Innovative approaches to control hypertension: *Systematic Review*

Abstract:

One of the leading causes of death and disability worldwide, high blood pressure is thought to have killed over 10 million people. One of the main goals of global health care is to improve the control of hypertension. Another significant risk factor for the majority of cardiac disorders is hypertension. Modern methods of controlling hypertension demand collaborative efforts from the patient, family, community, and health care providers. The researcher found after doing a thorough review of the literature that new methods of controlling hypertension are still being developed. It consists of surgical, technological, pharmaceutical, and non-pharmaceutical methods.

Key words: hypertension control, high blood pressure, diastolic blood pressure, physiological stress

Introduction:

With 17.3 million deaths per year due to cardiovascular disease (CVD), it is the leading cause of death globally. The main cause of mortality worldwide is high blood pressure, which increases the risk of ischemic heart disease, heart failure, and stroke (Vedanthan et al., 2017[1]).

The World Health Organization (WHO) estimates that hypertension kills around nine million people each year and has been designated as one of the major risk factors for morbidity and mortality worldwide (WHO., 2013[2]). High blood pressure (BP), also known as hypertension, is defined by the UK's National Institute for Health and Care Excellence (NICE) as a clinic blood pressure of 140/90 mmHg or higher, which is then confirmed by an ambulatory blood pressure monitoring daytime average (or home blood pressure monitoring average) of 135/85 mmHg or higher (Kitt et al., 2019[3]).

Blood pressure problems can not only affect elderly people. In England in 2015, more than 2.1 million people under 45 had high blood pressure. This is crucial

since managing hypertension lowers the chance of developing cardiovascular disease in the future significantly. Studies indicate that many people continue to have inadequate control despite the considerable evidence in favor of such treatment. To enhance screening, detection, and control of elevated blood pressure in the population, new strategies, including new technology, are consequently required (Kitt et al., 2019[3]).

Increased prevalence and inadequate illness management place a strain on medical facilities. This financial and health burden makes it necessary to tackle the issue using novel strategies (Vedanthan et al., 2017[1]).

The innovative approaches for controlling hypertension continue to advance and evolve today. These novel strategies and the justifications for each were the focus of this review.

Review:

According to Carey & Whelton (2017), hypertension is defined as a rise in systolic blood pressure above 130 mmHg and diastolic blood pressure above 80 mmHg (Carey& Whelton., 2017[4]). The signs and symptoms of hypertension can differ from person to person and can resemble those of other diseases. It is a silent killer. Hypertension is an independent risk factor for cardiovascular diseases, including coronary artery disease, ischemic stroke, peripheral arterial disease, and congestive heart failure (Strait & Lakatta., 2012[5]). 1.5 billion more people are expected to have hypertension, according to WHO 2013 estimates. In the long run, untreated hypertension will harm the arteries. Heart, brain, kidney, and ocular complications can result from hypertension (Trtica Majnarić et al., 2019[6]).

Forouzanfar et al., (2017[7]) estimate that 14% of fatalities worldwide are caused by hypertension alone. From 13,307/100,000 in 1990 to 20,525/100,000 in 2015, the rate of hypertension has grown. In many nations around the world, the prevalence of adult hypertension ranges from 30 to 45% (Mahmood et al., 2019) [8]

Modern methods of controlling hypertension demand collaborative efforts from the patient, family, community, and health team members. The researcher found after doing a thorough review of the literature that new methods of controlling hypertension are still being developed. It consists of surgical, technological, pharmaceutical, and non-pharmaceutical methods (Trtica Majnarić et al., 2019[6]).

Innovative pharmacological approaches to control hypertension:

The first clinical guidelines for hypertension from WHO will be completed in 2021. A clear consensus exists regarding the strong evidence for the effectiveness of four major classes of pharmacotherapies, including blockers of the renin-angiotensin-aldosterone system (RAAS), calcium channel blockers, B-blockers, and thiazide or thiazide-like diuretics. Although guidelines can differ in some features, such as the blood pressure threshold value required to start treatment or the target blood pressure for those on treatment, there is agreement that all antihypertensive medications have a similar impact on major cardiovascular outcomes, including mortality, despite the fact that some of the pharmacological groups have specific indications, such as -blockers for patients with coronary artery disease or heart failure and RAAS blockers for patients with chronic kidney disease. A key element of the modern medical management of hypertension is fixed-dose combination therapy, which contains two or more medicines in a single pill. This strategy is currently recommended as initial therapy in the majority of guidelines due to its numerous benefits, including pharmacological (synergies of mechanisms of action and fewer adverse effects due to lower doses) and practical (increasing adherence) aspects (Zhou et al., 2021[9]; Williams et al., 2018[10]).

Between 2005 and 2008 and 2013 and 2016, a significant number of US people with hypertension were only using one class of antihypertensive medication, even among those with uncontrolled blood pressure, **According to** Derington et al (2020)[11]. While the use of B-blocker monotherapy declined, the use of ACEI or ARB monotherapy grew. According to the current data, a large percentage of US people with hypertension who are taking antihypertensive medication have uncontrolled blood pressure. This may be due to an insufficient antihypertensive treatment regimen. Therefore, attempts to expand the use of antihypertensive drug regimens that include dual and triple therapy may offer a chance to resume the increasing trend in BP control rates in US adults.

Role of Interleukins in diagnosis and treatment of Arterial Hypertension:

One of the most significant cardiovascular risk factors is hypertension, a multifactorial pathology that affects up to 30–40% of the general population. Complex immune responses are involved in the inflammatory mechanism of

hypertension, with evidence pointing to increased inflammatory mediators even in prehypertensive patients. Chronic inflammation may be the cause of the increased vascular permeability, thrombogenesis, and fibrosis that are attributed to persistent hypertension. In hypertensive patients, elevated serum levels of proinflammatory cytokines like IL-1, IL-6, IL-8, IL-17, IL-23, TGF, and TNF have been linked to either elevated blood pressure readings or end-organ damage. Furthermore, independent of blood pressure levels, some cytokines, such as IL-6, appear to dictate a hypertensive response to angiotensin II. New treatment targets are made possible by realizing that hypertension is an inflammatory-based disorder. Statins, calcium channel blockers, and ACEIs/ARBs have therefore demonstrated additional anti-inflammatory benefits that may be related to their blood pressure reducing abilities. [12] Additionally, it has been demonstrated that anti-inflammatory medications (mycophenolate mofetil) can lower blood pressure in hypertension patients or stop it from developing in people with normal blood pressure[12]. Further studies are required to evaluate whether drugs targeting proinflammatory cytokines linked to hypertension, such as monoclonal antibodies, could become a new therapeutic option in treating arterial hypertension (Tanase et al., 2019[12]).

RNA Interference

A promising approach for developing new hypertension medications is RNA interference (RNAi). A naturally occurring regulatory mechanism to inhibit gene expression is RNA interference (RNAi). Short RNAs called RNAis cause homologous mRNA to be targeted by ribonucleases, which silences a particular gene (Ballicora et al., 2003[13]). RNAi is a crucial tool for researchers to understand how a gene works as well as for therapeutic intervention to target disorders that can be caused by unfavorable gene activity. RNAi has already been utilized effectively for cardiovascular research and is currently being tested for application in human therapeutics. Proprotein convertase subtilisin/kexin type 9 (PCSK9), for instance, is a recently discovered yet well-validated target for decreasing low-density lipoprotein cholesterol. PCSK9, an enzyme that is mostly produced and released into the bloodstream by the liver, is crucial for the metabolism of cholesterol and also appears to modulate hypertension (Melendez et al., 2017[14]). Notably, PCSK9 loss-of-function mutations are related with reduced cardiovascular risk and low levels of circulating low-density lipoprotein cholesterol, with no obvious adverse effects on health. RNAi has been demonstrated in phase 2 clinical trials to dramatically lower PCSK9 and

low-density lipoprotein cholesterol levels in humans for a 6-month follow-up. This demonstrates the potential of RNAi as a long-term therapy for cardiovascular disease (Dzau & Balatbat., 2[15]).

Angiotensinogen:

Angiotensinogen, the single substrate of the renin-angiotensin system, is a prime example of a therapeutic target in the treatment of hypertension. A decrease in angiotensinogen synthesis may be a suitable target for brand-new hypertension medications, according to studies showing a connection between angiotensinogen and hypertension. One may imagine using RNA interference to target angiotensinogen in the liver, which is where most of the circulating angiotensinogen is produced. In fact, studies have demonstrated that siRNA may be used to lower the amount of angiotensinogen produced by livers of rats, which lowers plasma levels of the substance and lowers blood pressure in both hypertensive and normotensive rats. These outcomes were maintained, indicating that daily administration of this medication was not necessary. To investigate effectiveness and safety for humans, more research is necessary (Dzau & Balatbat., 2019[15]).

Gene Editing—Somatic Gene Editing of PCSK9

Genome editing to target genes for human hypertension therapy is another potential approach. Researchers have already shown that CRISPRCas9 genome editing technology may be used to successfully target mouse PCSK9 in vivo as well as in real human hepatocytes in vivo in a liver-humanized mouse model (Wang et al., 2016[16]). This is similar to how RNAi is utilized. Additionally, researchers altered the monkeys' livers' genes to lower the animals' blood cholesterol levels. Wang et al (2018)[17] demonstrated that single infusion of adenoassociated virus vectors expressing an engineered meganuclease targeting PCSK9 cause dose-dependent liver PCSK9 disruption as well as a persistent decrease in circulating PCSK9 and serum cholesterol in nonhuman primates. PCSK9 levels decreased in treated monkeys by up to 84%, and low-density lipoprotein levels decreased by up to 60%. These findings imply that genome-editing medicines that target PCSK9 may be successful in treating humans. To avoid off-target effects and undesired immunological effects, as well as to confirm the technology's effectiveness in clinical trials, more study will be required. Genome editing (using CRISPR-Cas9) has the potential to one day treat genetic

hypertension, target angiotensinogen, and possibly even provide long-term management of essential hypertension (Dzau & Balatbat., 2019[15]).

Innovative Non pharmacological approaches to control hypertension:

Obesity, reduced physical activity, unhealthy eating habits, smoking, and alcohol use are the main contributors to the development of hypertension. In order to avoid its complications and enhance the patient's quality of life, hypertension must be properly managed. For effective control of hypertension, pharmacological and non-pharmacological measures are required. Approximately 70% of patients who exclusively get pharmacological treatment for hypertension are unable to regulate their blood pressure, despite the availability of very effective medications (Selçuk et al., 2017[18]). Before beginning pharmaceutical therapy, non-pharmacological approaches may be used alone or in combination with it (Mahmood et al., 2019[8]; Mercer et al., 2020[1]).

Dietary modifications:

Hypertension and diet are usually related. The results of the trials demonstrated the value of a diet rich in dietary products and fiber, low in sodium, high in polyunsaturated fatty acids, potassium, and rich in magnesium for the prevention and treatment of hypertension. For improved control of hypertension, current clinical guidelines propose lifestyle changes as a primary treatment in the prehypertension stage and in conjunction with pharmaceutical treatments in all later stages. Despite all the compelling evidence supporting the favorable impacts of dietary changes, healthcare professionals are still unsure of the best dietary strategy to advocate. Vegetarians have been found to have a lower risk of developing hypertension and other cardiovascular disorders The two dietary methods that are highly recommended for the prevention and management of hypertension are the Dietary Approach to Stop Hypertension (DASH) and the Traditional Mediterranean Diet (Mahmood et al., 2019[8]; Azadbakht et al., 2011[19]).

The DASH diet: DASH diet was designed for the prevention and effective management of hypertension. Now it is considered as diet of choice for the prevention and treatment of hypertension. The effectiveness of DASH diet has been established

through DASH trials conducted in different parts of the world. It composed of low sodium and low fat diet. While the main features of Mediterranean diet are (1) increase intake of fruits, vegetables, and pulses, (2) high consumption of monounsaturated fatty acids and polyunsaturated fatty acids, (3) less consumption of red meat, and (4) restricted intake of alcohol (Mahmood et al., 2019[8]; Saneei et al., 2014[20]).

Sodium restriction: Sodium plays a significant role in pathophysiology of hypertension. A high-sodium diet induces collagen synthesis, which causes profibrotic alterations in the vascular smooth muscles. The buildup of collagen in blood vessels makes the arteries stiff. A daily consumption of 2400 mg/24 hours of Na+ is regarded as normal and beneficial. However, it is advised to further reduction to 1500 mg per 24 hours in people who are at a greater risk of hypertension or stroke (Mahmood et al., 2019[8]; Van Horn., 2015[21]).

Potassium and magnesium supplementation:

Consuming potassium has a negative relationship with hypertension. Recent studies have demonstrated that salt-sensitive hypertension, particularly in the black population, is significantly influenced by K+ consumption. When given a low K+ diet, salt loading raises mean arterial blood pressure by 6.8 mmHg in African/Black people compared to 1.9 mmHg in white people. When participants were given a high K+ diet, i.e., 70mmol/day, the hypertensive effect was reduced by 4.9/3.3 mmHg in the black population against 2.5/1.9 mmHg in the white population. Magnesium and hypertension are inversely related, just as potassium. Mg+2 is abundant in fruits and vegetables, which are being researched for their potential anti-hypertension benefits. Intake of Mg+2 (368 mg/day) for three months lowered blood pressure to 2.0 mmHg SBP and 1.78 mmHg DBP, according to a meta-analysis of 34 trials involving 2028 normotensive and hypertensive patients (Mahmood et al., 2019[8]).

Antihypertensive Effects of Antioxidants

The idea of the potential benefits of antioxidants as pharmacological agents leading to counteract blood pressure increase has been presented from numerous sources, along with taking into account the role of ROS in the pathophysiology of hypertension. As a result, antioxidant-rich foods have helped hypertensive people have lower blood pressure, and antioxidant vitamin supplements have helped patients with essential hypertension lower both their systolic and diastolic blood pressure. Wine polyphenols, for example, are naturally occurring antioxidants that have also

been thought of as positive modulators of endogenous antioxidant defense mechanisms (Rodrigo et al., 2012[22]). Several preclinical studies and clinical trials have indicated that antioxidant therapy is important for the management of hypertension, using antioxidant compounds such as ascorbic acid (vitamin C), alpha-tocopherol (vitamin E) and polyphenols, and some antihypertensive drugs are now in clinical use (e.g., ACEIs, ARBs, novel B-blockers, dihydropyridine CCBs), which have anti-oxidative pleiotropic effects (Rodrigo et al., 2021[23]).

Minimizing alcohol intake:

One of the suggestions in the JNC-8 guidelines is to drink less alcohol. 5- 30% of all cases of hypertension are caused by excessive alcohol use. Elevated blood pressure is directly linked to alcohol consumption. According to research by (Mahmood et al., 2019[8]) cutting back on alcohol consumption each week from 452 to 64 ml was linked to a 5/3 mmHg drop in blood pressure over the course of three weeks. Reducing alcohol consumption was linked to a 3.3/2.04 mmHg drop in blood pressure, according to a meta-analysis of 15 randomized control studies including 2234 people (Xin et al., 2001[24]).

Body weight and exercise:

The main change in lifestyle for the treatment of hypertension is physical activity. Numerous studies have shown a connection between physical activity and low blood pressure. Hypertension is less likely to occur in people with higher fitness level (Faselis et al., 2021[25]). Dynamic resistance training exercise reduced both systolic and diastolic blood pressure by 2.6 and 3.11 mmHg, respectively, as compared to a non-training control group, and isometric handgrip training reduced both by 11.8 and 5.8 mmHg as compared to the non-training control group, according to a meta-analysis of 28 randomized controlled trials involving 1012 people divided into 33 subgroups (Cornelissen et al., 2011[26]).

Reduced physiological stress and anxiety:

Anxiety and physiological stress both cause a transient increase in blood pressure. The episodes of stress and anxiety may lead to persistently elevated blood pressure. Numerous studies have found a connection between depression and cardiovascular problems. Positive associations exist between stressful situations including grief, disappointment, catastrophes, and fear and high blood pressure. Elevated blood pressure is the result of increased sympathetic activity brought on by stress and worry, which is caused by the release of adrenaline into the circulation.

Second, stress causes the body to release more cortisol, which causes hypertension (Grassi., 2009[27]; Brettler & Sharman., 2023[28]).

Warm water foot bath therapy

Combining warm water foot bath therapy with progressive muscle relaxation is one non-pharmacological alternative therapy for lowering blood pressure. Scientifically warm water has physiological effects on the body that include improved blood circulation, regulating blood flow and heart rate, and strengthening of the muscles and ligaments that support the joints. Warm water immersion helps to vasodilate blood flow, which lowers blood pressure (Fadlilah et al., 2020[29]).

Progressive muscle relaxation technique

Progressive muscle relaxation is stretching and releasing muscle groups that will produce different sensations. progressive muscle relaxation has the advantages of lowering physical tension, decrease blood pressure, pulse and breathing without and any adverse effects. Warm foot soaks and gradual muscle relaxation are a better options because they are more convenient, simple, cheap, and accessible. Patients with hypertension can receive this treatment, and there are no negative side effects (Fadlilah et al., 2020[29]).

Innovative surgical approaches to control hypertension:

Resistant hypertension is defined by uncontrolled blood pressure despite the administration of three antihypertensive medications, one of which is a diuretic, at recommended dosages. It has been demonstrated that the sympathetic nervous system is activated and sympathetic outflow is elevated in the majority of patients with resistant hypertension and no discernible secondary reasons. Surgical sympathectomy was driven to total obscurity primarily due to serious adverse effects. It should be noted, however, that sympathectomy was the first attempt to effectively confront malignant hypertension and its consequences through an interventional approach. Indeed, a number of studies have demonstrated that sympathectomy is a highly successful method for lowering blood pressure, and the effects were sustained over time (Calhoun et al., 2008[30]).

Selective renal sympathetic denervation (RSD)

The most current and possibly most intriguing method to stop the effect of the sympathetic nervous system on the kidney and systemic hemodynamics is selective renal sympathetic denervation (RSD). Using a radiofrequency ablation catheter introduced into the femoral artery and selectively engaging the renal artery bilaterally, renal sympathetic ablation was accomplished (Papademetriou et al., 2011[31]).

Baroreceptor stimulation

This pulse generator, which is implanted subcutaneously (much like a pacemaker), connects to two leads that are rubbed around the carotid bulbs to stimulate baroreceptors. The two initial tests, which involved roughly 110 patients, showed the device's great efficacy with blood pressure reductions of up to 30/18 mmHg that could be sustained over time. A larger pivotal study, which included a blinded arm, recently completed recruitment of 300 patients. The study is currently ongoing, and no conclusions have been made (Courand et al., 2014[32]; Papademetriou et al., 2011[31]).

Role of mobile technology in controlling hypertension:

Undiagnosed comorbidities like anxiety, depression, and alcohol use disorders can make it more difficult for patients to adhere to treatment plans, and poor physician adherence to management guidelines is one of the difficulties in treating and managing chronic conditions (Jindal et al., 2018[33]). Although there is limited data on how mobile health (mHealth) technologies affect cardiovascular outcomes, systematic reviews have shown that mHealth-based Clinical Decision Support Systems (CDSS) improve preventive care and physicians' clinical decision-making in the management of hypertension and diabetes (Venkataraman et al., 2009[34]).

With the aim of integrating the management of hypertension, diabetes, and other comorbid conditions at the primary healthcare level in India, we developed a tablet-computer enabled mHealth intervention (called mWellcare) in light of the potential of mobile technology to address some of the challenges in the management of chronic diseases. This intervention is intended to be used by general health care providers (nurses/ physicians) in primary care settings. The goal of this paper is to describe the steps and processes in the design and development of the mWellcare intervention (Berntson et al., 2015[35]; Anchala et al., 2021[36]).

Role of Telemedicine in hypertension control:

Tele-monitoring is a particular application of telemedicine—the transfer of data remotely which in this case consists of automatic data transmission of BP readings. It can also be paired with the transmission of other data, such as heart rate, oxygen saturations, and pacemaker/defibrillator data, from the patient's home or place of employment to a setting that provides professional medical care, like a primary care clinic/surgery, the hospital, or another healthcare facility. There are a number of tele-monitoring systems that vary in the way that data is gathered, transmitted, and reported as well as in the presence or lack of extra features such alerts for when blood pressure measurements need to be taken or medicine reminders (Kitt et al., 2019[3]; Omboni & Ferrari., 2015[37]).

Role of Virtual clinics/visits:

'Virtual clinics/visits' provide a system-level option for the use of such technology and comprise structured asynchronous online interactions between a patient and a clinician to extend medical care beyond the initial office visit. There was no significant adjusted difference in systolic blood pressure control, the number of specialist visits, emergency department presentations, or inpatient admissions for primary care patients managed for hypertension using a virtual visit vs. a real-life in-person visit, according to a 2018 study by Levine et al (Kitt et al., 2019[3]; Levine et al., 2018[38]).

Artificial intelligence and controlling hypertension:

Data modeling, powerful statistical methods, and a more individualized approach are required to investigate both patients with hypertension and those whose hypertension is poorly controlled. Novel study designs can therefore enhance the identification, assessment, treatment, and prevention of hypertension, as well as adherence, in clinical trials. Artificial intelligence (AI) refers to a computer's capacity to mimic human brain processes (i.e., decision-making) using large amounts of data, sophisticated algorithms, and powerful computing resources. AI can be classified into several subfields such as deep learning (DL), machine learning (ML), or cognitive computing. ML quickly analyzes different texts, social media, vital signs, electrocardiograms (EKG), echocardiograms, and data collected by wearable devices in order to produce predictions. Personalized medicine can result from the formalization of highly complicated decisions and predictive analysis by AI. With the development of DL and pattern recognition, especially in EKG and echocardiographic video, the diagnosis of hypertension may be changed for the better through early

detection and preventive management. Additionally, an integrated combination of environmental factors and genetics could underpin the mechanism of poorly controlled hypertension. In this review, we cover the potentials of artificial intelligence (AI) for predicting the risk of developing hypertension, the potential uses of AI in the treatment of hypertensive patients, and the potential shift in hypertension clinical trials toward personalized medicine due to AI (Krittanawong et al., 2018[39]; Matsuoka et al., 2020[40]).

Conclusion:

One of the most important public health issues is hypertension. It is acknowledged as having the greatest impact on the burden of disease worldwide. The global burden of hypertension has been growing over time, largely driven by changes in lifestyle, population growth, and aging. Alarmingly, less than a fifth of patients around the world have their hypertension under control. Furthermore, the awareness, management, and control of hypertension vary widely around the globe. A cost-effective method to lessen the burden of hypertension-related diseases is to identify hypertension early and take steps to control it. Because it generally has no symptoms or warning signs, hypertension is known as the silent killer. There are many ways to control hypertension. Most of them become traditional and less effective due to increased pathophysiological causes of hypertension. This variety inspires scientists to innovate methods for controlling hypertension include pharmacological, non-pharmacological, surgical and technology based approaches.

References:

Mercer, T., Nulu, S., & Vedanthan, R. (2020). Innovative Implementation Strategies for Hypertension Control in Low- and Middle-Income Countries: a Narrative Review. *Current hypertension reports*, *22*(5), 39. https://doi.org/10.1007/s11906-020-01045-1
[1]

World Health Organization. (2013). A global brief on hypertension : silent killer, global public health crisis: World Health Day 2013. World Health Organization. https://apps.who.int/iris/handle/10665/79059
[2]

Kitt, J., Fox, R., Tucker, K. L., & McManus, R. J. (2019). New Approaches in Hypertension Management: a Review of Current and Developing Technologies and Their Potential Impact on Hypertension Care. Current hypertension reports, 21(6), 44. https://doi.org/10.1007/s11906-019-0949-4
[3]

Carey, R. M., Whelton, P. K., & 2017 ACC/AHA Hypertension Guideline Writing Committee (2018). Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline. *Annals of internal medicine*, *168*(5), 351–358. https://doi.org/10.7326/M17-3203
[4]

Strait, J. B., & Lakatta, E. G. (2012). Aging-associated cardiovascular changes and their relationship to [5] heart failure. *Heart failure clinics*, *8*(1), 143–164. https://doi.org/10.1016/j.hfc.2011.08.011

Trtica Majnarić, L., Martinović, I., Šabanović, Š., Rudan, S., Babič, F., & Wittlinger, T. (2019). The [6] Effect of Hypertension Duration and the Age of Onset on CV Risk Factors Expression in Perimenopausal Women. *International journal of hypertension*, *2019*, 9848125. https://doi.org/10.1155/2019/9848125

[7]

[8]Mahmood, S., Shah, K. U., Khan, T. M., Nawaz, S., Rashid, H., Baqar, S. W. A., & Kamran, S. (2019). Non-pharmacological management of hypertension: in the light of current research. *Irish journal of medical science*, *188*(2), 437–452. https://doi.org/10.1007/s11845-018-1889-8

Zhou, B., Perel, P., Mensah, G. A., & Ezzati, M. (2021). Global epidemiology, health burden and [9] effective interventions for elevated blood pressure and hypertension. *Nature reviews. Cardiology*, *18*(11), 785–802. https://doi.org/10.1038/s41569-021-00559-8

Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D. L., Coca, A., de Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S. E., Kreutz, R., Laurent, S., Lip, G. Y. H., … Authors/Task Force Members: (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *Journal of hypertension*, *36*(10), 1953–2041. https://doi.org/10.1097/HJH.0000000000001940[10]

Derington, C. G., King, J. B., Herrick, J. S., Shimbo, D., Kronish, I. M., Saseen, J. J., Muntner, P., Moran, A. E., & Bress, A. P. (2020). Trends in Antihypertensive Medication Monotherapy and Combination Use Among US Adults, National Health and Nutrition Examination Survey 2005-2016. *Hypertension (Dallas, Tex. : 1979)*, *75*(4), 973–981. https://doi.org/10.1161/HYPERTENSIONAHA.119.14360
[11]

Tanase, D. M., Gosav, E. M., Radu, S., Ouatu, A., Rezus, C., Ciocoiu, M., Costea, C. F., & Floria, M. (2019). Arterial Hypertension and Interleukins: Potential Therapeutic Target or Future Diagnostic Marker?. *International journal of hypertension*, *2019*, 3159283. https://doi.org/10.1155/2019/3159283
[12]

Ballicora, M. A., Iglesias, A. A., & Preiss, J. (2003). ADP-glucose pyrophosphorylase, a regulatory enzyme for bacterial glycogen synthesis. *Microbiology and molecular biology reviews : MMBR*, *67*(2), 213–225. https://doi.org/10.1128/MMBR.67.2.213-225.2003
[13]

Melendez, Q. M., Krishnaji, S. T., Wooten, C. J., & Lopez, D. (2017). Hypercholesterolemia: The role of PCSK9. *Archives of biochemistry and biophysics*, *625-626*, 39–53. https://doi.org/10.1016/j.abb.2017.06.001
[14]

Dzau, V. J., & Balatbat, C. A. (2019). Future of Hypertension. *Hypertension (Dallas, Tex. : 1979)*, *74*(3), 450–457. https://doi.org/10.1161/HYPERTENSIONAHA.119.13437
[15]

Wang X, Raghavan A, Chen T, Qiao L, Zhang Y, Ding Q, Musunuru K. CRISPR-Cas9 Targeting of PCSK9 in Human Hepatocytes In Vivo-Brief Report. Arterioscler Thromb Vasc Biol. 2016 May;36(5):783-6. doi: 10.1161/ATVBAHA.116.307227. Epub 2016 Mar 3. PMID: 26941020; PMCID: PMC4850082.[16]

Wang L, Smith J, Breton C, Clark P, Zhang J, Ying L, Che Y, Lape J, Bell P, Calcedo R, Buza EL, Saveliev A, Bartsevich VV, He Z, White J, Li M, Jantz D, Wilson JM. Meganuclease targeting of PCSK9 in macaque liver leads to stable reduction in serum cholesterol. Nat Biotechnol. 2018 Sep;36(8):717-725. doi: 10.1038/nbt.4182. Epub 2018 Jul 9. PMID: 29985478.[17]

Selçuk, K. T., Çevik, C., Mercan, Y., & Koca, H. (2017). Hypertensive patients' adherence to pharmacological and non-pharmacological treatment methods, in Turkey. International Journal Of Community Medicine And Public Health, 4(8), 2648–2657. https://doi.org/10.18203/2394-6040.ijcmph20173308
[18]

Azadbakht, L., Fard, N. R., Karimi, M., Baghaei, M. H., Surkan, P. J., Rahimi, M., Esmaillzadeh, A., & Willett, W. C. (2011). Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial. *Diabetes care*, *34*(1), 55–57. https://doi.org/10.2337/dc10-0676
[19]

Saneei, P., Salehi-Abargouei, A., Esmaillzadeh, A., & Azadbakht, L. (2014). Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials. *Nutrition, metabolism, and cardiovascular diseases : NMCD*, *24*(12), 1253–1261. https://doi.org/10.1016/j.numecd.2014.06.008[20]

Van Horn L. (2015). Dietary Sodium and Blood Pressure: How Low Should We Go?. *Progress in cardiovascular diseases*, *58*(1), 61–68. https://doi.org/10.1016/j.pcad.2015.05.008 [21]

Rodrigo, R., Gil, D., Miranda-Merchak, A., & Kalantzidis, G. (2012). Antihypertensive role of polyphenols. *Advances in clinical chemistry*, *58*, 225–254. https://doi.org/10.1016/b978-0-12-394383-5.00014-x[22]

Rodrigo, R., González-Montero, J., & Sotomayor, C. G. (2021). Novel Combined Antioxidant Strategy against Hypertension, Acute Myocardial Infarction and Postoperative Atrial Fibrillation. *Biomedicines*, *9*(6), 620. https://doi.org/10.3390/biomedicines9060620[23]

Xin, X., He, J., Frontini, M. G., Ogden, L. G., Motsamai, O. I., & Whelton, P. K. (2001). Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension (Dallas, Tex. : 1979)*, *38*(5), 1112–1117. https://doi.org/10.1161/hy1101.093424[24]

Faselis, C., Doumas, M., Kokkinos, J. P., Panagiotakos, D., Kheirbek, R., Sheriff, H. M., Hare, K., Papademetriou, V., Fletcher, R., & Kokkinos, P. (2012). Exercise capacity and progression from prehypertension to hypertension. *Hypertension (Dallas, Tex. : 1979)*, *60*(2), 333–338. https://doi.org/10.1161/HYPERTENSIONAHA.112.196493[25]

Cornelissen, V. A., Fagard, R. H., Coeckelberghs, E., & Vanhees, L. (2011). Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. *Hypertension (Dallas, Tex. : 1979)*, *58*(5), 950–958. https://doi.org/10.1161/HYPERTENSIONAHA.111.177071[26]

Grassi G. (2009). Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives. *Hypertension (Dallas, Tex. : 1979)*, *54*(4), 690–697. https://doi.org/10.1161/HYPERTENSIONAHA.108.119883[27]

Ordunez, P., Campbell, N. R. C., Giraldo Arcila, G. P., Angell, S. Y., Lombardi, C., Brettler, J. W., Rodriguez Morales, Y. A., Connell, K. L., Gamarra, A., DiPette, D. J., Rosende, A., Jaffe, M. G., Rodriguez, L., Piñeiro, D. J., Martinez, R., & Sharman, J. E. (2022). HEARTS en las Américas: innovaciones para mejorar el manejo del riesgo de hipertensión y enfermedades cardiovasculares en la atención primaria. Revista Panamericana de Salud Publica/Pan American Journal of Public Health, 46, [e96]. https://doi.org/10.26633/RPSP.2022.96[28]

Fadlilah, S., Erwanto, R., Sucipto, A., Anita, D. C., & Aminah, S. (2020). Soak feet with warm water and progressive muscle relaxation therapy on blood pressure in hypertension elderly. Pakistan Journal of Medical and Health Sciences, 14(3), 1444-1448.[29]

Calhoun, D. A., Jones, D., Textor, S., Goff, D. C., Murphy, T. P., Toto, R. D., White, A., Cushman, W. C., White, W., Sica, D., Ferdinand, K., Giles, T. D., Falkner, B., Carey, R. M., & American Heart Association Professional Education Committee (2008). Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*, *117*(25), e510–e526. https://doi.org/10.1161/CIRCULATIONAHA.108.189141[30]

Papademetriou, V., Doumas, M., & Tsioufis, K. (2011). Renal Sympathetic Denervation for the Treatment of Difficult-to-Control or Resistant Hypertension. International journal of hypertension, 2011, 196518. https://doi.org/10.4061/2011/196518[31]

Courand, P. Y., Feugier, P., Workineh, S., Harbaoui, B., Bricca, G., & Lantelme, P. (2014). [32] Baroreceptor stimulation for resistant hypertension: first implantation in France and literature review. *Archives of cardiovascular diseases*, *107*(12), 690–696. https://doi.org/10.1016/j.acvd.2014.08.002
Jindal, D., Gupta, P., Jha, D., Ajay, V. S., Goenka, S., Jacob, P., Mehrotra, K., Perel, P., Nyong, J., Roy, A., Tandon, N., Prabhakaran, D., & Patel, V. (2018). Development of mWellcare: an mHealth intervention for integrated management of hypertension and diabetes in low-resource settings. *Global health action*, *11*(1), 1517930. https://doi.org/10.1080/16549716.2018.1517930
[33]

[34]Venkataraman, K., Kannan, A. T., & Mohan, V. (2009). Challenges in diabetes management with particular reference to India. *International journal of diabetes in developing countries*, *29*(3), 103–109. https://doi.org/10.4103/0973-3930.54286

Berntson, J., Stewart, K. R., Vrany, E., Khambaty, T., & Stewart, J. C. (2015). Depressive symptoms and self-reported adherence to medical recommendations to prevent cardiovascular disease: NHANES 2005-2010. *Social science & medicine (1982)*, *138*, 74–81. https://doi.org/10.1016/j.socscimed.2015.05.041
[35]

Anchala R, Pinto MP, Shroufi A, Chowdhury R, Sanderson J, Johnson L, Blanco P, Prabhakaran D, Franco OH. The role of Decision Support System (DSS) in prevention of cardiovascular disease: a systematic review and meta-analysis. PLoS One. 2012;7(10):e47064. doi: 10.1371/journal.pone.0047064. Epub 2012 Oct 10. PMID: 23071713; PMCID: PMC3468543.[36]

Omboni, S., & Ferrari, R. (2015). The role of telemedicine in hypertension management: focus on blood pressure telemonitoring. *Current hypertension reports*, *17*(4), 535. https://doi.org/10.1007/s11906-015-0535-3[37]

Levine, D. M., Dixon, R. F., & Linder, J. A. (2018). Association of Structured Virtual Visits for Hypertension Follow-Up in Primary Care with Blood Pressure Control and Use of Clinical Services. *Journal of general internal medicine*, *33*(11), 1862–1867. https://doi.org/10.1007/s11606-018-4375-0 [38]

Krittanawong, C., Bomback, A. S., Baber, U., Bangalore, S., Messerli, F. H., & Wilson Tang, W. H. (2018). Future Direction for Using Artificial Intelligence to Predict and Manage Hypertension. *Current hypertension reports*, *20*(9), 75. https://doi.org/10.1007/s11906-018-0875-x [39]

Matsuoka, R., Akazawa, H., Kodera, S. et al. The dawning of the digital era in the management of hypertension. Hypertens Res 43, 1135–1140 (2020). https://doi.org/10.1038/s41440-020-0506-1 [40]