocative vasospasm testing in 1,089 consecutive patients (excluding patients with spontaneous spasm, left main narrowing

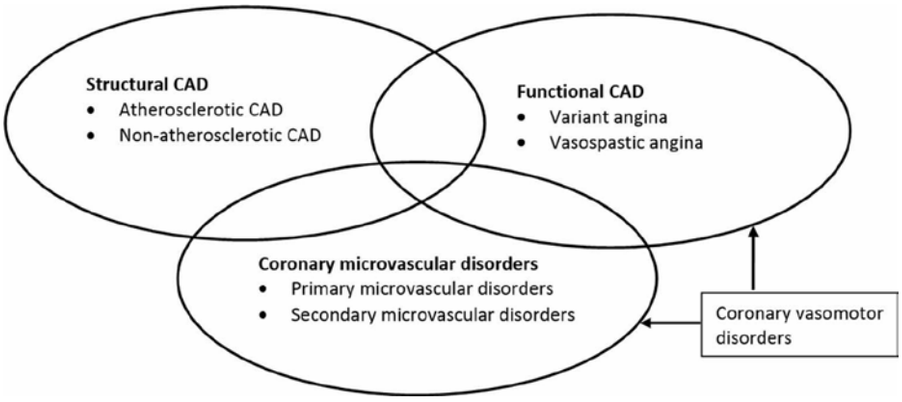

Fig. 1: Ischaemic heart disease (*CAD* coronary artery disease).

or severe three-vessel disease) showed that EV was present in 38% of patients with angina only at rest, 14% of those with angina at rest and during exercise, 4% with only exertional angina, 1% with atypical chest pain, 20% of patients with a recent AMI, 6% of patients with an 'old' myocardial infarction, and 0% of patients with congestive cardiomyopathy [13]. Importantly, VSA can be induced by exercise, especially in the morning [14]. Even though brief episodes of vasospasm can be asymptomatic, they may generate silent myocardial ischaemia [12]. Moreover, various arrhythmias are associated with VSA even in the absence of angina, including sinus bradycardia, sinus arrest with or without junctional escape beats, complete atrioventricular block, paroxysmal atrial fibrillation, ventricular tachycardia, ventricular fibrillation and asystole [11, 15, 16]. It is noteworthy that VSA-related SCD is most frequently related to bradyarrhythmia rather than tachyarrhythmia [17].

The prognosis of patients diagnosed with VSA is variable and depends on the degree of vasospasm. A novel scoring system, the Japanese Coronary Spasm Association (JCSA), may provide a comprehensive risk assessment and prognostic stratification for VSA patients [18]. Although not validated in Caucasian patients, the JCSA score includes predictors of major adverse cardiac events (MACE): history of out-of-hospital cardiac arrest (OHCA) (4 points); multivessel EV, smoking, angina at rest alone, coronary stenosis (2 points each); ST-segment elevation during angina, and beta-blocker use (1 point each). Patients can be categorised as low risk (score 0–2), intermediate risk (score 3–5) or high risk (score ≥6), resulting in an incidence of MACE of 2.5%, 7.0%, and 13%, respectively at a median follow-up of 32 months.

Risk factors and Pathogenesis

Vasospastic angina is more prevalent among females than males [19, 20]. The importance of recognising sex differences is enhanced by the fact that VSA in female patients can present with different symptoms than those in male patients. This may lead to an underestimation of cardiac causes of chest-related symptoms in female patients, in particular if the CAG is normal. In the largest European study including 1,379 consecutive patients with stable angina and unobstructed coronary arteries, acetylcholine (ACH) tests were performed, 59% had a positive ACH test (33% for CMD, 26% for EV) [19]. A positive ACH test was more common in females (70% vs 43%; $p < 0.001$). In a multivariable logistic regression model the sex difference was statistically significant with a female-male odds ratio for CMD and EV of 4.2 (95% confidence interval: 3.1–5.5; $p < 0.001$) and 2.3 (95% confidence interval: 1.7–3.1; $p < 0.001$), respectively.

In general, most patients with VSA are diagnosed between 40 and 70 years of age. While smoking and high-sensitivity C-reactive protein are risk factors for VSA [21, 22], it can be precipitated by many factors such as physical and/or emotional stress, alcohol consumption, magnesium deficiency, and the administration of stimulant drugs (cocaine, amphetamines, etc.), sympathomimetic agents (epinephrine, norepinephrine, etc.), parasympathomimetic agents (methacholine, pilocarpine, etc.), vasoconstrictor agents (beta-blockers, anti-migraine drugs, etc.) and ergot alkaloids (ergonovine (ER), ergotamine, etc.) [23–26]. Genetic mutations were found to be associated with VSA in genes coding for proteins for adrenergic or serotoninergic receptors, angiotensin-converting enzyme, and inflammatory cytokines [11]. Polymorphisms of paraoxonase I gene and mutations or polymorphisms of the endothelial NO synthase gene are also found, albeit NO gene polymorphisms are only found in one-third of VSA patients [11]. The pathophysiology of VSA is the result of the interaction of two components: (1) hyperreactivity of vascular smooth muscle cells (VSMCs; localised or diffuse) and (2) a transient vasoconstrictor stimulus acting on the hyperreactive VSMCs [9]. The main cause of VSMC hyperreactivity seems to be enhanced Rho kinase activity [1]. In summary, considering the abundance of triggers and the various vasoconstrictors that can be used to provoke coronary vasospasm, this suggests it is not the consequence of a single receptor pathway problem, but rather multifactorial.

Evaluation of Patients with Vasospastic Angina

Non-invasive Evaluation

Non-invasive, non-pharmacological evaluation for the diagnosis of VSA includes standard 12-lead ECG during an attack, Holter monitoring, and exercise testing [20]. ECG changes are related to the severity of vasospasm. EV is more frequently associated with ST-segment depression rather than ST-segment elevation, indicating less severe subendocardial myocardial ischaemia [27]. Total or subtotal vasospasm of a major coronary artery may result in ST-segment elevation in the leads

corresponding to the distribution of that coronary artery. Other ECG changes associated with VSA include a delay in the peak of the R wave, an increase in the height and width of the R wave, a decrease in magnitude of the S wave, peak T wave, and/or negative U wave [11].

In order to identify or exclude potential aetiologies of MINOCA in patients suspected of VSA, the use of additional diagnostic tests is recommended. Echocardiography should be performed in the acute setting to assess regional wall motion abnormality (RWMA) or pericardial effusion. Computed tomography CAG may be considered for detection of atherosclerosis but does not identify plaque rupture or erosion. Cardiac magnetic resonance imaging allows the identification of RWMA, the presence of myocardial oedema or fibrosis/scar. An area of late gadolinium enhancement in the subendocardium suggests an ischaemic cause of injury (ie, plaque disruption, vasospasm, thromboembolism or dissection), while a subepicardial localisation speaks in favour of cardiomyopathy (ie, myocarditis or an infiltrative disorder) [28].

Non-invasive, non-pharmacological vasospasm testing showed a lower sensitivity compared with pharmacological testing [13]. Non-invasive IV ER testing using continuous monitoring of ST-segment deviation by ECG or RWMA by echocardiography to detect vasospasm-induced ischaemia in patients with near-normal angiographic findings has been described, but published data is limited. Ultimately, the cornerstone for the VSA diagnosis is based on provocative vasospasm testing with intracoronary administration of ACH or ER.

Table 3: Indications for provocative coronary artery spasm testing.

Class I (strong indication)
History suspicious of vasospastic angina without documented episodes: – Nitrate-responsive rest angina – Marked diurnal variation in symptom onset/exercise tolerance – Rest angina without obstructive coronary artery disease – Unresponsive to empiric therapy
Presentation with acute coronary syndrome in the absence of a culprit lesion on angiography
Unexplained resuscitated cardiac arrest
Unexplained syncope with antecedent chest pain
Recurrent rest angina following angiographically successful PCI
Class IIa (good indication)
Invasive testing for non-invasively diagnosed patients unresponsive to drug therapy
Documented spontaneous episode of vasospastic angina to determine the 'site and mode' of spasm
Class IIb (controversial indication)
Invasive testing for non-invasively diagnosed patients responsive to drug therapy
Class III (contra-indication)
Emergent acute coronary syndrome
Severe fixed multi-vessel coronary artery disease including left main stenosis
Severe myocardial dysfunction
No symptoms suggestive of vasospastic angina

PCI percutaneous coronary intervention

Table 4: Advice and dosing of medication for provocative coronary artery spasm testing.

Prior to procedure:		
Withhold for 48 h	Long-acting calcium antagonists	
Withhold for 24 h	Caffeine	
	Long-acting nitrates	
	Short-acting calcium antagonists	
	α-blockers	
	β-blockers	
	ACE inhibitor	
	Angiotensin receptor blockers	
	Renin inhibitors	
	Aldosterone inhibitors	
Withhold for 4 h	Sublingual nitrates	
During procedure:		
Agent	Administration	*Dose*
– Acetylcholine	Intracoronary (manual) bolus injection	LCA: 20/50/100/200 µg RCA: 20/50/80 µg over 20 s with at least 3 min interval between each injection
	Intracoronary (continuous) infusion	LCA or RCA: incremental doses of 0.288/2.88/28.8/288 µg during 3 min (maximal highest dose 864 µg)
– Ergonovine	Intracoronary (continuous) infusion	LCA: 16 µg/min during 4 min (maximal dose 64 µg) RCA: 10 µg/min during 4 min (maximal dose 40 µg)
	Intravenous (continuous) infusion	Incremental doses of 50/100/150 µg during 5 min

ACE angiotensin-converting enzyme, *LCA* left coronary artery, *RCA* right coronary artery

Invasive Evaluation

Coronary angiogram, during an episode of VSA most frequently shows vasospasm at a localised segment of an epicardial artery. However, multifocal, multi-vessel or diffuse vasospasm in one or multiple coronary arteries may occur. In most patients the location of vasospasm is fixed over time, but fluctuations from one vessel to another have been reported [29]. The frequency of multiple vasospasms during provocative vasospasm testing in Caucasians is 7.5%, markedly lower than in Japanese (24%) and Taiwanese populations

(19%) [13, 30]. The angiographic criterion for 'non-obstructive' CAD (ie, <50 stenosis) is hampered by the dynamic pathophysiological nature of an AMI, which may result in significant changes arising from fluctuating coronary vasomotor tone and the unstable coronary plaque [31]. In contrast, the finding of angiographically smooth coronary arteries does not preclude an aetiologic role of thrombotic disease, as intravascular ultrasound studies (IVUS) have demonstrated significant atherosclerotic burden in these patients [32]. IVUS or optimal coherence tomography may identify atherosclerotic plaque disruption, plaque erosion, coronary dissection or thrombosis.

Indication and Pharmacological Agents for Invasive Provocative Coronary Vasospasm Testing

Provocative coronary vasospasm testing has been used clinically for >40 years and should be undertaken in patients with suspected VSA if the diagnosis is to be pursued. It should be restricted to specialised centres and has been safely performed in patients with a recent AMI but must not be performed in the acute phase [33]. Tab. 3 summarises recommended indications for provocative testing as proposed by the COVADIS group [4]. We advise that provocative testing be performed in patients presenting with MINOCA unless there is a clear epicardial (plaque rupture, dissection), myocardial or non-cardiac cause. Although multiple provocative testing protocols have been developed to evaluate VSA, the gold standard method for provocative coronary vasospasm testing involves the administration of a provocative drug (typically ACH or ER) during CAG while monitoring patient symptoms, ECG and documentation of the coronary artery [4].

The pharmacological agents most often used in provocative coronary vasospasm testing for the diagnosis of VSA are ACH and ER. Adverse reactions to ACH include hypotension, bradycardia, ventricular tachycardia, dyspnoea, and flushing [34]. Adverse reactions to ER are diverse and include angina, ischaemia/AMI, arrhythmia, nausea, allergic reaction, and ergotism [35]. The risks of invasive provocative vasospasm testing are low, as it allows rapid detection and treatment of the induced vasospasm. No deaths have been reported, although there is a 6.8% incidence of cardiac arrhythmias (ie, comparable with that observed during spontaneous vasospasm episodes) [35]. Despite its high sensitivity, false-negatives have been reported; therefore, a negative test cannot always exclude vasospasm [36].

Invasive Provocative Coronary Vasospasm Testing Protocol

At the Academic Medical Centre, University of Amsterdam, we perform provocative coronary vasospasm testing on a regular basis using intracoronary continuous infusion of ACH. The preparation of medication prior to provocative coronary vasospasm testing is summarised in Tab. 4. According to our institutional protocol, a 6 French sheath is inserted via the femoral or radial artery, whereafter patients are administered 70–100 IU/kg heparin. When using the radial approach the administration of vasospastic agents ('radial cocktail') is prohibited. During the entire procedure, the ECG and aortic pressure are monitored. After CAG has been performed, a Doppler guidewire (either FloWire or Combowire, both Volcano, Rancho Cordova, CA, U.S.A.) is introduced into the right or left coronary artery depending on the clinical presentation. The continuous flow measurement enables documentation of flow alterations such as early detection of reduction/cessation of blood flow due to EV and/or CMD. ACH is infused in continuous incremental doses until vasospasm is provoked (Tab. 4). If there are no signs of vasospasm, the coronary artery is visualised after each dose. If, before the third minute chest pain, ECG changes, arrhythmia or flow alterations detected by Doppler occur, the coronary artery is immediately visualised. If the criteria of vasospasm are fulfilled, the infusion of ACH is stopped and an immediate dose of nitroglycerin (200 µg) is administered intracoronarily. Visualisation of the coronary artery is repeated every minute to monitor the disappearance of the vasospasm. Finally, coronary flow reserve

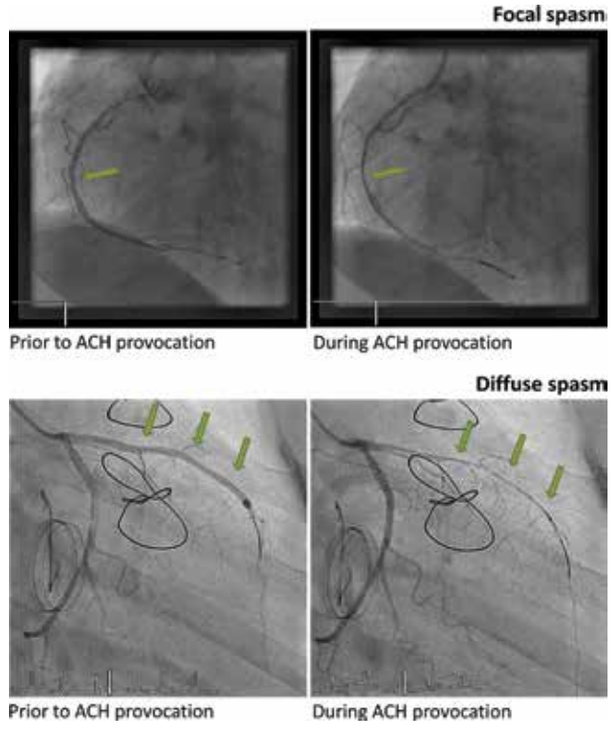

Fig. 2: Epicardial coronary spasm. Example of focal coronary spasm (*upper panel*) and diffuse coronary spasm (*lower panel*) during provocative coronary vasospasm testing with intracoronary acetylcholine (*ACH*).

(CFR) measurement is performed (normal value CFR ≥2.5).

Diagnostic Criteria for Positive Coronary Vasospasm Testing

A positive response to ACH testing for EV is defined as the test inducing all of the following: (1) reproduction of the previously reported chest pain, (2) ischaemic ECG changes (ST-segment elevation or depression), and (3) >90% vasoconstriction on angiography (see Fig. 2).

A positive response to ACH testing for CMD due to microvascular spasm is defined as the test inducing the following: (1) reproduction of the previously reported chest pain, (2) ischaemic ECG changes, (3) no signs of EV (≥90% diameter reduction) but an evident reduction (ie, cessation or slow) of coronary flow as measured with the Doppler flow wire, (4) normal microvascular function documented with a CFR of ≥2.5 and/or normal myocardial blush (see Fig. 3; [37]).

A negative response to ACH may provide evidence for CMD due to causes other than microvascular spasm, ie, (1) endothelial dysfunction (>20%, but <90% reduction in coronary luminal diameter during ACH provocation), (2) impaired epicardial and microvascular dilatation (CFR <2.5), (3) increased microvascular resistance (HMR ≥25, IMR >2.4), aside from EV and microvascular vasospasm [38].

Treatment of Patients with Vasospastic Angina

Lifestyle Adaptations

Before initiating pharmacotherapy, risk factor modification should be taken into consideration. Importantly, smoking cessation is one of the most compelling risk factors that can be modified [21]. Obese patients must be advised to lose weight. Exercise training, cardiac rehabilitation, and cognitive behavioural therapy are other important interventions. Excessive fatigue and mental stress must be avoided and patients should be advised to limit alcohol consumption. In addition, pharmacotherapy must aim at controlling blood pressure, impaired glucose tolerance and lipid abnormalities [39].

Pharmacological Treatment for VSA

Pharmacological treatment of VSA includes calcium channel blockers (CCBs) and non-specific vasodilators such as nitrates. The two different subclasses of CCBs, the dihydropyridine (DHP) and the non-DHP (diltiazem and verapamil), both induce vasodilation of the peripheral arteries and on the myocardium via inhibition of calcium influx through the L-type calcium channels in excitable membranes [40]. As a result of extensive first pass metabolism, higher doses of non-DHP CCBs are recommended during initiation of therapy, an effect not observed with DHPs. Compared to short-acting CCBs, verapamil's extended release has been shown to significantly improve symptoms of limited exercise tolerance, angina episode duration, and heart rate [40]. Adverse events associated with DHP are mainly caused by peripheral vasodilating properties, whereas negative chronotropic effects of non-DHP cause bradycardia and atrioventricular conduction delay, including second- and third-degree block [40]. Short-acting DHP can worsen cardiac outcomes through induction of reflex sympathetic activation leading to an increase in cardiac oxygen demand, tachycardia, and increased myocardial ischaemia [41]. Non-DHP can be harmful in patients with heart failure with reduced ejection fraction due to worsening of heart failure from their negative inotropic effects and should be prescribed with caution in elderly patients and those with chronic kidney disease due to suppression of the sinoatrial activity [40].

Nitrates dilate the coronary vasculature and reduce ventricular filling pressures through venodilation enhancing subendocardial perfusion of ischaemic areas in the myocardium [42]. However, the antianginal effect results mostly from the ability to decrease myocardial oxygen demand through systemic venodilation. Short-acting, sublingual nitroglycerin is preferred for acute angina, while long-acting nitrates are important for the chronic treatment of VSA, as they suppress acute angina attacks and may

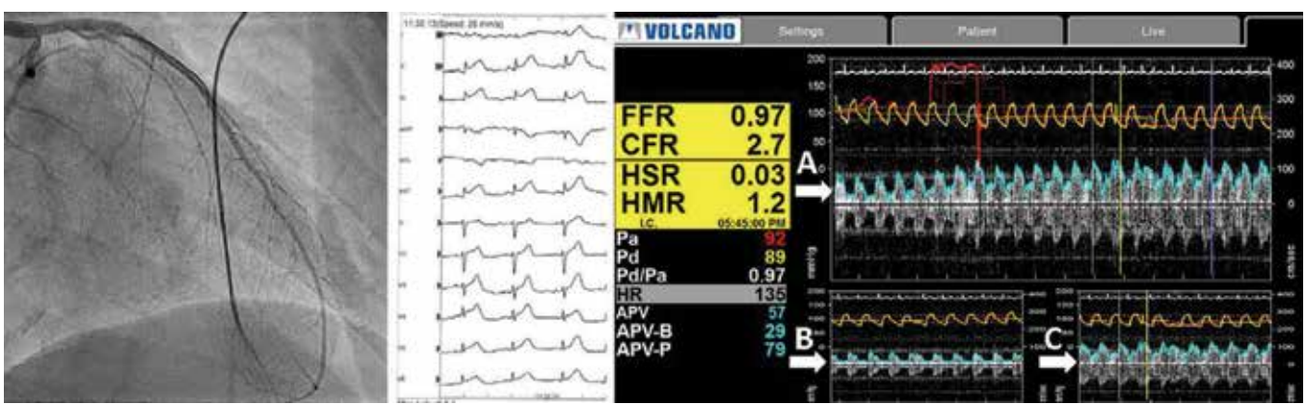

Fig. 3: Coronary microvessel spasm. Example of coronary microvascular dysfunction. During infusion of intracoronary acetylcholine (IC ACH) there is no visible spasm of the left coronary artery (*left panel*). During infusion the ECG shows diffuse ST-segment elevation (*mid panel*). The coronary flow reserve (*CFR*) prior to IC ACH administration is 2.7 (*right panel*, *A*), a reduced CFR during IC ACH infusion (*right panel*, *B*), and recovery of the CFR after administration of nitroglycerin IC (*right panel, C*). (*FFR* fractional flow reserve, *HSR* hyperaemic stenosis resistance, *HMR* hyperaemic microvascular resistance)

prevent recurrent attacks [43]. In practice, CCBs are preferred over long-acting nitrates, due to potential nitrate tolerance. However, combination therapy of a CCB and a nitrate may have a synergistic effect and provide relief when a patient has VSA refractory to monotherapy. Common adverse effects associated with the use of nitrates include headache, flushing, and tachycardia (which increases myocardial oxygen demand).

Low-dose aspirin (<100 mg daily) appears to be safe and may be effective in preventing acute attacks; nevertheless, robust data are lacking [44]. The use of high-dose aspirin (>325 mg daily) should be avoided as it may provoke exacerbations. Similarly, beta-blockers should be avoided as they can exacerbate VSA [45]. If a beta-blocker is absolutely indicated, labetalol or carvedilol may be considered because these agents possess mixed (alpha$_1$- and beta-adrenergic receptor antagonist) properties which may result in overall vasodilation. It should also be noted that beta-blockers are indicated in cases of CMD, due to endothelial dysfunction and impaired vasodilation, in the absence of evidence of VSA [38]. Statins should be considered as the pleiotropic effects, such as antioxidant activity, may help attenuate vasoconstriction and prevent VSA [46]. Moreover, statins may help to improve endothelial function and thereby mitigate vasoconstriction. Currently, the effects of alpha-adrenergic receptors on coronary vasospasm have yet to be elucidated.

Despite pharmacotherapy, refractory angina remains in 10–20% of patients.

Invasive/Non-pharmacological Treatment

Invasive, non-pharmaceutical treatment includes stent implantation. However, it has been reported that vasoconstriction in segments adjacent to stents occurs in response to intracoronary ACH infusion. Partial sympathetic denervation can be considered in selected cases [8]. Thus far, there has been no sufficient evidence regarding the indication of implantable cardioverter defibrillators (ICDs) in survivors of OHCA with non-obstructive CAD in whom coronary vasospasm was induced during a provocation test. These patients should be treated with adequate pharmacotherapy, and physicians may consider ICD implantation for secondary prevention of cardiac arrest [47]. A recent study evaluated the long-term prognosis in Caucasian patients presenting with OHCA caused by coronary vasospasm [48]. All patients received a CCB or nitrates or both. With a mean follow-up of 7.5 ± 3.3 years, 2 out of 8 patients had an appropriate shock therapy.

Conclusions

Vasospastic angina is more common in female patients and remains a challenging diagnosis. In females, VSA may present with different symptoms than those in males. Particularly in patients with a MINOCA and/or suspected VSA, invasive provocative coronary vasospasm testing is recommended to confirm the diagnosis. Untreated VSA patients are at risk for major adverse cardiac events such as AMI, arrhythmias or SCD. Treatment should focus on lifestyle adaptation and pharmacotherapy with CCB with the addition of nitrates when symptoms remain.

Conflict of interest: M.A. Beijk, W.V. Vlastra, R. Delewi, T.P. van de Hoef, S.M. Boekholdt, K.D. Sjauw and J.J. Piek declare that they have no competing interests.

References available on request
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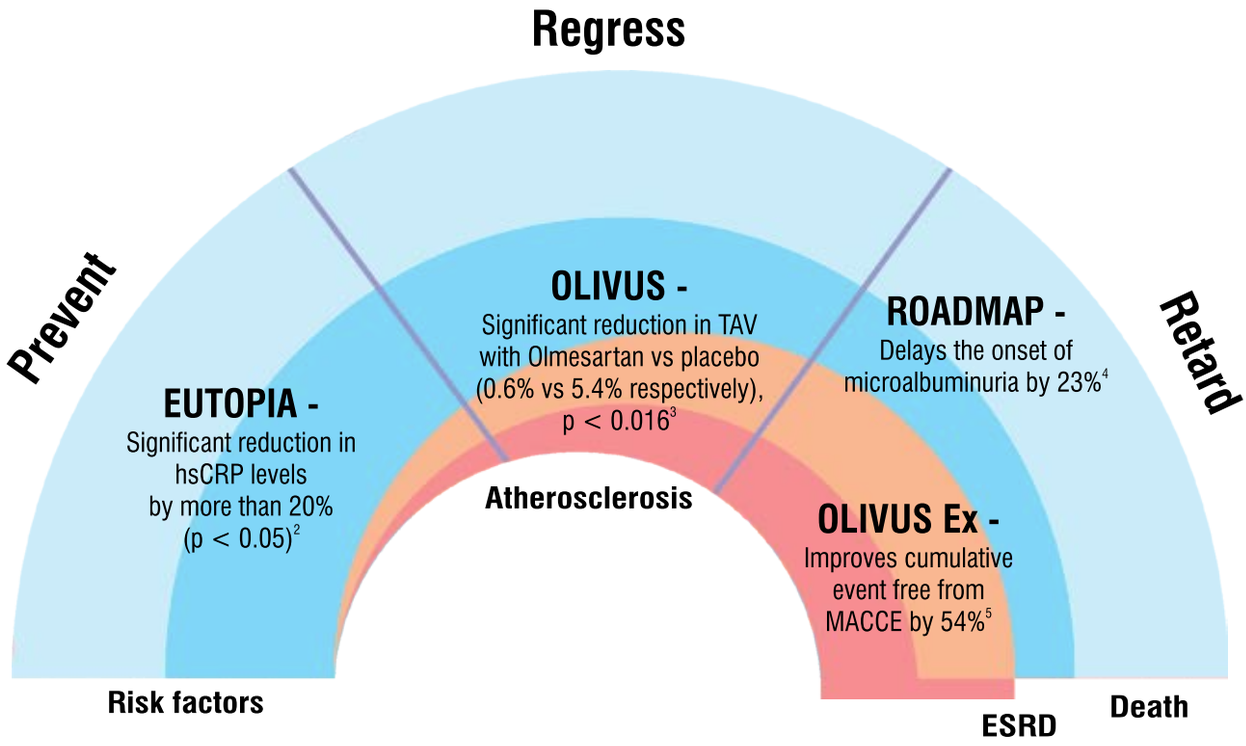

TAV – Total Atheroma Volume, MACCE - Major Adverse Cardio- and Cerebrovascular Events

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