Springer Healthcare Education

reachOut

ISSUE-1, 2018 CARDIOLOGY

Views & Reviews

Therapeutic Updates

Challenging Cases

Practice Guide

ECG Diagnostics

Read Online

http://www.medengine.com/Collections/060F81EA

Hypertension and Atherosclerosis: Pathophysiology, Mechanisms and Benefits of BP Control

Misbah Zaheer, Paola Chrysostomou, Vasilios Papademetriou

Hypertension contributes to atherosclerosis at different levels: to the development of endothelial dysfunction, fatty streaks, early atherosclerotic plaque, plaque progression and plaque rupture. This paper explores the pathophysiology, the pathways by which hypertension contributes and accelerates atherosclerosis and final evidence that treatment and control of hypertension leads to reduced cardiovascular events.

M. Zaheer, M.D.
Department of Medicine, Georgetown University, Washington, DC, USA

P. Chrysostomou
Department of Veterans Affairs Medical Center, and National Institutes of Health (NIH), Intramural Research Program (IRP), Institute of Clinical Research, Washington, DC, USA

V. Papademetriou, M.D. (✉)
Department of Medicine, Georgetown University, Washington, DC, USA

Division of Hypertension and Vascular Medicine, Veteran Affairs Medical Center, Washington, DC, USA
e-mail: vpapademetriou@va.gov

Introduction

Hypertension is a leading identifiable and reversible risk factor for myocardial infarction, heart failure, atrial fibrillation, aortic dissection, peripheral arterial disease, stroke and kidney failure [1, 2]. Hypertension is ranked first worldwide in an analysis of all risk factors for global disease burden in 2010 [2]. By the year 2025, hypertension is expected to increase in prevalence worldwide by 60 % and will affect 1.56 billion people [3]. Developing nations will experience an increase in the prevalence of hypertension by 80 % (from 639 million to 1.15 billion afflicted persons). As emerging countries have improved sanitation and other basic public health measures, cardiovascular (CV) disease has or soon will become the most common cause of death, and hypertension will be its most common reversible risk factor, as it already is in the United States.

Hypertension contributes to atherosclerosis at different levels: to the development of endothelial dysfunction, fatty streaks, early atherosclerotic plaque, plaque progression and plaque rupture. In this chapter we'll explore the pathophysiology, the pathways by which hypertension contributes and accelerates atherosclerosis and final evidence that treatment and control of hypertension leads to reduced cardiovascular events.

HTN and Cardiovascular Risk

Hypertension is the most important modifiable risk factor for stroke [1]. Current estimates are that 77 % of those who have a first stroke have had a blood pressure (BP) above 140/90 mmHg. High BP is the leading antecedent condition for either the systolic or diastolic type of heart failure and the most common reason for acute care hospitalization among Medicare beneficiaries (approximately

1.023 million in 2010); approximately 74 % of people experiencing an initial hospitalization for heart failure either had or have BP of 140/90 mmHg or higher [1].

The risks attributable to elevated BP levels are documented in numerous epidemiologic studies, beginning in 1948 with the Framingham Heart Study and extending to the present [4, 5]. Meta-analyses of pooled data confirm the robust, continuous relationship between BP level and cerebrovascular disease and coronary heart disease in both Western and Eastern populations [6]. In addition, BP is linked directly in epidemiologic studies to incident left ventricular hypertrophy (LVH), heart failure, peripheral vascular disease, carotid atherosclerosis, end-stage kidney disease, and "subclinical CV disease." Out–of-office blood pressure measurements have also been shown to correlate with chronic kidney disease [7, 8]. The highest risk is at levels above the auto regulatory range of the kidney (i.e., a systolic BP >180 mmHg). CV risk factors tend to cluster; thus hypertensive individuals are much more likely than normotensive people to have type 2 diabetes mellitus or dyslipidemia, especially elevated triglyceride levels and low high-density lipoprotein cholesterol levels.

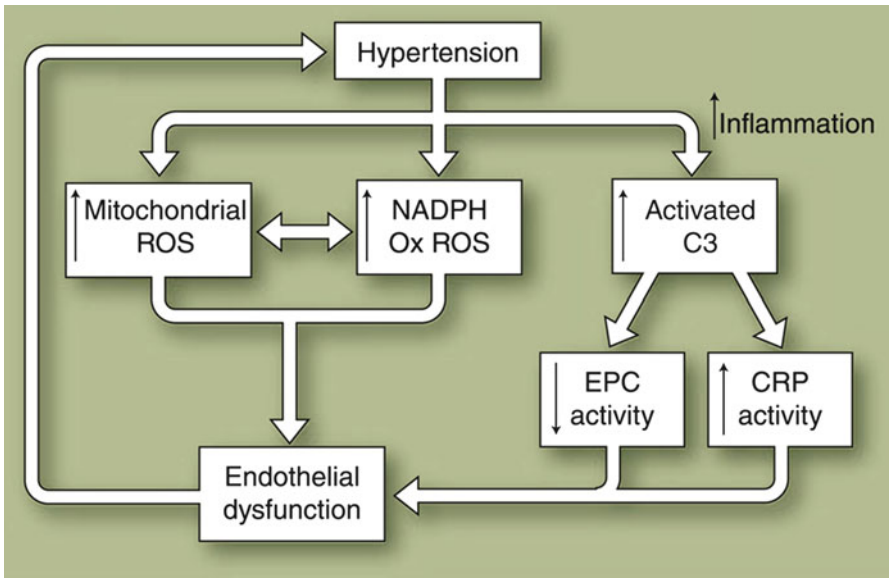


Fig. 1: Mechanism by which hypertension contributes to endothelial dysfunction [13].

Pathophysiology of HTN Leading to Atherosclerosis

Arterial Stiffness

In primary hypertension, the column of blood in the arterial tree between aortic valve and capillaries moves at abnormally high pressure throughout cardiac cycle of contraction and relaxation. However, cardiac output is usually normal or close to normal. Thus, the main determinant of the sustained elevated blood pressure is an increase in peripheral arterial resistance. Under normal circumstances, peripheral resistance is determined predominantly by precapillary vessels with a luminal diameter of approximately 100–300 μm [7, 8]. In human hypertension and in experimental animal models of hypertension, structural changes in these resistance vessels are commonly observed. Small artery remodeling is initiated by vasoconstriction, which normalizes wall stress and averts a trophic response. Normal smooth muscle cells rearrange themselves around a smaller lumen diameter, a process termed inward eutrophic remodeling. The media-to-lumen ratio increases but the media cross sectional area remains unchanged. By decreasing lumen diameter in the peripheral circulation, inward eutrophic remodeling increases systemic vascular resistance, the hemodynamic hallmark of diastolic hypertension.

Cyclic laminar sheer stress that accompanies hypertension, particularly with widened pulse pressure in isolated systolic hypertension leads to endothelial dysfunction.

In contrast large artery remodeling is characterized by the expression of hypertrophic changes, triggering increases in medial thickness as well as the media-to-lumen ratio. Such hypertrophic remodeling involves not only an increase in the size of vascular smooth muscle cells but also an accumulation of extracellular matrix proteins such as collagen and fibronectin, because of activation of TGF-β. The resultant large artery stiffness is the hemodynamic hallmark of isolated systolic hypertension. Increased carotid pulse wave velocity hallmark of arterial stiffness PWV is associated with increased mortality and CV events [9], as well as with a variety of subclinical CV injury markers, such as coronary calcification, cerebral white matter lesions, ankle-brachial index, and albuminuria. The relationship with cardiac complications is easily grasped: increased impedance to left ventricular ejection results in LVH, diastolic dysfunction, and sub-endocardial myocardial ischemia.

Anti-hypertensive therapy may not provide optimal cardiovascular protection and less vascular remodeling is prevented or reversed by normalizing hemodynamic load, restoring normal endothelial dysfunction and eliminating underlying neurohumoral activation [10].

Endothelial Dysfunction

The endothelial lining of blood vessels is critical to vascular health and constitutes a major defense against hypertension. Cyclic laminar sheer stress that accompanies hypertension, particularly with widened pulse pressure in isolated systolic hypertension leads to endothelial dysfunction.

Several elements are responsible for endothelial dysfunction in hypertension. Normotensive offspring of patients with hypertension have impaired endothelium dependent vasodilation despite normal endothelium-independent responses, thus suggesting a genetic component to the development of endothelial dysfunction. Besides direct pressure-induced injury in the setting of chronically-elevated BP, a mechanism of major importance is increased oxidative stress. Reactive oxygen species are generated from enhanced activity of several enzyme systems, reduced nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase), xanthine oxidase, and cyclo-oxygenase in particular, and decreased activity of the detoxifying enzyme superoxide dismutase (Fig. 1) [11-13]. Excess availability of superoxide anions leads to

their binding to NO, leading to decreased NO bioavailability, in addition to generating the oxidant, proinflammatory peroxynitrite. It is the decreased NO bioavailability that links oxidative stress to endothelial dysfunction and hypertension [13]. Angiotensin II is a major enhancer of NADPH-oxidase activity and plays a central role in the generation of oxidative stress in hypertension, although several other factors are also involved, including cyclic vascular stretch, ET-1, uric acid, systemic inflammation, norepinephrine, free fatty acids, and tobacco smoking [14]. ET-1 is the endothelial cell product that counteracts NO to maintain balance between vasodilation and vasoconstriction. ET-1 expression is increased by shear stress, catecholamines, angiotensin II, hypoxia, and several proinflammatory cytokines such as tumor necrosis factor-α, interleukins 1 and 2, and transforming growth factor-β [15]. ET-1 is a potent vasoconstrictor through stimulation of ET-A receptors in vascular smooth muscle. In hypertension, increased ET-1 levels are not consistently found. However, there is a trend of increased sensitivity to the vasoconstrictor effects of ET-1. ET-1 therefore is considered a relevant mediator of BP elevation, as ET-A and ET-B receptor antagonists attenuate or abolish hypertension in several experimental models of hypertension (angiotensin II–mediated models, deoxycorticosterone acetate–salt hypertension, and Dahl salt-sensitive rats) and are effective in lowering BP in humans [12]. Endothelial cells also secrete a variety of other vasoregulatory substances. These include the vasodilating prostaglandin prostacyclin and several vasodilating endothelium-derived hyperpolarizing factors, the identity of which remains uncertain. There are also endothelium-derived contracting factors besides ET-1, such as locally generated angiotensin II and vasoconstricting prostanoids such as thromboxane A2 and prostaglandin A2. The balance of these factors, along with NO and ET-1, determine the final impact of the endothelium on vascular tone.

In cross-sectional analyses, the lower the degree of forearm flow-mediated vasodilation, the greater the prevalence of hypertension [14, 16]. Prospective cohort studies have used flow-mediated vasodilation as a measure of endothelial dysfunction (regardless of specific mechanism) to evaluate its relationship with hypertension and test whether endothelial dysfunction is a cause or a consequence of hypertension, or both [17]. These studies have shown conflicting results, but the larger of them was unable to demonstrate an association between endothelial dysfunction and incident hypertension among 3500 patients followed for 4.8 years [17], so as it stands, the evidence is stronger for endothelial dysfunction as a consequence, not a cause, of hypertension [16].

Activation of renin-angiotensin-aldosterone system (RAAS) is one of the most important mechanisms contributing to endothelial cell dysfunction, vascular remodeling, and hypertension.

Renin Angiotensin System

Activation of renin-angiotensin-aldosterone system (RAAS) is one of the most important mechanisms contributing to endothelial cell dysfunction, vascular remodeling, and hypertension. Activation of RAAS occurs by afferent arteriolar narrowing in kidneys [11]. This abnormality is characterized by a spectrum of histologic changes including focal spasm of otherwise normal afferent arterioles, endothelial edema, vascular smooth muscle hypertrophy and widening of internal elastic lamina with deposition of material that stains with periodic acid Schiff stain, and degenerative changes and hyalinization with focal luminal narrowing. In addition juxtaglomerular cells are hyperplastic, which signifies increased renin biosynthesis. However, it should be emphasized that these renal vascular changes are focal with relatively few obsolescent glomeruli being present, which supports the clinical observation that significant nephron loss and overt renal insufficiency are not major contributing factors in pathogenesis of uncomplicated primary hypertension.

The RAAS has wide-ranging effects on BP regulation. The different elements of the RAAS have key roles in mediating sodium retention, pressure natriuresis, salt sensitivity, vasoconstriction, endothelium dysfunction, and vascular injury. Taken together, the RAAS has an important role in the pathogenesis of hypertension. Renin and pro-renin are synthesized and stored in the juxtaglomerular cell apparatus and released in response to decreased renal afferent perfusion pressure, decreased sodium delivery to the macula densa, activation of renal nerves (via β1-adrenergic receptor stimulation), and a variety of metabolic products, including prostaglandin E2 and several others. Renin's main function is to cleave angiotensinogen into angiotensin I. Pro-renin, previously viewed as an inactive substrate for renin production, is now known to also stimulate the (pro)renin receptor (PRR). This receptor leads to more efficient cleavage of angiotensinogen and activates downstream intracellular signaling through the mitogen-activated protein (MAP) kinases extracellular signal–regulated kinases 1 and 2 (ERK1/2) pathways that have been associated with profibrotic effects in some, but not all, experimental models [18, 19]. At this point, it is uncertain that the PRR is involved in the genesis or complications of hypertension in a manner that is independent of the effects of angiotensin II. Angiotensin II, formed by the cleavage of angiotensin I by the ACE, is at the center of the pathogenetic role of the RAAS in hypertension. Primarily through its actions mediated by the angiotensin II type 1 receptor (AT1R), angiotensin II is a potent vasoconstrictor of vascular smooth muscle, causing systemic vasoconstriction as well as increased renovascular resistance and decreased medullary flow, which is a mediator of salt sensitivity. It produces increased sodium reabsorption in the proximal tubule by increasing the activity of NHE3, the sodium-bicarbonate exchanger, and Na+−K+−ATPase and by inducing aldosterone synthesis and release from the adrenal zona glomerulosa. In addition, it is associated with endothelial cell dysfunction and produces extensive profibrotic and proinflammatory changes, largely mediated by increased oxidative stress, resulting in renal, cardiac, and vascular injury, thus giving angiotensin II a tight link to target-organ injury in hypertension [22]. Conversely, stimulation of the angiotensin II type 2 receptor (AT2R) is associated with opposite effects, resulting in vasodilation, natriuresis, and antiproliferative effects. The relative importance of the renal and vascular effects of angiotensin II was evaluated in classical cross-transplantation studies using both wild-type mice and mice lacking the AT1R [23, 24]. By cross transplanting the kidneys of wild-type mice into AT1R

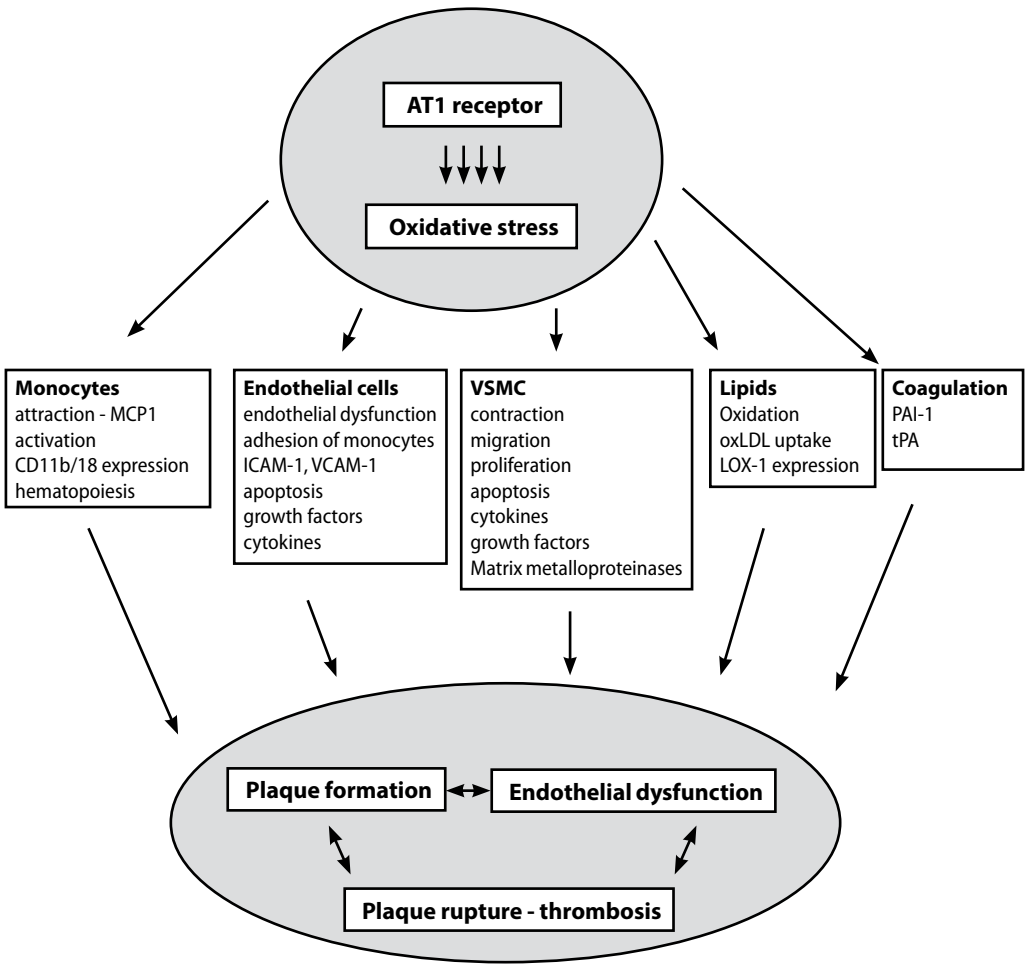


Fig. 1: AT_1 receptor-induced oxidative stress and atherosclerosis. AT_1 receptor activation leads to the release of reactive oxygen species in various vascular cells. Oxidative stress is in turn involved in monocyte attraction and activation. This involves increased production of monocyte chemoattractant protein-1 (*MCP-1*). In endothelial cells, adhesion molecules that are essential for the adhesion of monocytes, such as intercellular adhesion molecule-1 (*ICAM-1*) and the vascular adhesion molecule-1 (*VCAM-1*), are induced by angiotensin II via superoxide anions. In vascular smooth muscle cells (*VSMCs*), numerous biological processes are induced by reactive oxygen species. AT1 receptor activation increases expression of the oxLDL receptor LOX-1 resulting in an increased oxLDL uptake. Expression of plasminogen activator inhibitor-1 (*PAI-1*) is increased via AT1 receptor activation predisposing to a procoagulant state. The effects of angiotensin II on tissue plasminogen activator (*tPA*) are controversial.

knockout mice and vice versa, investigators were able to generate animals that were selective renal AT1R knockouts or selective systemic (nonrenal) AT1R knockouts (Fig. 2). In physiologic conditions, renal, systemic, and total knockout animals had lower BP than wild-type animals, indicating a role of both renal and extrarenal AT1R in BP regulation [24]. The systemic AT1R absence was associated with approximately 50 % lower aldosterone levels, but the lower BP observed in this group was independent of this lower aldosterone production, as BP remained low despite aldosterone infusions to supraphysiologic levels following adrenalectomy in the systemic knockout animals. In addition, the BP reduction in kidney knockout animals occurred despite normal aldosterone excretion, again confirming the independence of renal angiotensin II effects from aldosterone. In the hypertensive environment, it is the presence of renal AT1R that mediates both hypertension and organ injury [24]. When animals were infused with angiotensin II for 4 weeks, animals lacking renal AT1R did not develop sustained hypertension, whereas wild-type and systemic knockout mice had a significant increase in BP. Additionally, only animals with elevated BP developed cardiac hypertrophy and fibrosis. This indicates that cardiac injury is largely dependent on hypertension and not on the presence of AT1R in the heart, as the (hypertensive) systemic knockout animals developed significant cardiac abnormalities despite the absence of AT1R in the heart. [22]. In summary, these experiments indicate that both systemic and renal actions of angiotensin II are relevant to physiologic BP regulation, but in hypertension, the detrimental effects of angiotensin II are mediated via its renal effects. Aldosterone, the adrenocortical hormone synthesized in the zona glomerulosa, plays a critical role in hypertension through its well-known effects on sodium reabsorption that are largely mediated by genomic effects through the mineralocorticoid receptor leading to increased expression of ENaC. An extensive body of literature has identified other genomic and nongenomic effects of aldosterone with relevance to hypertension. Extensive nonepithelial effects include vascular smooth muscle cell proliferation, vascular extracellular matrix deposition, vascular remodeling and fibrosis, and increased oxidative stress leading to endothelial dysfunction and vasoconstriction [21, 23]. Several other elements of the RAAS have been identified as having potentially important roles in hypertension. The renovascular importance of ACE2 and angiotensin-(1–7) to BP regulation and angiotensin II–associated target-organ injury has become apparent. ACE2 is expressed largely in heart, kidney, and endothelium; it has partial homology to ACE and is unaffected directly by ACEIs [25]. It has a variety of substrates, but its most important action is the conversion of angiotensin II to angiotensin-(1–7). Angiotensin-(1–7) is formed primarily though the hydrolysis of angiotensin II by ACE2, and its actions are opposite to those of angiotensin II, including vasodilatory and anti-proliferative properties that are mediated by the Mas receptor, a G protein–coupled receptor that, upon activation, forms complexes with the AT1R, thus antagonizing the effects of angiotensin II. The vasodilatory effects are mediated by increased cyclic guanosine monophosphate, decreased norepinephrine release, and amplification of bradykinin effects. Studies have identified ACE2 and angiotensin-(1–7) as protective factors in the development of atherosclerosis and cardiac and renal injury [25, 26], and administration of recombinant ACE2 or its activator, xanthenone, has resulted in improved endothelial function, decreased BP, and improved renal, cardiac, and perivascular fibrosis in hypertensive animals [27–29].

Sympathetic Nervous System

The sympathetic nervous system (SNS) is activated consistently in patients with hypertension compared with normotensive individuals, particularly in the obese. Many patients with hypertension are in a state of autonomic imbalance that encompasses increased sympathetic and decreased parasympathetic activity [30, 31].

SNS hyperactivity is relevant to both the generation and maintenance of hypertension and is observed in human hypertension from very early stages. Among patients with hypertension, increasing severity of hypertension is associated with increasing levels of sympathetic activity measured by microneurography [32, 33]. In human hypertension, plasma catecholamine levels, microneurographic recordings, and systemic catecholamine spillover studies have shown consistent elevation of these markers in obesity, the metabolic syndrome, and hypertension complicated by heart failure or kidney disease [31]. In addition, SNS hyperactivity is observed in most hypertensive subgroups, though it appears more pronounced in men than in women, and in younger than in older patients.

Several experimental models have outlined the importance of the SNS in generating hypertension. Different models of obesity-related hypertension indicate that the SNS is activated early in the development of increased adiposity [32], and the key factor in the maintenance of sustained hypertension is increased renal sympathetic nerve activity and its attendant sodium avidity [32]. Enhanced SNS activity results in α1-receptor–mediated endothelial dysfunction, vasoconstriction, vascular smooth muscle proliferation, and arterial stiffness, all of which contribute to the development of hypertension. Finally, evidence indicates that sympathetic overactivity results in salt sensitivity due to a reduction in the activity of WNK4. This results in increased sodium avidity through the thiazide-sensitive NCC [34].

Increased SNS activity is associated with vascular smooth muscle proliferation, LVH, large artery stiffness, myocardial ischemia, and arrhythmogenesis. There is also a mechanistic role for the SNS in the complications of hypertension. In support of this concept, there are several cohort studies reporting an association between physiologic or biochemical markers of SNS activation and adverse outcomes in heart failure, stroke, and end-stage kidney disease [31, 35]. However, there are no such studies among patients with hypertension, and the indirect evaluation of the impact of treatment-induced heart rate reduction in hypertension has yielded "paradoxical" results.

In a meta-analysis of hypertension trials, heart rate reduction during treatment with β-blockers was associated with increased risk for death and CV events in patients with hypertension [36]. In contrast, in a very large (n = 10,000) patient outcome trial, a post hoc analysis of heart rate at baseline demonstrated that those with a resting heart rate above 80 beats per minute even with a BP below 140/90 mmHg had a higher mortality rate [37]. Therefore, while apparent that SNS activation is deleterious to patients with CV disease, and presumably with hypertension, a cause for the over-activity should be sought and an attempt made to affect that mechanism.

Pathogenesis of Hypertensive Heart Disease

Hypertension is a major risk factor not only for CAD but also for left ventricular hypertrophy (LVH) and heart failure. In hypertensive patients, LVH powerfully and independently predicts morbidity and mortality, predisposing them to heart failure, ventricular tachyarrhythmia, ischemic stroke, atrial fibrillation, and embolic stroke. Major advances have increased our understanding of the molecular signal transduction pathways underlying pressure overload cardiomyocyte hypertrophy [38]. Moreover, the structural abnormalities in the hypertensive heart extend beyond myocyte hypertrophy; they also include medial hypertrophy of the intramyocardial coronary arteries and collagen deposition, leading to cardiac fibrosis [39]. These changes result from pressure overload and the neurohormonal activation that contributes to hypertension. In animal models, A II, aldosterone, norepinephrine, and prorenin accelerate pressure overload cardiomyocyte hypertrophy and promote cardiac fibrosis, the hallmarks of pathologic LVH (in contrast with the physiologic hypertrophy of exercise training, which involves less fibrosis).

Meta-analyses of all commonly used antihypertensive drug classes demonstrate that, regardless of the agent used, reduction in BP corresponds to reduction in CV events.

Impaired Coronary Vasodilator Reserve: The hypertrophied hypertensive heart has normal resting coronary blood flow, but vasodilator reserve becomes impaired when myocyte mass outstrips the blood supply. Even in the absence of atherosclerosis, the hypertensive heart has blunted or absent coronary vasodilator reserve, leading to sub endocardial ischemia under conditions of increased myocardial oxygen demand. The combination of sub endocardial ischemia and cardiac fibrosis impairs diastolic relaxation, leading to exertional dyspnea and heart failure with preserved systolic function.

Before the advent of effective drug therapy for hypertension in the late 1950s, heart failure caused most deaths from hypertension. Better management has substantially reduced hypertension-related deaths from heart failure and significantly delayed its onset, but hypertension remains the most common cause of heart failure with preserved systolic function. In addition, hypertension indirectly leads to systolic heart failure as a major risk factor for MI. Whether mild or moderate hypertension without MI leads to systolic heart failure is unclear [39].

Treatment

Despite major progress in identifying the risks associated with elevated BP and demonstration that reducing BP to within a certain range reduces risk for death from CV disease and stroke as well as kidney disease progression, control rates are poor in the world. There are over 125 different medications encompassing eight different antihypertensive drug classes to help lower BP, as well as more than 20 single-pill combination agents for BP control. In spite of this, BP control remains suboptimal in many parts of the world [39–41]. BP control rates (to <140/90 mmHg) have improved substantially in the United States since 1974 and have stabilized at just over 50 % in the last three biennial NHANES reports [1]. Successful national efforts to increase hypertension treatment and control rates have been associated with significant reductions in CV hospitalizations or death in both Canada [33] and the United Kingdom [42]. The prevalence of uncontrolled hypertension is greater for undiagnosed, untreated, or older individuals and for systolic (rather than diastolic) BP.

Meta-analyses of all commonly used antihypertensive drug classes demonstrate that, regardless of the agent used, reduction in BP corresponds to reduction in CV events if BP reduction is achieved [44,

45]. This reduction in CV risk, however, is predominantly seen in people with stage 2 hypertension with much less outcome data to support risk reduction in stage 1 hypertension. Events that drive the risk reduction are derived predominantly from reduced incidence of stroke, myocardial infarction, and heart failure. In all trials to date it is the group with the best overall BP control that has the best outcomes [46].

In large-scale randomized trials, it has been shown that reduction of BP by 5–6 mmHg diastolic or 10–12 mmHg systolic resulted in more than 50 % relative risk reduction in the incidence of heart failure, a 30–40 % relative risk reduction in stroke, and a 20–25 % relative risk reduction in myocardial infarction [46].

These relative risk reductions correspond to the following absolute benefits: antihypertensive therapy for 4–5 years prevents a coronary event in 0.7 % of patients and a cerebrovascular event in 1.3 % of patients for a total absolute benefit of approximately 2 % [47]. Thus, 100 patients must be treated for 4–5 years to prevent a complication in two patients. It is presumed that these statistics underestimate the true benefit of treating stage 1 hypertension since these data were derived from trials of relatively short duration (5–7 years); this may be insufficient to determine the efficacy of antihypertensive therapy on longer-term diseases such as atherosclerosis and heart failure. Equal if not greater relative risk reductions have been demonstrated with antihypertensive treatment of older hypertensive patients (over age 65 years), most of whom have isolated systolic hypertension. Because advanced age is associated with higher overall cardiovascular risk, even modest and relatively short-term reductions in blood pressure may provide absolute benefits that are greater than that observed in younger patients.

The benefits of antihypertensive therapy are less clear and more controversial in patients who have mild hypertension and no preexisting cardiovascular disease, and in elderly patients who are frail.

The benefit of blood pressure (BP) reduction in patients at increased risk of a cardiovascular event has been investigated in a number of major clinical trials of differing designs. Some of these trials compared one BP goal with a lower BP goal, while others compared an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) with placebo. Until recently evidence existed that reduction of systolic BP to around 140 mmHg systolic benefitted high risk patients but the evidence was weak among elderly patients, diabetics and patients with CVD. Because of that, recent national guidelines accepted systolic BP up to 150 mmHg in patients >60 years of age.

However recent data from two large trials (SPRINT and ACCORD) may change guidelines [48, 49]. These two studies compared BP goals to test the hypothesis that attained lower systolic BPs (as low as less than 120 mmHg) and improve outcomes in patients with cardiovascular disease or those at high risk. These trials provide support for the concept that the BP goal in patients with CVD or at high risk (this definition includes age >75 with no other cardiovascular risk factors) should be lower than that for the general population.

In large-scale randomized trials, it has been shown that reduction of BP by 5–6 mmHg diastolic or 10–12 mmHg systolic resulted in more than 50 % relative risk reduction in the incidence of heart failure, a 30–40 % relative risk reduction in stroke, and a 20–25 % relative risk reduction in myocardial infarction.

SPRINT randomly assigned 9361 patients aged 50 years or older with a systolic BP of 130–180 mmHg, and an increased risk of an adverse cardiovascular outcome (but without diabetes), to a systolic BP target of <120 mmHg (intensive treatment group) or <140 mmHg (standard treatment group). Increased cardiovascular risk was defined as: age greater than or equal to 75 years; clinically evident cardiovascular disease (i.e., previously documented coronary, peripheral arterial, or cerebrovascular disease [except for stroke]); subclinical cardiovascular disease (i.e., an elevated coronary artery calcification score by computerized tomography scan, left ventricular hypertrophy, or an ankle-brachial index <0.9); an estimated glomerular filtration rate of 20–59 mL/min/1.73 m^2; or a 10-year Framingham Risk Score greater than or equal to 15 %.

The primary composite outcome included myocardial infarction (MI), other acute coronary syndromes, stroke, heart failure, hospitalization, or death from cardiovascular causes. The mean BP at baseline was approximately 138/78 mmHg in patients treated with 2 antihypertensive agents.

The trial was stopped early for benefit after median follow-up of 3.26 years. The mean number of BP medications was 2.8 and 1.8 in the intensive and standard groups, respectively. At 1 year, the mean systolic BP was 121.4 and 136.2 mmHg in the intensive and standard treatment groups, respectively. There was a lower rate of the primary outcome in the intensive treatment group (1.65 versus 2.19 % per year; hazard ratio [HR] 0.75; 95 % CI 0.64–0.89). The primary outcome occurred in 562 patients. All-cause mortality was also significantly lower in the intensive treatment group (HR 0.73; 95 % CI 0.60–0.90). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury were higher in the intensive treatment group presumably because of higher diuretic use. Patients with established cardiovascular disease accounted for approximately 20 % of enrollees and outcomes were similar in this subgroup relative to the entire population.

In The ACCORD BP trial 4733 patients were randomly assigned with type 2 diabetes who had cardiovascular disease or at least two additional risk factors for cardiovascular disease to systolic BP targets of either less than 120 mmHg or less than 140 mmHg. Patients were followed for mean of 4.7 years. The mean attained systolic pressures were 119 and 134 mmHg, respectively, compared to 139/76 mmHg at baseline. There was no significant difference in the annual rate of the primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes between the intensive versus standard therapy groups (1.87 versus 2.09 %, hazard ratio [HR] 0.88, 95 % CI 0.73–1.06). There was no difference in the annual all-cause mortality rate between intensive and standard therapy groups (1.28 versus 1.19 %) or in the rate of death from cardiovascular causes between groups (0.52 versus 0.49 %). Intensive therapy was associated with significant reductions in the annual rates of total stroke and nonfatal stroke (0.32 versus 0.53 %, HR 0.59, 95 % CI 0.39–0.89 for total stroke and 0.3 versus 0.47 %, HR 0.63, 95 % CI 0.41–0.96 for nonfatal stroke). Serious adverse events attributable to antihypertensive drugs

(e.g., hypotension, syncope, bradycardia or arrhythmia, hyperkalemia, angioedema, and renal failure) occurred significantly more frequently in the intensive versus standard therapy group (3.3 versus 1.3 %). Intensive therapy was also associated with a significantly higher rate of an increase in serum creatinine of more than 1.5 mg/dL (133 micromol/L in men or more than 1.3 mg/dL (115 micromol/L) in women).

Hypertension is a major contributor to endothelial dysfunction, atherosclerosis and cardiovascular events. Treatment and gradual control of hypertension to levels below 120 mmHg systolic and below 65 mmHg diastolic continues to reduce cardiovascular events and improve survival.

Placebo-controlled trials such as HOPE, EUROPA, PEACE, CAMELOT, TRANSCEND, and NAVIGATOR [50–52, 53–55] evaluated the hypothesis that ACE inhibitors or ARBs might have a direct and clinically-significant cardiovascular benefit in patients with a mean baseline BP between (approximately) 130/75 and 140/90 mmHg. In addition, CAMELOT and ACTION compared long-acting dihydropyridine calcium channel blockers to placebo. However, these trials were not designed to determine the optimal BP. Any benefit seen might be due to another mechanism than BP lowering. In the aggregate, these trials suggest a benefit from the agents used in patients with a baseline BP between (approximately) 130/75 and 140/90 mmHg. As the decrease in BP was modest in these studies (average of 3–5 mmHg systolic), they do not provide evidence that BP lowering below 130 mmHg is of benefit. In addition, as the mean age in these trials was about 60 years, they do not provide evidence on how to manage older patients (>70 years) with diastolic BP levels below 65 or 70 mmHg.

A 2009 meta-analysis focused on seven trials that limited therapy to either an ACE inhibitor or an ARB to placebo in patients with ischemic heart disease and preserved left ventricular systolic function [56]. Six trials of ACE inhibitor therapy (including HOPE, EUROPA, CAMELOT, and PEACE) significantly reduced both total mortality (RR 0.87, 95 % CI 0.81–0.94) and nonfatal MI (RR 0.83, 95 % CI 0.73–0.94). A limitation to this meta-analysis is that it does not distinguish between angiotensin inhibition and lower attained BPs as the mechanism of benefit.

This limitation was overcome in a 2011 meta-analysis that included 25 placebo-controlled trials with more than 63,000 patients in which active treatment consisted of all major classes of antihypertensive drugs, including ACE inhibitors, ARBs, beta blockers, calcium channel blockers, diuretics, or combination therapy [57]. Drug therapy significantly lowered the risks of all-cause mortality and MI to the same degree as in the earlier meta-analysis (pooled relative risks 0.87, 95 % CI 0.80–0.95 and 0.80, 95 % CI 0.69–0.93, respectively), suggesting that there was no specific benefit from therapy with angiotensin inhibitors compared with other antihypertensive drugs. The absolute risk reductions in all-cause mortality and MI were 14 and 13 per 1000 persons treated.

Threshold for Low Blood Pressure

There is a blood pressure (BP) threshold for all patients below which tissue perfusion is reduced to vital organs. As long as the BP is lowered gradually, this threshold does not appear to occur at current BP goals [49].

For patients with coronary heart disease without heart failure, it is possible that a lower limit exists for desirable diastolic pressure because much of coronary filling occurs during diastole. Observations from the Framingham study and a post-hoc analysis from the INVEST trial suggested an increase in risk for patients with cardiovascular disease at a diastolic pressure below 70 to 75 mmHg [58, 59]. However in the ACCORD study diastolic BP was reduced to 62 mmHg in high risk diabetics with no evidence of J-shaped curve.

Other analyses from placebo-controlled trials of hypertension found a similar J-shaped curve for diastolic and systolic pressures in both treated and untreated groups and for both cardiovascular and non-cardiovascular mortality [60, 61]. These findings indicate that the worse outcomes at lower pressures are independent of antihypertensive therapy as long as the BP is lowered slowly. Although there must be a level of diastolic BP and perhaps systolic, that organ hypo perfusion occurs and CV mortality and cardiovascular events increase, but evidence suggest that it must be well below current targets.

In summary, presented evidence strongly suggest that hypertension is a major contributor to endothelial dysfunction, atherosclerosis and cardiovascular events. Treatment and gradual control of hypertension to levels below 120 mmHg systolic and below 65 mmHg diastolic continues to reduce cardiovascular events and improve survival. Implementation of wide scale programs to treat and control hypertension to these low levels will improve longevity and reduce CV outcomes around the world.

References available on request
Healthcare.India@springer.com

Source: Misbah Zaheer, Paola Chrysostomou, Vasilios Papademetriou. Hypertension and Atherosclerosis: Pathophysiology, Mechanisms and Benefits of BP Control. In: E.A. Andreadis (ed). Hypertension and Cardiovascular Disease. 1st ed. Switzerland: Springer International Publishing; 2016, pp 201-216. DOI 10.1007/978-3-319-39599-9_14.

Contemporary Drug Treatment of Hypertension: Focus on Recent Guidelines

Wilbert S. Aronow[1], William H. Frishman[1]

Hypertension guidelines from 2011 through 2017 have differed on what the optimal BP goal should be in adults with hypertension. This review article discusses the optimal BP goals recommended by these different guidelines. It also discusses antihypertensive drug treatment recommendations, especially those reported in the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) hypertension guidelines.

Key Points from the 2017 ACC/AHA Hypertension Guidelines

- Use lifestyle measures plus blood pressure (BP)-lowering drugs for secondary prevention of recurrent cardiovascular disease (CVD) events in adults with clinical CVD (coronary heart disease [CHD], congestive heart failure [CHF], and stroke) and an average systolic BP (SBP) ≥ 130 mmHg or an average diastolic BP (DBP) ≥ 80 mmHg.
- Use lifestyle measures plus BP-lowering drugs for primary prevention of CVD in adults with an estimated 10-year risk of atherosclerotic CVD (ASCVD) ≥ 10 % and an average SBP ≥ 130 mmHg or an average DBP ≥ 80 mmHg.
- Use lifestyle measures plus BP-lowering drugs for primary prevention of CVD in adults with an estimated 10-year risk of ASCVD < 10 % and an average SBP ≥ 140 mmHg or an average DBP ≥ 90 mmHg.
- Lower BP to < 130/80 mmHg in adults with ischemic heart disease, in heart failure with a reduced left ventricular ejection fraction, in heart failure with a preserved left ventricular ejection fraction, in chronic kidney disease, after renal transplantation, for secondary prevention of stroke, in lacunar stroke, in peripheral arterial disease, in diabetes mellitus, in thoracic aortic aneurysm, and in ambulatory community-dwelling adults aged > 65 years.

Wilbert S. Aronow (✉)
wsaronow@aol.com
[1] Cardiology Division and the Department of Medicine, Westchester Medical Center and New York Medical College, Macy Pavilion, Room 141, Valhalla, NY 10595, USA

Introduction

Worldwide, hypertension is the leading modifiable risk factor for cardiovascular (CV) events and mortality [1]. Hypertension is a major risk factor for CV events and mortality in adults [2]. Hypertension is present in 69 % of adults with a first myocardial infarction (MI) [2], in 77 % of adults with a first stroke [2], in 74 % of adults with heart failure (HF) [2], and in 60 % of older adults with peripheral arterial disease (PAD) [3]. Hypertension is also a major risk factor for development of sudden cardiac death, a dissecting aortic aneurysm, angina pectoris, left ventricular (LV) hypertrophy, thoracic and abdominal aortic aneurysms, chronic kidney disease (CKD), atrial fibrillation, diabetes mellitus, the metabolic syndrome, vascular dementia, Alzheimer's disease, and ophthalmologic disease [4]. A meta-analysis of 61 prospective studies including 1 million adults without prior CV disease (CVD) showed that CV risk increases progressively from a blood pressure (BP) level of 115/75 mmHg with a doubling of the incidence of coronary heart disease (CHD) and of stroke for every 20/10 mmHg increase in BP [5]. Numerous randomized, double-

blind, placebo-controlled clinical trials have also shown that treatment of hypertension with antihypertensive drug therapy in adults decreases CV events and mortality [4, 6–8].

A systematic review and meta-analysis included 123 randomized studies of antihypertensive drug therapy in 613,815 individuals [8]. The review found that every 10 mmHg decrease in systolic BP (SBP) significantly decreased major CV events by 20 %, CHD by 17 %, stroke by 27 %, and HF by 28 %, which—in the populations studied—reduced all-cause mortality by 13 % [8].

SPRINT (Systolic Blood Pressure Intervention Trial) randomized 9361 adults to an SBP goal of < 120 or < 140 mmHg [6]. These patients had a mean age of 67.9 years, SBP 130–180 mmHg, and an increased CV risk; no diabetes mellitus, history of stroke, or symptomatic HF within the past 6 months; an LV ejection fraction < 35 %; and an estimated glomerular filtration rate < 20 ml/min/1.73 m^2 [6]. At 3.26-year follow-up, intensive BP treatment reduced the primary composite outcome of MI, other acute coronary syndromes, stroke, HF, or death from CV causes by 25 %, all-cause mortality by 27 %, HF by 38 %, CV death by 43 %, and the primary composite outcome or death by 22 % [6]. Intensive BP treatment reduced the primary composite outcome by 33 % in adults aged ≥ 75 years and the primary composite outcome by 20 % in adults aged 50–74 years [6].

Of the 2636 adults aged ≥ 75 years (mean 79.9 years) in SPRINT, 33.4 % of those randomized to an SBP goal < 120 mmHg and 28.4 % of those randomized to an SBP goal < 140 mmHg were frail [7]. At 3.14-year follow-up, compared with an SBP goal < 140 mmHg, an SBP goal < 120 mmHg decreased the primary composite endpoint by 34 %, all-cause mortality by 33 %, HF by 38 %, and the primary composite outcome or death by 32 %. Absolute CV event rates were lower for the intensive treatment group within each frailty stratum [7].

Hypertension guidelines from 2011 through 2017 have differed on what the optimal BP goal should be in adults with hypertension. This review article discusses the optimal BP goals recommended by these different guidelines (Table 1). We also discuss antihypertensive drug treatment recommendations, especially those reported in the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) hypertension guidelines [9].

Blood Pressure (BP) Goals Recommended by Different Guidelines

The ACC/AHA 2011 expert consensus document on hypertension in the elderly, developed in collaboration with the American Academy of Neurology (AAN), the American Geriatrics Society (AGS), the American Society for Preventive Cardiology (ASPC), the American Society of Hypertension (ASH), the American Society of Nephrology (ASN), the Association of Black Cardiologists (ABC), and the European Society of Hypertension (ESH), recommended that BP be lowered to < 140/90 mmHg in individuals aged < 80 years (Table 1) [4]. Based on the clinical trial data from the HYVET (Hypertension in the Very Elderly) trial [10] and the SHEP (Systolic Hypertension in the Elderly) trial [11–13], these hypertension guidelines recommended that BP be lowered to 140–145/90 mmHg if tolerated in those aged ≥ 80 years [4].

The ESH/European Society of Cardiology (ESC) 2013 guidelines for management of hypertension recommended reducing BP to < 140/90 mmHg in adults at low to moderate CV risk, with diabetes mellitus, prior stroke or transient ischemic attack (TIA), CHD, or diabetic or non-diabetic CKD [14]. In older adults aged < 80 years with SBP of ≥ 160 mmHg, BP should be reduced to between 140 and 150/< 90 mmHg with consideration of a BP target of < 140/90 mmHg [14]. In adults aged > 80 years with SBP ≥ 160 mmHg, BP should be reduced to between 140 and 150/< 90 mmHg provided they are in good physical and mental condition [14].

The 2013 Eighth Joint National Committee (JNC 8) guidelines for management of hypertension recommended lowering BP to < 150/90 mmHg in adults aged ≥ 60 years without diabetes mellitus or CKD and to < 140/90 mmHg in adults with diabetes mellitus or CKD [15]. The minority view from JNC 8 recommended that the BP goal in adults aged < 80 years with hypertension without diabetes mellitus or CKD should be < 140/90 mmHg [16].

Older adults are currently being undertreated for hypertension [4, 17]. BP is adequately controlled in 36 % of men

Table 1: BP goals recommended by different scientific society guidelines.

Society and year [reference]	Recommendations
ACC/AHA guidelines 2017 [9]	< 140/90 mm Hg if 10-year ASCVD risk is < 10 %
	< 130/80 mm Hg for primary prevention if 10-year ASCVD risk is ≥ 10 % and for secondary prevention
ACP/AAFP guidelines 2017 [25]	SBP < 150 mm Hg in adults ≥ 60 years
	SBP < 140 mm Hg if stroke or TIA or at high CV risk
NHF of Australia guidelines 2016 [24]	< 140/90 mm Hg
	SBP < 120 mm Hg in selected high CV risk persons
Canadian guidelines 2016 [23]	SBP < 120 mm Hg in high-risk persons
AHA/ACC/ASH guidelines 2015 [22]	< 140/90 mm Hg
	< 150 /90 mm Hg if ≥ 80 years
ASH/ISH guidelines 2014 [21]	< 140/90 mm Hg
	< 150 /90 mm Hg if ≥ 80 years
ABC and Working Group on Women's Cardiovascular Health guidelines 2014 [19]	< 140/90 mm Hg
	< 150/90 mm Hg in debilitated or frail persons ≥80 years
ESC guidelines 2013 [14]	< 140/90 mm Hg
	140–150/<90 mm Hg if ≥ 80 years
NICE guidelines 2013 [20]	< 140/90 mm Hg
	< 150 /90 mm Hg if ≥ 80 years
JNC 8 guidelines 2013 [15]	< 150/90 mm Hg if ≥ 60 years without CKD or diabetes mellitus
ACC/AHA guidelines 2011 [4]	< 140/90 mm Hg
	140–145/< 90 mm Hg if ≥ 80 years

AAFP American Academy of Family Physicians, *ABC* Association of Black Cardiologists, *ACC* American College of Cardiology, *ACP* American College of Physicians, *AHA* American Heart Association, *ASCVD* atherosclerotic cardiovascular disease, *ASH* American Society of Hypertension, *CKD* chronic kidney disease, *CV* cardiovascular, *ESC* European Society of Cardiology, *ISH* International Society of Hypertension, *JNC 8* Eighth Joint National Committee, *NHF* National Heart Foundation, *NICE* National Institute on Health and Clinical Excellence, *SBP* systolic BP, *TIA* transient ischaemic attacks.

and 28 % of women aged 60–79 years, respectively, and in 38 % of men and 23 % of women aged ≥ 80 years, respectively [17]. If the JNC 8 panel recommendations were implemented, 6 million US adults aged ≥ 60 years would not be eligible for antihypertensive drug therapy, and treatment intensity would be decreased for an additional 13.5 million older patients [18], causing increased incidences of CHD events, stroke, HF, CV mortality, and other adverse events associated with poorly controlled hypertension.

The ABC and the Working Group on Women's Cardiovascular Health 2014 recommendations supported a BP goal of < 140/90 mmHg in adults aged ≥ 60 years and of < 150/90 mmHg in debilitated or frail individuals aged ≥ 80 years [19]. The ABC stated that the JNC 8 recommendations would endanger the more than 36 million Americans aged ≥ 60 years with hypertension, with a disproportionate negative effect on Blacks and those with CKD or cerebrovascular disease [19]. The Working Group on Women's Cardiovascular Health 2014 recommendations stated that hypertension is the major modifiable risk factor for CHD, HF, stroke, atrial fibrillation, diabetes mellitus, and CKD in women [19]. These guidelines stated that the JNC 8 guidelines did not recognize that the hypertensive population is primarily women, that older women generally have poorly controlled hypertension, and that approximately 40 % of adults with poorly controlled BP are Black women, who are at the highest risk for stroke, HF, and CKD [19].

The UK National Institute for Health and Care Excellence (NICE) hypertension guideline, updated in 2013, recommended lowering BP to < 140/90 mmHg in older adults aged < 80 years [20]. These guidelines recommended lowering BP to < 150/90 mmHg in adults aged ≥ 80 years [20].

The 2014 ASH/International Society of Hypertension (ISH) guidelines recommended reducing BP to < 140/90 mmHg in adults aged ≤ 80 years [21]. These guidelines also recommended lowering BP to < 150/90 mmHg in adults aged > 80 years with BP ≥ 150/90 mmHg unless these adults have diabetes mellitus or CKD, in which case a target goal of < 140/90 mmHg should be considered [21].

The AHA/ACC/ASH 2015 guidelines on treatment of hypertension in patients with CHD recommended that target BP should be < 140/90 mmHg in adults with CHD and acute coronary syndromes if they are aged ≤ 80 years but < 150/90 mmHg if they are aged > 80 years [22]. These guidelines also stated that consideration can be given to lowering BP to < 130/80 mmHg in adults with CHD who have had an MI, stroke, TIA, carotid artery disease, PAD, or an abdominal aortic aneurysm. Caution was advised when lowering DBP to < 60 mmHg in adults with diabetes mellitus or in adults aged > 60 years [22].

The Canadian 2016 hypertension guidelines recommended that high-risk individuals aged ≥ 50 years with SBP ≥ 130 mmHg obtained by an automated office BP measurement should have a target SBP goal of ≤ 120 mmHg [23]. High-risk individuals for treatment with intensive BP management include those with clinical or subclinical CVD or CKD or an estimated 10-year global CV risk of ≥ 15 % or aged ≥ 75 years [23]. A standing SBP < 110 mmHg must be avoided [23].

The National Heart Foundation (NHF) of Australia 2016 hypertension guidelines stated that, in patients with uncomplicated hypertension, the target BP should be < 140/90 mmHg or lower if tolerated [24]. In selected high CV risk individuals, an SBP goal < 120 mmHg can improve CV outcomes [24]. These adults should be closely monitored to identify treatment-related adverse effects, including hypotension, syncope, electrolyte abnormalities, and acute kidney injury [24].

The 2017 American College of Physicians (ACP)/American Academy of Family Physicians (AAFP) hypertension guidelines made the following three recommendations [25]: (1) adults aged ≥ 60 years with SBP ≥ 150 mmHg should have SBP reduced to < 150 mmHg to reduce their risk for mortality, stroke, and CV events; (2) adults aged ≥ 60 years with a history of stroke or TIA should have SBP reduced to < 140 mmHg to decrease their risk for recurrent stroke; and (3) some adults aged ≥ 60 years at high CV risk based on individualized assessment should have their target SBP reduced to < 140 mmHg to reduce their risk for stroke and CV events [25].

The 2017 ACC/AHA hypertension guidelines stated that a normal BP is < 120/80 mmHg [9]. Elevated BP was defined as SBP 120–129 mmHg with DBP < 80 mmHg and should be treated with lifestyle measures as discussed elsewhere [26]. Stage 1 hypertension is SBP 130–139 mmHg or DBP of 80–89 mmHg. Stage 2 hypertension is SBP ≥ 140 mmHg or DBP ≥ 90 mmHg [9].

The 2017 ACC/AHA hypertension guidelines stated that the absolute CV risk reduction attributable to BP lowering is greater at higher absolute levels of CV risk [9]. Predicted CV risk in conjunction with BP should be used to guide antihypertensive drug treatment [9, 27–29].

The 2017 ACC/AHA hypertension guidelines recommended lifestyle measures plus BP-lowering drugs for secondary prevention of recurrent CV events in adults with clinical CVD (CHD, congestive HF [CHF], and stroke) and an average SBP ≥ 130 mmHg or an average DBP ≥ 80 mmHg [8, 9, 30, 31]. These guidelines recommended lifestyle measures plus BP-lowering drugs for primary prevention of CVD in adults with an estimated 10-year risk of atherosclerotic CVD (ASCVD) ≥ 10 % [32] and an average SBP ≥ 130 mmHg or an average DBP ≥ 80 mmHg [6, 7, 9, 33]. These guidelines recommended lifestyle measures plus BP-lowering drugs for primary prevention of CVD in adults with an estimated 10-year risk of ASCVD < 10 % [32] and an average SBP ≥ 140 mmHg or an average DBP ≥ 90 mmHg [5, 9, 33]. White coat hypertension must be excluded before starting antihypertensive drug treatment in adults with hypertension who have a low risk for ASCVD [9].

The 2017 ACC/AHA hypertension guidelines recommended lowering BP to < 130/80 mmHg in adults with CHD [6, 7, 9, 31, 34], HF with a reduced LV ejection fraction (HFrEF) [9, 35], HF with a preserved LV ejection fraction (HFpEF) [9, 35], or CKD [9, 36]; after renal transplantation [9]; in adults with lacunar stroke [9, 37], PAD [9, 30], or diabetes mellitus [9, 38–41]; for secondary prevention of stroke [9, 42]; and in ambulatory community-dwelling adults aged > 65 years [6, 7, 9].

Ambulatory BP Monitoring

The 2017 ACC/AHA hypertension guidelines recommended the use of ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) for the diagnosis of white coat hypertension or masked hypertension [9]. White coat hypertension is diagnosed if BP is increased in clinic but normal when measured via ABPM or HBPM. Masked

hypertension is diagnosed if BP is normal in clinic but increased when measured via ABPM or HBPM. ABPM can measure BP while patients perform normal daily activities and can determine mean BP during the entire monitoring period, mean BP during daytime and nighttime, the daytime-to-nighttime BP ratio to measure the extent of nocturnal dipping and the early morning surge pattern, and can also measure BP variability and diagnose symptomatic hypotension [9].

Antihypertensive Drug Treatment

A meta-analysis of 147 randomized controlled trials of 464,000 patients with hypertension demonstrated that—except for the major effect of beta-blockers administered after MI in reducing CHD events and a minor additional effect of calcium channel blockers (CCBs) in reducing stroke—all major antihypertensive drug classes (diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], beta-blockers, and CCBs) caused a similar reduction in CHD events and stroke for a given reduction in BP [43]. The 2011 ACC/AHA hypertension guidelines stated that the choice of specific antihypertensive drugs such as diuretics, ACE inhibitors, ARBs, beta-blockers, or CCBs in the treatment of adults with hypertension depends on efficacy, tolerability, presence of specific comorbidities, and cost [4].

The 2011 ACC/AHA hypertension guidelines recommended that elderly patients with primary hypertension may be treated with diuretics, ACE inhibitors, ARBs, beta-blockers, or CCBs [4]. The 2013 ESH/ESC guidelines for management of hypertension recommended that adults with primary hypertension may be treated with diuretics, ACE inhibitors, ARBs, CCBs, or beta-blockers [14]. The 2013 JNC 8 guidelines for management of hypertension recommended that non-Black adults with primary hypertension may be treated with diuretics, ACE inhibitors, ARBs, or CCBs [15]. These guidelines recommended that Black adults with primary hypertension should initially be treated with diuretics or CCBs [15]. The 2014 ASH/ISH guidelines recommended that non-Black adults with primary hypertension aged < 60 years should initially be treated with an ACE inhibitor or an ARB [21]. These guidelines recommended that non-Black adults aged ≥ 60 years with primary hypertension may initially be treated with diuretics, CCBs, ACE inhibitors, or ARBs [21]. These guidelines recommended that Black adults with primary hypertension should initially be treated with CCBs or thiazide diuretics [21]. The different guidelines stated that the choice of antihypertensive drugs for the treatment of secondary hypertension depends on the comorbidities being treated. The next section discusses the recommendations of the 2017 ACC/AHA hypertension guidelines regarding antihypertensive drug treatment for primary hypertension and for secondary hypertension [9].

Initiation of Antihypertensive Drug Treatment

The 2017 ACC/AHA hypertensive guidelines recommended initiation of antihypertensive drug treatment with two first-line drugs from different classes, either as separate agents or in a fixed-dose combination, in adults with BP ≥ 140/90 mmHg or with a BP that is > 20/10 mmHg above their BP target [9, 44].

White and Other Non-Blacks Aged < 60 Years with Primary Hypertension

The first antihypertensive drug should be an ACE inhibitor or ARB, the second a thiazide diuretic (preferably chlorthalidone) or a CCB, and—if a third antihypertensive drug is needed—a combination of an ACE inhibitor or ARB plus a thiazide diuretic plus a CCB should be administered [9, 21].

White and Other Non-Blacks Aged ≥ 60 Years with Primary Hypertension

The first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a CCB, and—if a third antihypertensive drug is needed—a combination of a thiazide diuretic plus a CCB plus an ACE inhibitor or ARB should be administered [9, 21].

Blacks with Primary Hypertension

The first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a CCB, and—if a third antihypertensive drug is needed—a combination of a thiazide diuretic plus a CCB plus an ACE inhibitor or ARB should be administered [9, 21].

Stable Coronary Heart Disease and Hypertension

Patients with stable CHD and hypertension should be treated with a beta-blocker plus an ACE inhibitor or ARB, and—if a third antihypertensive drug is needed—a combination of a beta-blocker plus an ACE inhibitor or ARB plus a thiazide diuretic or a CCB should be administered [9, 22, 43, 45–55]. If a fourth antihypertensive drug is needed to control hypertension, a mineralocorticoid receptor antagonist should be added [9]. In adults with stable CHD with angina pectoris despite beta-blocker therapy and persistent uncontrolled hypertension, a dihydropyridine CCB should be added [9, 22, 43, 56]. Beta-blockers that should be used to treat CHD with hypertension include carvedilol, metoprolol tartrate, metoprolol succinate, bisoprolol, nadolol, propranolol, and timolol [9]. Atenolol should be avoided [9, 22, 46, 57, 58]. Nondihydropyridine CCBs such as verapamil and diltiazem cannot be used in patients with LV systolic dysfunction [9, 22]; carvedilol, metoprolol succinate, or bisoprolol are the beta-blockers of choice [9, 22, 45].

If hypertension persists after use of a beta-blocker plus an ACE inhibitor or ARB in patients with acute coronary syndromes, a long-acting dihydropyridine CCB may be added to the therapeutic regimen [22]. Aldosterone antagonists are indicated in patients receiving beta-blockers plus ACE inhibitors or ARBs after MI who have LV systolic dysfunction and either HF or diabetes mellitus [22, 59].

Heart Failure with a Reduced Left Ventricular Ejection Fraction and Hypertension

Adults with hypertension who have HFrEF should be treated with a beta-blocker (carvedilol, metoprolol succinate, or bisoprolol) plus an ACE inhibitor or ARB or, preferably, an angiotensin receptor–neprilysin inhibitor plus a diuretic and, if needed, a mineralocorticoid receptor antagonist [9, 35, 46, 59–65]. Nondihydropyridine CCBs are contraindicated in patients with HFrEF [9, 35, 66, 67].

Heart Failure with a Preserved Left Ventricular Ejection Fraction and Hypertension

In patients with HFpEF, volume overload should be treated with diuretics, other

comorbidities should be treated, and hypertension should treated with a beta-blocker plus an ACE inhibitor or ARB plus a mineralocorticoid receptor antagonist [9, 35, 68, 69].

Chronic Kidney Disease and Hypertension

Adults with hypertension who have CKD stage 3 or higher or stage 1 or 2 CKD with albuminuria ≥ 300 mg/day should be treated with an ACE inhibitor to slow progression of CKD [9, 36, 70–72]. If they do not tolerate an ACE inhibitor, patients should be treated with an ARB [9]. Adults with stage 1 or 2 CKD without albuminuria may be treated with usual first-line antihypertensive drugs [9]. If three antihypertensive drugs are needed, patients should be treated with an ACE inhibitor or ARB plus a thiazide diuretic plus a CCB. After kidney transplantation, it is reasonable to treat hypertension with a CCB to improve glomerular filtration rate and kidney survival [9, 73].

Stroke or Transient Ischemic Attack and Hypertension

Adults with hypertension who have had a stroke or TIA should be treated with a thiazide diuretic or ACE inhibitor or ARB [9, 74–76]. If a third antihypertensive drug is needed, a thiazide diuretic plus an ACE inhibitor or ARB plus a CCB should be added.

Peripheral Arterial Disease and Hypertension

Adults with hypertension who have PAD should be treated with antihypertensive drug therapy similar to that in patients without PAD [9, 77]. No evidence indicates that any one class of antihypertensive drugs is superior in the treatment of hypertension in patients with PAD [9, 77].

Diabetes Mellitus and Hypertension

In adults with hypertension and diabetes mellitus, thiazide diuretics, ACE inhibitors, ARBs, and CCBs are effective and may be used as initial therapy [9, 78–80]. In patients with diabetes mellitus with hypertension and persistent albuminuria, initial treatment with ACE inhibitors or ARBs should be considered [9, 81, 82]. ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) showed that chlorthalidone was better than lisinopril, amlodipine, or doxazosin in reducing CV and renal outcomes in nondiabetic adults with hypertension and the metabolic syndrome [83].

Thoracic Aortic Aneurysm and Hypertension

Beta-blockers are the preferred antihypertensive drugs in adults with hypertension and thoracic aortic aneurysm [9]. Beta-blockers are also associated with improved survival in adults with type A or B acute and chronic thoracic aortic dissection [9, 84, 85].

Pregnancy and Hypertension

Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, direct renin inhibitors, or atenolol [9, 86–88]; they may be with methyl-dopa, nifedipine, and/or labetalol [9, 89, 90].

Resistant Hypertension

Resistant hypertension is diagnosed if BP is uncontrolled despite adequate doses of three first-line classes of antihypertensive drugs, including a thiazide diuretic, or if adequate BP control requires four or more antihypertensive drugs of different classes [9, 91]. Treatment of resistant hypertension includes improving compliance with medication, detection and treatment of secondary hypertension, use of lifestyle measures, and treating obesity and other comorbidities [9, 26]. If a fourth antihypertensive drug is required to control BP in adults treated with adequate doses of antihypertensive drugs from different classes, including a thiazide diuretic, a mineralocorticoid receptor antagonist should be added to the therapeutic regimen [92].

The PATHWAY-2 (Spironolactone Versus Placebo, Bisoprolol, and Doxazosin to Determine the Optimal Treatment for Drug-Resistant Hypertension) trial was a randomized, double-blind, crossover trial in which 314 patients with drug-resistant hypertension were randomized for 12 weeks to spironolactone (285 patients), doxazosin (282 patients), bisoprolol (285 patients), or placebo (274 patients) [93]; 230 patients received all four drugs. This study showed that spironolactone was the most effective add-on drug for the treatment of drug-resistant hypertension [93].

Treatment of Hypertension in SPRINT-Eligible Adults

The SPRINT (Systolic Blood Pressure Intervention Trial) eligibility criteria [6, 7] were applied to the 1999–2006 National Health and Nutrition Examination Survey and linked with the National Death Index through December 2011 [93]. This study demonstrated that reducing SBP to < 120 mmHg in all eligible US adults could prevent 107,500 deaths and 46,100 cases of HF each year but would also result in an increased incidence of serious adverse events [94].

Conclusion

Use lifestyle measures plus BP-lowering drugs for secondary prevention of recurrent CV events in adults with clinical CVD (CHD, CHF, and stroke) and an average SBP ≥ 130 mmHg or an average DBP ≥ 80 mmHg [9]. Use lifestyle measures plus BP-lowering drugs for primary prevention of CVD in adults with an estimated 10-year risk of ASCVD ≥ 10 % and an average SBP ≥ 130 mmHg or an average DBP ≥ 80 mmHg [9]. Use lifestyle measures plus BP-lowering drugs for primary prevention of CVD in adults with an estimated 10-year risk of ASCVD < 10 % and an average SBP ≥ 140 mmHg or an average DBP ≥ 90 mmHg [9]. White coat hypertension must be excluded before starting antihypertensive drug treatment in adults with hypertension who have a low risk for ASCVD [9].

BP should be lowered to < 130/80 mmHg in adults with CHD, in HFrEF, in HFpEF, in CKD, after renal transplantation, for secondary stroke prevention, in lacunar stroke, in PAD, in diabetes mellitus, and in ambulatory community-dwelling adults aged > 65 years [9].

Compliance with Ethical Standards
Funding: No external funding was used in the preparation of this manuscript.
Conflict of interest: Wilbert S. Aronow and William H. Frishman have no conflicts of interest that might be relevant to the contents of this manuscript.

References available on request
Healthcare.India@springer.com

Source: Wilbert S. Aronow, William H. Frishman. Contemporary Drug Treatment of Hypertension: Focus on Recent Guidelines. Drugs 2018; 78(5): 567–576. DOI 10.1007/s40265-018-0887-5.

Olmesartan vs. Ramipril in Elderly Hypertensive Patients: Review of Data from Two Published Randomized, Double-Blind Studies

Stefano Omboni, Ettore Malacco, Jean-Michel Mallion, Paolo Fabrizzi, Massimo Volpe

Up to date, few randomized clinical studies have directly compared the activity and safety of ARBs and ACE-inhibitors in elderly hypertensive patients. The present review summarizes the results of published and unpublished data from two recent randomized, double-blind, parallel-group studies comparing the efficacy and safety of olmesartan medoxomil with that of the ACE inhibitor ramipril in elderly patients with mild to moderate essential hypertension.

S. Omboni (✉)
Italian Institute of Telemedicine, Via Colombera 29, 21048 Solbiate Arno (Varese), Italy
e-mail: stefano.omboni@iitelemed.org

E. Malacco
Department of Internal Medicine, Ospedale L. Sacco, University of Milan, Milan, Italy

J.-M. Mallion
Cardiology and Arterial Hypertension, CHU de Grenoble, Grenoble, France

P. Fabrizzi
Laboratori Guidotti S.p.A, Pisa, Italy

M. Volpe
Cardiology, Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, University of Rome "Sapienza" and IRCCS Neuromed, Pozzilli, Italy

Introduction

Because the vascular system is a typically ageing tissue, development of essential hypertension generally manifests itself with older age [1]. In fact, one of the primary causes of blood pressure (BP) elevation in the elderly is increased arterial stiffness, caused by age-associated structural modifications in the arterial wall and by molecular changes in the nitric oxide and angiotensin II pathways leading to endothelial dysfunction [2].

Hypertension (defined as a systolic BP or SBP ≥140 mmHg and/or diastolic BP or DBP ≥90 mmHg) has an estimated prevalence of approximately 55 % in men and 62 % in women over 65 years in the worldwide population [3, 4], and according to one of the main epidemiological studies, the Framingham Heart Study, the residual lifetime risk for developing hypertension in normotensive people aged 55–65 years exceeds 90 % [5]. Consequently, given the trend for progressive aging of the global population, the burden of hypertension on public health is expected to rise in future years.

Elevated BP, particularly SBP, is recognized as an important risk factor for cardiovascular (CV) morbidity and mortality and renal disease [6, 7]. Hypertension adds to- and potentiates- the effects of other CV risk conditions such as diabetes, metabolic syndrome and subclinical organ damage, which are more frequently found in elderly people [8, 9]. Hence, recent guidelines

underline the importance of BP control in the elderly and recommend treating hypertension to achieve the goals of 140 mmHg of SBP and 90 mmHg of DBP [8, 9].

A large number of randomized placebo-controlled trials carried out in patients with systolic and diastolic hypertension or isolated systolic hypertension aged 60 years and older have shown that antihypertensive drug treatment is associated with a marked reduction in CV morbidity and mortality [10–18], mainly due to a significant decrease in the incidence of stroke, coronary heart disease and heart failure [19, 20]. Despite these findings clearly demonstrating the benefits in lowering BP, current data indicate that the rate of treatment and control for hypertension among older patients is still suboptimal [21, 22], and that - in the absence of other complications—a significant proportion of primary care physicians do not have their elderly patients begin active drug therapy unless SBP is greater than 160 mmHg [23].

On the other hand, adequate BP control in elderly hypertensive patients is more difficult to achieve as this population is usually characterized by multiple CV risk factors, target organ damage and associated CV conditions [24]. This is further complicated by occurrence of side effects, which frequently lead patients to discontinue antihypertensive therapy [25].

Thus, long-term control of BP in older people could greatly benefit from antihypertensive drugs that combine established efficacy and improved tolerability, and may ensure target organ protection [26]. In addition, because age is associated with a larger 24-h BP variability and constitutes an independent risk factor for early morning BP surge [27], an ideal therapy should possibly blunt the excessive BP changes related to the altered circadian rhythm [28] and provide a sustained and homogeneous BP control during the 24 h, with long-lasting efficacy in the critical early morning period when the occurrence of CV events is higher [29].

Currently, hypertension is treated by means of several classes of antihypertensive drugs, including thiazide diuretics, beta-adrenergic blockers, calcium antagonists, and inhibitors of the renin–angiotensin system (RAS), such as angiotensin-converting-enzyme or ACE-inhibitors, angiotensin receptor blockers or ARBs and renin inhibitors [9]. According to recent meta-analyses all major classes of antihypertensive agents are equally effective in reducing BP [30], and among these, ACE-inhibitors and ARBs are supposed to have a superior tolerability profile, making them an attractive option for the management of hypertension in older people [20].

In the present paper we will summarize the current evidence on efficacy of ACE-inhibitors and ARBs in elderly hypertensive. In particular, we will review results of published and unpublished pooled data from two recent randomized, double-blind, trials, comparing the antihypertensive efficacy of the ARB olmesartan medoxomil vs. that of the ACE-inhibitor ramipril in a large study population including more than 1,400 hypertensive subjects aged 65–89 years with mild-to-moderate essential hypertension.

Angiotensin-Converting-Enzyme (ACE) Inhibitors and Angiotensin II Receptor Blockers (ARB) in the Treatment of Hypertension in the Elderly

Results of major published randomized clinical trials comparing efficacy and tolerability of ACE-inhibitors or ARBs vs. placebo or other active drug treatment on elderly hypertensive patients are summarized in Table 1. According to most studies, ARBs appear as possibly the best well-tolerated antihypertensive drugs, with side effects comparable to those of placebo. In particular, ARBs have the advantage to be associated with a lower incidence of cough, that is instead an adverse event frequently connected to treatment with ACE-inhibitors.

Furthermore, owing to the wide spectrum of their pharmacological activities, RAS inhibitors are supposed to convey other benefits and provide end-organ protection beyond any effect simply attributable to BP lowering, particularly for kidneys, heart and blood vessels [44, 45]. At the vascular level, RAS blockade could inhibit the proatherogenic and prothrombotic effects of an inappropriate activation of angiotensin II [46]. In a number of clinical trials, both ACE-inhibitors and ARBs proved to be more effective in retarding progression of renal damage in hypertensive diabetic and non-diabetic patients with albuminuria as well as in preventing and delaying the first onset of microalbuminuria, when compared to other drugs with similar antihypertensive efficacy [47–51]. More recently, the ONTARGET trial, one of the first large-scale trial to directly compare an ARB with an ACE-inhibitor, performed in patients at high vascular risk, reported a comparable efficacy of the two drugs concerning renal protection, with a better tolerability in favour of the ARB [52]. None of these trials, however, was specifically conceived to investigate renal outcomes in the elderly population.

Several studies also indicate that RAS inhibition could be associated with the delay or prevention of development of diabetes, in respect to placebo or other antihypertensive therapy [44]. Post-hoc analyses of both ACE-inhibitor and ARB trials report an average reduction by about 25 % in the incidence of new-onset diabetes. In addition, RAS inhibitors are supposed to improve insulin sensitivity [53].

Finally, in most of clinical studies, ARBs and ACE-inhibitors have been found to provide cardiac protection and improve CV outcomes in the elderly. Large trials, including the Heart Outcomes Prevention Evaluation (HOPE) study [54] and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) [55], have shown that ACE-inhibitors significantly reduce the risk of CV events in high-risk patients. On the other hand, ARB therapy has been associated with a marked reduction in the rate of fatal and non-fatal strokes when tested against placebo or other active antihypertensive treatment [56]. In the LIFE study, comparing the ARB losartan with the beta-blocker atenolol in elderly patients with left ventricular hypertrophy, ARB treatment is shown to decrease to a greater extent the risk of stroke, CV mortality and new-onset diabetes, while providing a similar BP reduction [57]; more, losartan is associated with a lower discontinuation rate than atenolol as a result of fewer adverse events. However, results of other studies have not demonstrated a clear additional advantage of antihypertensive therapy based on RAS inhibiting agents respect to other drugs as regards the prevention in total CV events [58, 59].

Up to date, comprehensive head-to-head randomized studies to directly compare the efficacy of ARBs vs. ACE-inhibitors in elderly hypertensive patients have been rarely performed, and often only in relatively small samples of population [32, 35].

Olmesartan and Ramipril in the Treatment of Elderly Hypertensive Subjects

Olmesartan medoxomil is one of the most recent members of the ARBs class to have

Table 1: Antihypertensive drug trials comparing efficacy and tolerability of ARBs or ACE inhibitors vs. placebo or other active drug treatment in elderly patients.

References	Tested drug	Comparator	n	Study design	Main inclusion criteria	Results
Leonetti *et al.* [31]	Fosinopril 10 mg/day	Chlorthalidone 12.5 mg/day	312	Double-blind, randomized, parallel group (9 weeks)	Age >60 years, SBP 160–200 mmHg	No statistical difference in SBP and DBP reductions. The ACE-inhibitor was better tolerated
Lacourcière *et al.* [32]	Irbesartan 150 mg/day	Enalapril 10 mg/day	141	Double-blind, randomized, parallel group (8 weeks)	Age ≥65 years, DBP 95–110 mmHg	No statistical difference in blood pressure reduction between treatments. Significantly lower incidence of cough in the ARB group
Neutel *et al.* [33]	Valsartan 80–100 mg/day	Placebo	146	Double-blind, randomized, placebo controlled, parallel group (8 weeks)	Age >65 years, SBP ≥160 mmHg	Statistical difference vs. placebo in blood pressure reduction. ARB tolerability profile similar to that of placebo
Neldam *et al.* [34]	Candesartan 8–16 mg/day	HCTZ 12.5 mg/day	185	Double-blind, randomized, parallel group (24 weeks)	Age ≥75 years, DBP 95–114 mmHg	No significant differences in BP reduction and tolerability profile
Ruilope *et al.* [35]	Eprosartan 600–800 mg/day	Enalapril 5–20 mg/day	334	Double-blind, randomized, parallel group (12 weeks)	Age >65 years, SBP ≥160 mmHg, DBP 90–114 mmHg	Similar BP reduction with better tolerability for ARB based treatment
Bendersky *et al.* [36]	Enalapril 10–20 mg/day	Amlodipine 5–10 mg/day	89	Open-label, randomized, parallel group (8 weeks)	Age ≥60 years, SBP 160–220 mmHg	Similar BP reduction with both drugs, with few side effects in the ACE-inhibitor group
Volpe *et al.* [37]	Losartan 50–100 mg/day (+HCTZ 12.5–25 mg/day)	Amlodipine 5–10 mg/day (+HCTZ 25 mg/day)	857	Double-blind, randomized, parallel group (18 weeks)	Mean age 68 years, SBP ≥160 mmHg	No significant differences in BP reduction between groups. The ARB regimen had a better tolerability profile
Malacco *et al.* [38]	Valsartan 80–160 mg/day (+HCTZ 12.5 mg/day)	Amlodipine 5–10 mg/day (+HCTZ 12.5 mg/day)	421	Double-blind, randomized, parallel group (24 weeks)	Age 60–80 years, SBP ≥160 mmHg	Similar antihypertensive efficacy of valsartan and amlodipine, but better tolerability of the former drug
Punzi *et al.* [39]	Eprosartan 600–1,200 mg/day (+HCTZ 12.5 mg/day)	Placebo	283	Double-blind, randomized, placebo controlled, parallel group (13 weeks)	Age ≥60 years, SBP ≥160 mmHg	Significantly greater sitting SBP reduction with the ARB than with placebo. Good tolerability of the ARB with dizziness and asthenia being the most common side effects
Fogari *et al.* [40]	Telmisartan 80 mg/day + HCTZ 12.5 mg/day	Lisinopril 20 mg/day + HCTZ 12.5 mg/day	160	Open label, randomized, blinded endpoint, parallel group (24 weeks)	Age 61–75 years, DBP 91–109 mmHg, SBP >140 mmHg	ARB produced a larger 24-h BP reduction than the ACE-inhibitor and improved some of the components of cognitive function
Neldam *et al.* [41]	Telmisartan 40–80 mg/day (+HCTZ 12.5 mg/day)	Amlodipine 5–10 mg/day (+HCTZ 12.5 mg/day)	872	Open label, randomized, blinded endpoint, parallel group (14 weeks)	Age ≥60 years, SBP ≥160 mmHg	Significant difference in favor of the ARB in terms of BP reduction and tolerability profile
Borghi *et al.* [42]	ARBs or ACE-inhibitors (various formulations)	Ca^{2+} channel blockers, ß-blockers, or diuretics (various formulations)	301	Open-label, single-blind, randomized (24 months)	Age >65 years, SBP >140 mmHg, DBP >90 mmHg	Greater BP decreases with ARBs, ACE-inhibitors and CCBs. Rate of therapy discontinuation was lower in patients treated with ARBs or ACE-inhibitors
Ambrosioni *et al.* [43]	Eprosartan 600 mg/day (+HCTZ 12.5 mg/day)	Losartan 50 mg/day (+HCTZ 12.5 mg/day)	155	Double-blind, randomized, double-dummy, parallel group (12 weeks)	Age ≥60 years, SBP 160–179 mmHg	No statistically significant difference in 24-h SBP reduction between the two treatments

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HCTZ* hydrochlorothiazide

been introduced in the clinical practice for treating hypertension. Likely due to its greater affinity for the angiotensin II type 1 receptor, olmesartan can apparently provide a higher degree of antihypertensive efficacy and 24-h BP control and at lower doses than other angiotensin II receptor antagonists, including irbesartan, valsartan, and losartan [60, 61]. Oral olmesartan medoxomil at doses ranging between 10 and 40 mg once daily is recommended for the treatment of adult patients with arterial hypertension; moreover extensive clinical evidence supports the efficacy and good tolerability profile of this drug, either used as monotherapy or in combination with the diuretic hydrochlorothiazide (HCTZ) in elderly patients with systolic and diastolic, or isolated systolic hypertension [62, 63].

A pooled analysis of seven randomized double-blind efficacy trials, collecting data from overall 1,777 hypertensive patients treated with olmesartan or placebo, has shown that a same substantial SBP reduction can be obtained after active drug treatment either by considering the population as a whole or in the cohort of patients with a wide pulse pressure (>55 mmHg) and age of 65 years and older [64]. In another randomized study comparing the efficacy of olmesartan medoxomil with that of the calcium-channel blocker nitrendipine in subjects ≥65 years with isolated systolic

hypertension, a similar SBP reduction accompanied by a good tolerability could be achieved with both drugs over a period of 24 weeks of treatment [65]. In addition, in an integrated efficacy and safety trial, olmesartan medoxomil has been demonstrated to be equally effective in BP control and well-tolerated, both in hypertensive patients aged 65–74 years and in very elderly patients (≥75 years) [63].

The present review is aimed to summarize the results of published and unpublished data from two recent randomized, double-blind, parallel-group studies comparing the efficacy and safety of olmesartan medoxomil with that of the ACE-inhibitor ramipril, which has been widely employed in the clinical practice and in controlled trials for more than twenty years, in elderly patients with mild to moderate essential hypertension [66, 67]. The efficacy assessment has been performed not only on conventional office BP measurements taken 24 h post-dosing, but also on ambulatory BP monitoring throughout the 24 h, with particular attention on evaluation of antihypertensive control in the early morning hours.

In brief, data from the ESPORT study involving 102 centres in Italy [66], and from a parallel multinational study, enrolling patients from 31 centres across Europe [67], have been collected forming a whole study population of 1,426 patients, aged between 65 and 89 years, of either gender, with grade 1 or 2 essential arterial hypertension (sitting clinic SBP 140–179 mmHg and/or sitting clinic DBP 90–109 mmHg). Both studies adopted the same protocol design, the details of which have been described in the original papers [66, 67]. Briefly, following two weeks of placebo wash-out, patients were randomized (1:1) to 12 weeks of double-blind treatment with olmesartan medoxomil (n = 712) or ramipril (n = 714), at the initial doses of 10 mg/day or 2.5 mg/day, respectively. Control visits with office BP measurement were performed after the second, sixth and twelfth week, with the eventual doubling of the drug dose in case of lack of normalization (office SBP ≥140 mmHg or office DBP ≥90 mmHg for non-diabetic, and office SBP ≥130 mmHg or office DBP ≥80 mmHg for diabetic patients). Moreover, at randomization and at the end of the 12 weeks of treatment, an ambulatory 24-h BP monitoring (ABPM) was also foreseen.

The main end-points of the original, previously published, studies [66, 67] included the between-treatment comparison of sitting office SBP and DBP changes, percentage of normalized and normalized plus responder patients (sitting office SBP reduction >20 mmHg or DBP reduction >10 mmHg), and changes in 24-h average SBP and DBP, from baseline to the end of the 12-week of double-blind treatment.

Both studies indicated that greater BP reductions could be achieved after 12 weeks of treatment with olmesartan 10–40 mg/day in respect to ramipril 2.5–10 mg/day.

Both studies indicated that greater BP reductions could be achieved after 12 weeks of treatment with olmesartan 10–40 mg/day in respect to ramipril 2.5–10 mg/day. Results from the ESPORT study, collecting data from more than one thousand patients, showed significant differences between the two treatments for either SBP or DBP at all time visits [66]. In the multinational study, though a statistical significance was not reached (likely explained by the reduced number of patients), a difference in favour of olmesartan was, however, observed at the end of the 12 weeks, with comparable or even superior absolute BP reductions to those reported in the Italian study [67]. As a confirmation, when analysing pooled data from the two studies, both SBP and DBP mean changes at the end of the 12 weeks were significantly superior after treatment with olmesartan than ramipril (p = 0.003 for SBP and p = 0.001 for DBP) (Fig. 1).

On the other hand, the rate of BP normalization after 12 weeks of treatment was always significantly larger under olmesartan than ramipril (49.3 vs. 41.3 %, p = 0.002 for the pooled population). Overall, the percentage of normalized plus responder patients was 71.3 % under olmesartan and 62.7 % under ramipril (p = 0.01), for the whole study population (Fig. 1).

In general, subjects treated with olmesartan achieved the goal of BP lowering at lower drug doses than subjects under treatment with ramipril, with a minor proportion of people taking the full drug dosage at the end of the 12 weeks (47.1 % for olmesartan vs. 55.3 % for ramipril, p = 0.008). The average study drug dose at the end of the study was 27.2 ± 12.6 mg (68 % of the maximal dose) and 7.3 ± 3.1 mg for ramipril (73 % of the maximal dose).

24-Hour BP Control and BP Variability

The use of antihypertensive agents able to provide a long-lasting BP control throughout a 24-h dosing interval is considered of great clinical importance in the management of hypertension, especially in older patients [28, 29]. Indeed, an increased 24-h BP variability and high SBP levels during the early morning hours appear to be strongly associated with an increased risk of stroke and CV events in elderly hypertensive people [68, 69]. Morning hours are particularly critical not only as a consequence of the physiological BP surge on awakening, but also because they are usually the farthest from the last drug intake. Thus, comparison of the antihypertensive activity of olmesartan vs. ramipril over the 24 h was performed in a subgroup of 715 patients from the two parallel studies, which had valid 24-h ambulatory BP recordings at baseline and at the end of double-blind treatment [70]. In addition to provide a better estimation of the global efficacy of the two drugs, an evaluation of the homogeneity of the antihypertensive control in relation to the circadian BP variability was also performed [71].

Data analysis revealed that olmesartan medoxomil could always determine significantly superior SBP and DBP reductions in respect to ramipril, as concerned the whole 24-h period, or even by separately considering the day-time and

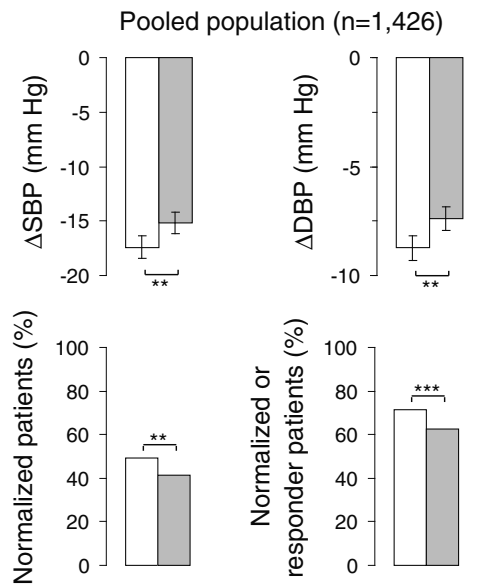


Fig. 1: Baseline-adjusted office sitting systolic (SBP) and diastolic blood pressure (DBP) mean changes (95 % confidence intervals) from baseline (*top*), and percentage of normalized and normalized plus responder patients (*bottom*) after 12 weeks of double-blind treatment with olmesartan medoxomil 10–40 mg (*open bars*) or ramipril 2.5–10 mg (*gray bars*), for the pooled intention-to-treat population. The statistical significance of between-treatment differences is indicated by *asterisks* (***p < 0.001; **p < 0.01).

night-time intervals [70] (Fig. 2). When the study population was restricted to sustained hypertensive patients (n = 582), namely those patients with the concomitant occurrence of elevated office (SBP ≥140 mmHg and/or DBP ≥90 mmHg) and ambulatory BP (SBP ≥130 mmHg and/or DBP ≥80 mmHg), similar results were obtained with the only exception of night-time DBP reduction, for which the difference was still in favour of olmesartan, though not significantly greater.

The higher efficacy of antihypertensive treatment with olmesartan in comparison with ramipril was particularly remarkable in the last 6-h period from the dosing interval, including the last part of the night and the hours of awakening, when average SBP and DBP differences between the two drugs were respectively of 3.6 and 2.0 mmHg (p = 0.001 for both). Indeed, olmesartan could still exercise an effective antihypertensive activity during the early morning hours and prevent the morning BP rise, whereas ramipril treatment failed to provide an adequate BP control [70] (Fig. 3). Thus, findings of this study were in agreement with the conclusions of another recent analysis, performed on pooled data of PRISMA I and II randomized trials, that showed a long-lasting efficacy of another ARB, telmisartan, in comparison with ramipril, in a large sample of elderly hypertensive patients [72].

The better performance of olmesartan medoxomil in providing a more homogeneous BP control over the 24 h was confirmed by a significantly higher smoothness index, calculated for each patient by dividing the average of the 24-h BP changes after treatment by the corresponding standard deviation (SD) [73].

The better performance of olmesartan medoxomil in providing a more homogeneous BP control over the 24 h was confirmed by a significantly higher smoothness index, calculated for each patient by dividing the average of the 24-h BP changes after treatment by the corresponding standard deviation (SD).

We also evaluated the effect of olmesartan and ramipril on BP variability by using the average real variability (ARV) index. This is an alternative method to estimate BP variability based on the total variability concept of real analysis in mathematics, which has been recently proposed as a more reliable measure for the prognostic evaluation of ambulatory BP recording data than the 24-h standard deviation [74, 75]. ARV analysis, performed after 12 weeks of treatment with olmesartan or ramipril, revealed that neither drug increased 24-h BP variability, while olmesartan could even produce a slight but significant reduction of BP variability in respect to baseline (p < 0.05) (Fig. 4). This reduction was larger than that observed with ramipril, but unfortunately, no significant difference between the two treatments was observed. This result could be expected as consistent with literature reporting calcium channel blockers, mainly belonging to the class of dihydropyridines, as the more effective antihypertensive agents in reducing BP variability, while ARBs and ACE-inhibitors have a modest effect on this parameter [76–78]. However, the positive impact of olmesartan on BP variability might be enhanced in combination with a dihydropyridine calcium channel blocker. As a matter of fact, the use of olmesartan/amlodipine combination therapy, by associating drugs with complementary mechanisms of action, has been suggested as a promising strategy in order to improve the achievement of a sustained BP control throughout the whole 24-h period [79]. According to preliminary results of some trials, treatment with olmesartan/amlodipine combination (at doses of 10/5, 20/5 and 40/5 mg daily) was associated with a significantly greater 24-h, daytime and night-time BP lowering efficacy when compared with amlodipine (5 mg) monotherapy [79]. In addition, 24-h efficacy and safety of triple combination therapy with olmesartan (40 mg), amlodipine (10 mg) and HCTZ (25 mg) has been recently explored in a substudy of the TRINITY trial [80]: findings of this randomized, double-blind, 4-arm study, including overall 440 patients with moderate to severe hypertension, showed a

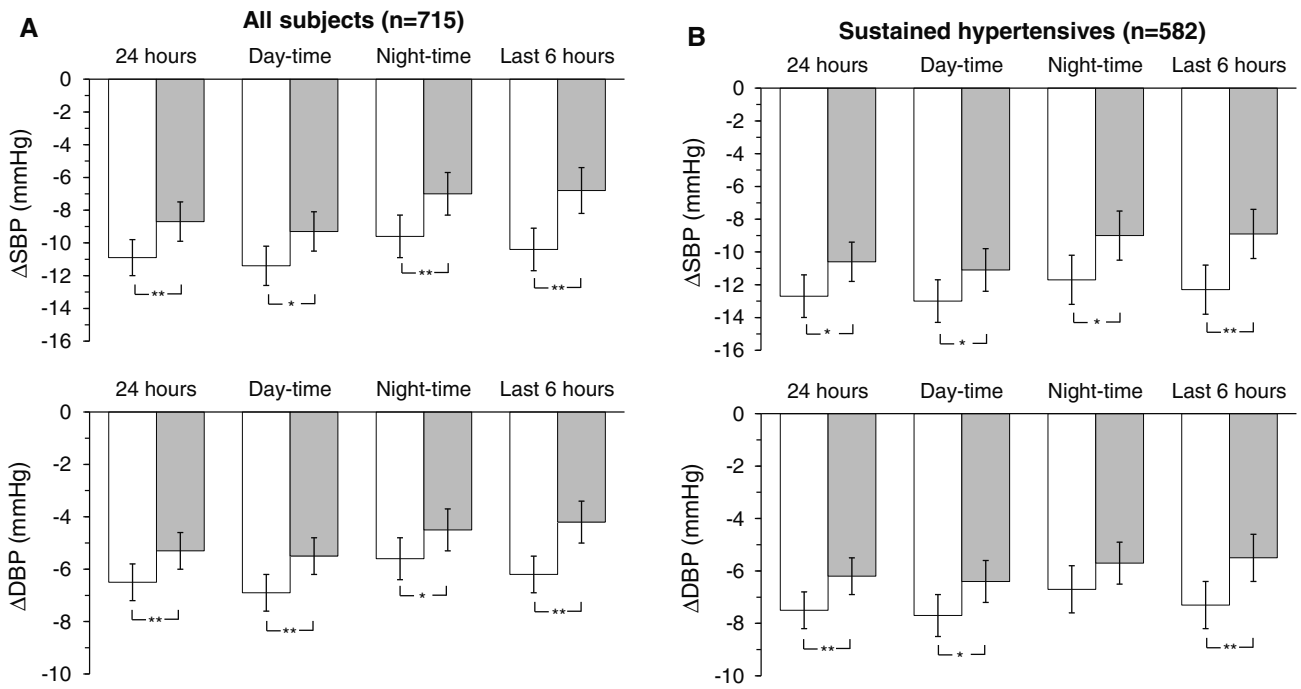


Fig. 2: Baseline-adjusted 24-h, day-time, night-time and last 6-h SBP and DBP mean changes (95 % confidence intervals) after 12 weeks of double-blind treatment with olmesartan 10–40 mg (*open bars*) and ramipril 2.5–10 mg (*gray bars*). Data are shown for the whole population (n = 715, **A**) and for sustained hypertensive patients (n = 582, **B**). *Asterisks* refer to the statistical significance of between-treatment differences (**p < 0.01; *p < 0.05) (from [70] by permission).

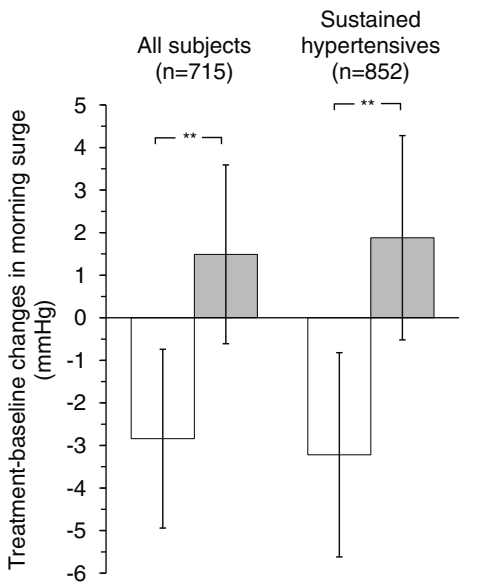


Fig. 3: Baseline-adjusted changes (and 95 % confidence interval) in morning surge after 12 weeks of double-blind treatment with olmesartan (*open bars*) and ramipril (*gray bars*). Data are shown for the whole population (n = 715) and for sustained hypertensive patients (n = 582). *Asterisks* refer to the statistical significance of between-treatment differences (**p < 0.01) (from [70] by permission).

greater antihypertensive efficacy for the triple drug combination during daytime, nighttime, and the last 6, 4 and 2 h of the dosing intervals, in comparison with each of its dual-combination components at similar doses.

Therefore, despite clinical trials specifically aimed to elderly people are still lacking, the association of olmesartan with amlodipine or other calcium antagonists may be expected to provide a greater and a smoother 24-h BP control even for this category of hypertensive patients. At the light of results of our studies, further investigations are needed in the future to explore this possibility.

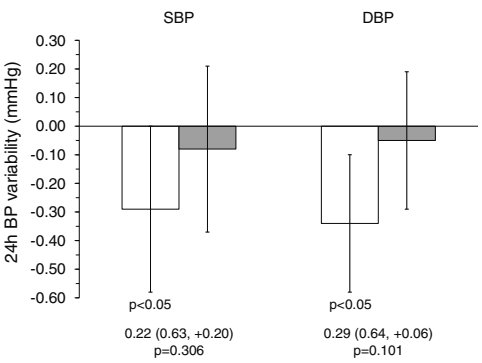


Fig. 4: 24-hour SBP and DBP variability, calculated according to ARV analysis, after 12 weeks of treatment with olmesartan medoxomil (*open bars*, n = 356) or ramipril (*gray bars*, n = 359). For olmesartan, the statistical significance (p < 0.05) of BP variability reduction in respect to baseline is indicated in the graph. The between-treatment differences, 95 % confidence intervals and p values for SBP and DBP are also reported.

Drug Efficacy in Metabolic Syndrome

One of the conditions often associated with the increase in BP is the metabolic syndrome (MS): in fact patients with MS require close monitoring and control of BP as they are also at higher risk of CV events [9, 81]. MS is characterized by multiple CV risk factors, including abdominal or central obesity, atherogenic dyslipidemia, and insulin resistance and its development is largely influenced by the dysregulation of the RAS, which is why hypertensive patients with obesity or metabolic syndrome undergo treatment based on ARBs or ACE-inhibitors [82, 83]. In a placebo-controlled trial, olmesartan medoxomil administered as monotherapy or in combination with amlodipine resulted in significant BP reductions in different groups of patients with difficult-to-treat hypertension, such as elderly (≥65 years), type 2 diabetics and obese (body mass index ≥30 kg/m^2) [84]. More recently, the OLAS study has shown that the combination of olmesartan medoxomil with amlodipine or HCTZ can effectively reduce BP in 120 non-diabetic hypertensive subjects with metabolic syndrome, aged 25–75 years [85].

Post-hoc analyses were carried out in subgroups of patients of the pooled population of the ESPORT and the twin European study, classified on the basis of having or not MS. This condition was defined according to the definition provided by the International Diabetes Federation, namely by presence of central obesity in association with hypertension, and additional risk factors such as dyslipidemia or impaired glucose tolerance [86]. Overall, more than a half of the study population (51.5 %) had MS, with equal distribution in the two randomized groups of treatment. Most patients with MS had elevated fasting glucose (70.1 %), while a minor proportion of subjects with MS had elevated triglycerides (41.6 %) or low HDL cholesterol (37.1 %).

Similar SBP and DBP reductions were observed after 12 weeks of treatment in subjects with or without MS, but the difference from baseline was significantly larger with olmesartan medoxomil than with ramipril (p < 0.05) (Fig. 5) [86]. The superior antihypertensive efficacy of olmesartan vs. ramipril was particularly remarkable when separately considering patients with central obesity only [olmesartan-ramipril difference for SBP: 3.1 (95 % confidence interval: 4.7, 1.4) mmHg, p = 0.0001; DBP: 1.5 (2.4, 0.6) mmHg, p = 0.001], probably due to a more specific inhibiting action of the ARB on the systemic and adipose tissue RAS [82].

Among elderly hypertensive subjects with MS, both the proportion of normalized and normalized plus responder patients were significantly greater in the olmesartan group (p < 0.01). In addition, a minor percentage of patients with MS under treatment with olmesartan needed the full drug dosage in comparison with those treated with ramipril (62.2 vs. 48.2 %, p = 0.001), while there was no significant between-treatment difference for patients without MS [86].

In a placebo-controlled trial, olmesartan medoxomil administered as monotherapy or in combination with amlodipine resulted in significant BP reductions in different groups of patients with difficult-to-treat hypertension, such as elderly (≥65 years), type 2 diabetics and obese (body mass index ≥30 kg/m^2).

Drug Efficacy in Relation to Renal Function

Renal impairment is a common finding in elderly people with hypertension, and a low glomerular filtration rate (GFR) in high-risk patients is associated with a higher probability of CV events and mortality [87, 88]; coexistence of hypertension and kidney disease can facilitate the development and progression of target organ damage [89]. Current evidence supports the use of ACE-inhibitors or angiotensin receptor antagonists as the therapy of choice for hypertension in patients with chronic kidney disease, due to specific reno-protective effects of these drugs [9, 90, 91].

In this context, the antihypertensive efficacy of olmesartan vs. ramipril was analysed according to different stages of renal impairment [92] in the pooled population of ESPORT and the parallel international study [93]. Renal function was assessed on the basis of estimated GFR calculated by the Cockcroft-Gault formula [94]. Consistently with the age of patients, only a minority of them (12.7 %) had a normal or increased eGFR (≥90 mL/min/1.73 m^2),

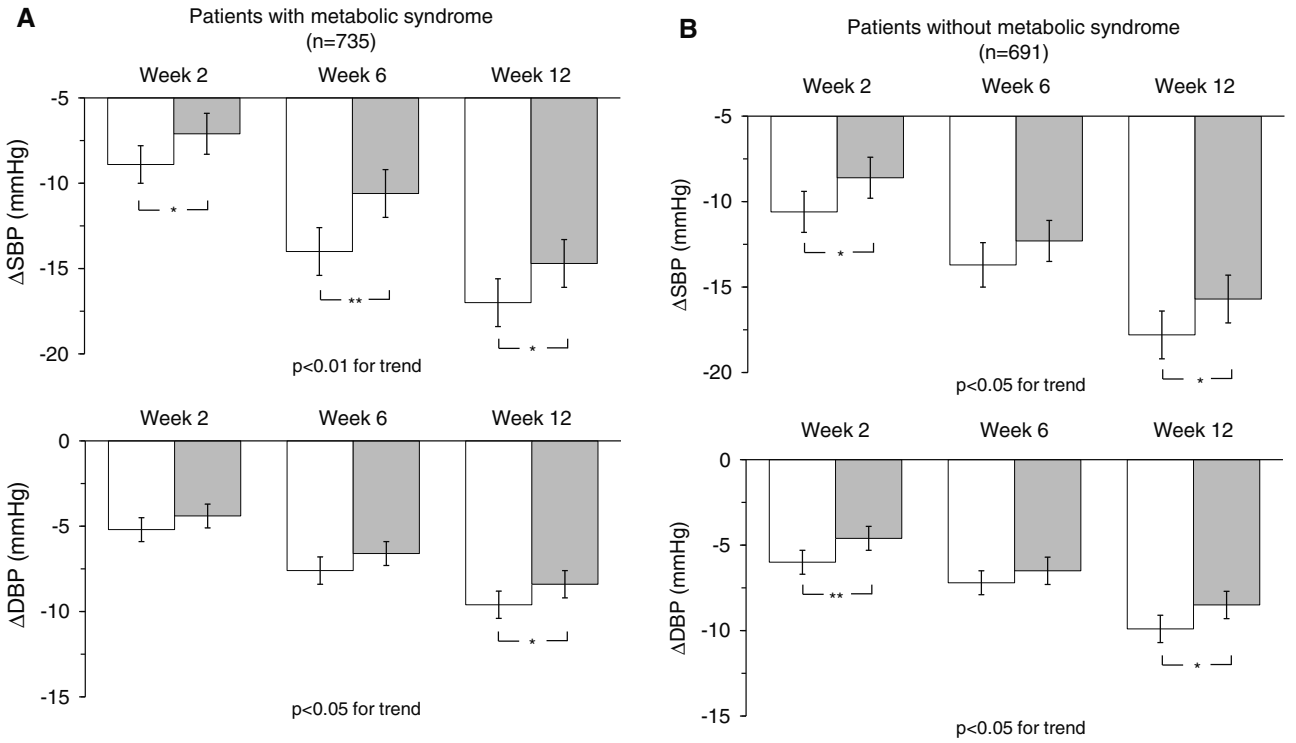


Fig. 5: Baseline-adjusted office sitting systolic (SBP) and diastolic blood pressure (DBP) mean changes (95 % confidence intervals) from baseline after 2, 6 and 12 weeks of double-blind treatment with olmesartan medoxomil 10–40 mg (*open bars*) or ramipril 2.5–10 mg (*gray bars*), in the intention-to-treat population with (n = 735) or without (n = 691) metabolic syndrome. *Asterisks* refer to the statistical significance of between-treatment differences (**p < 0.01; *p < 0.05). The p value for the trend analysis of the between-treatment difference is also reported (from [86] by permission).

whereas the most of the population (about 60 %) exhibited a mild eGFR reduction (60–90 mL/min/1.73 m^2, corresponding to stage 2 chronic kidney disease or CKD) and a minor proportion of subjects (28.4 %) was concerned with a moderate or severe renal impairment (eGFR <60 mL/min/1.73 m^2). In the last group, however, only two patients had an eGFR level inferior to 30 mL/min/1.73 m^2 (stage 4 CKD), while no subject belonged to end-stage CKD. Patients with different renal function were equally distributed in the two treatment groups.

Pooled data analysis showed that, at the end of the 12-week double-blind phase, the frequency of normalized and normalized plus responder patients was significantly larger after treatment with olmesartan in respect to ramipril in the group of patients with a normal ($p < 0.01$) and in those with a mildly reduced renal function ($p < 0.05$) (Fig. 6). In agreement with these findings, greater office SBP and DBP reductions were obtained after 12 weeks with olmesartan in both groups of normal or increased ($p < 0.05$ in respect to ramipril for either SBP or DBP) and slightly reduced eGFR ($p = 0.08$ for SBP; $p = 0.02$ for DBP). In the low eGFR group, including elderly patients with a moderate or severe kidney disease, the two drugs could provide an even more sustained, although not significantly different, antihypertensive action, with mean SBP and DBP reductions of respectively 18.9/10.5 mmHg for olmesartan, and 17.0/9.7 mmHg for ramipril, at the end of the 12 weeks (Fig. 6) [93].

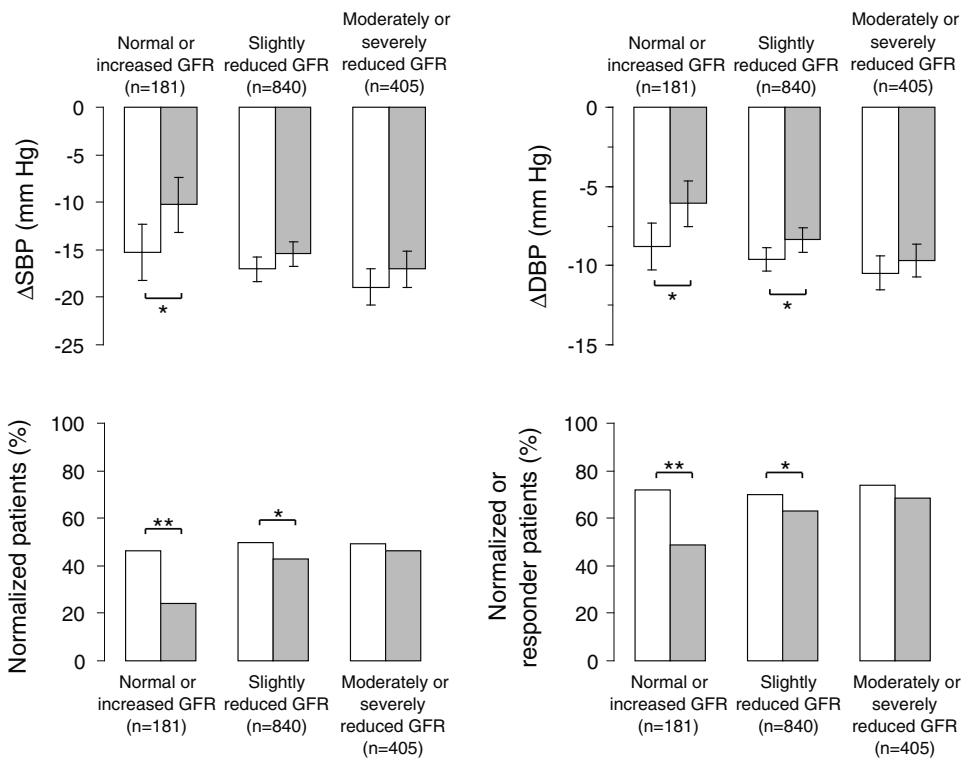


Fig. 6: Baseline-adjusted office sitting systolic (SBP) and diastolic blood pressure (DBP) mean changes (95 % confidence intervals) from baseline (*top*), and percentage of normalized and normalized plus responder patients (*bottom*) after 12 weeks of treatment with olmesartan medoxomil 10–40 mg (*open bars*) or ramipril 2.5–10 mg (*gray bars*), for the pooled intention-to-treat population, classified according to renal function. The statistical significance of between-treatment differences is indicated by asterisks (**p < 0.01, *p < 0.05) (redrawn from [93] by permission).

On the other hand, despite their efficacy in lowering BP, inhibitors of the RAS have been also reported to potentially contribute to eGFR decline, particularly in a short-term scale; therefore a special attention is needed when treating patients with advanced stages of kidney disease [95, 96]. Creatinine clearance changes after drug treatment were carefully monitored in the three groups of patients with different baseline renal function. According to this study, eGFR reductions were mainly observed for subjects with normal or increased baseline values (7.9 % reduction in respect to baseline after 12 weeks of treatment with olmesartan vs. 2.2 % reduction with

ramipril). On the contrary, no significant variation occurred in the intermediate eGFR group, whereas a slight improvement in creatinine clearance was reported after both antihypertensive treatments in patients with baseline reduced renal function (2.3 % increase after olmesartan vs. 6.2 % increase after ramipril) [93].

Thus, olmesartan medoxomil was shown to provide an effective BP control, equivalent or in some cases superior to ramipril, together with a certain degree of renal protection, especially in elderly patients at the early stage of kidney disease. These results were in agreement with conclusions of other recent trials, showing that olmesartan was associated with reduction or with a delayed onset of microalbuminuria on type-2 diabetic patients [97, 98].

Drug Efficacy and CV Risk

The central role of the RAS in the regulation of the CV function is well established and an impaired activation of the angiotensin II pathway, resulting in vasoconstrictive, proliferative and pro-inflammatory effects, has been implicated at all stages of CV disease [99]. RAS blockade, by the use of ACE-inhibitors or angiotensin receptor antagonists, is supposed to provide CV protection beyond BP lowering and it could therefore represent an ideal therapeutic strategy in patients at high CV risk [45, 100].

A number of studies in the recent years have supported beneficial effects of olmesartan in preventing ventricular remodelling [101, 102], slowing the progression of atherosclerosis [103, 104], reducing arterial stiffness [105] and improving endothelial function [106]. Conversely, the efficacy of ramipril in the prevention of CV events in high-risk patients has been assessed in large clinical studies, such as the HOPE and the ONTARGET [54, 107].

A post-hoc analysis has been performed on pooled population of the two parallel studies in order to evaluate the efficacy of olmesartan medoxomil vs. ramipril in patients grouped according to the individual CV risk level. For each patient, an estimation of 10-year absolute risk of fatal CV disease has been carried out on the basis of the SCORE (Systematic COronary Risk Evaluation) algorithm [108]. The SCORE risk charts, based on data from the European population, take into consideration several factors, including sex, age, smoking habit, total cholesterol and SBP.

Although this algorithm has not been validated for people over 65 years, it is still considered more accurate than the Framingham risk function, that is derived from American data, to provide a realistic risk estimation for population of the European countries, also by distinguishing between high- and low-risk regions.

For the purpose of this study, in order to fit the SCORE estimation system to elderly people, calculation methods described in the paper by Conroy *et al.* [108] were applied by forcing total cholesterol level in the range of 130–320 mg/dL and SBP in the range of 90–200 mmHg. Smoking habit was coded as 0 when the data was not available.

Thus, on the basis of the absolute risk of 10-year CV mortality calculated by the SCORE algorithm, the study population was classified into different groups according to a low (<5 %), moderate (5–10 %), high (10–15 %) and very high (≥15 %) risk level. Overall, the population was composed of 159 subjects at low CV risk (11 % of the total), 516 with a moderate risk level (36 %), 320 with a 10–15 % risk level (22 %), while 431 patients (30 % of the population) had an estimated CV risk level superior to 15 %.

Baseline-adjusted SBP and DBP mean reductions after 12 weeks of treatment with olmesartan or ramipril in the different classes of CV risk are illustrated in Fig. 7. BP reduction with both drugs was consistent across the four risk classes and in general, a superior antihypertensive efficacy of olmesartan vs. ramipril was observed for patients belonging to lower risk classes, even if a statistical significance was achieved only in the group with a moderate (5–10 %) risk level. For patients at high CV risk, the two drug treatments were substantially equivalent, determining in both cases reductions of about 18 mmHg for SBP and 10 mmHg for DBP in the group at higher risk level (Fig. 7). Similar results were also obtained by classifying patients into quartiles of increasing CV risk (not shown).

Therefore, conclusions of this head-to-head comparison evaluating the activity of olmesartan vs. ramipril according to CV risk level agreed with the results of ONTARGET trial reporting the equivalency of the ARB telmisartan in respect to ramipril in treating patients at high risk for CV events [107]. Despite the limitations of applying the SCORE algorithm to elderly population -which may be considered at high risk for itself-findings of this study could so support the use of ARBs in alternative to treatment with ACE-inhibitors for the prevention of CV events in hypertensive patients.

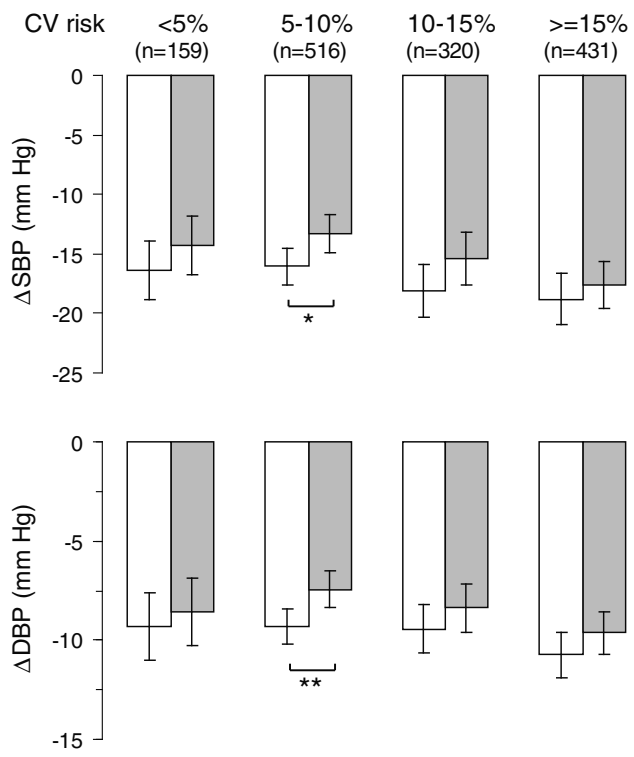


Fig. 7: Baseline-adjusted office sitting systolic (SBP) and diastolic blood pressure (DBP) mean changes (95 % confidence intervals) from baseline after 2, 6 and 12 weeks of treatment with olmesartan 10–40 mg (n = 712) and ramipril 2.5–10 mg (n = 714) for the intention-to-treat population, according to the cardiovascular (CV) risk level. The statistical significance of between-treatment differences is indicated by *asterisks* (***p < 0.001; **p < 0.01; *p < 0.05).

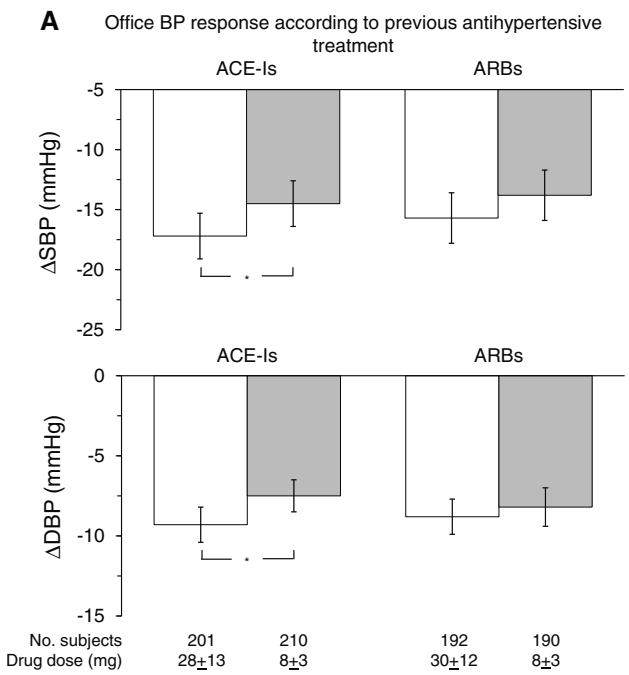


Fig. 8: Baseline-adjusted office and 24-h BP mean reductions (95 % confidence intervals) observed after 12 weeks of treatment with olmesartan medoxomil (*open bars*) or ramipril (*gray bars*) in subgroup of patients divided according to previous antihypertensive treatment with ACE-inhibitors or ARBs. The number of subjects in each group and the mean drug doses (±SD) are reported on the bottom of the graph. The statistical significance of between-treatment differences is indicated by asterisks (*p < 0.05).

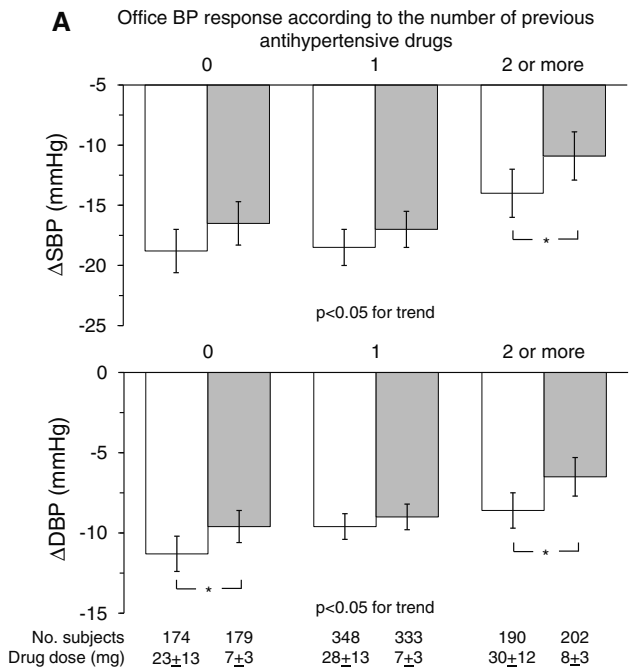


Fig. 9: Baseline-adjusted mean SBP and DBP reductions (95 % confidence intervals) after 12 weeks of treatment with olmesartan (*open bars*) or ramipril (*gray bars*) according to the number of previous antihypertensive drugs assumed by each patient. The number of subjects in each group and the mean drug doses (±SD) are reported on the *bottom* of the graph. The statistical significance of between-treatment differences is indicated by *asterisks* (*p < 0.05).

Drug Efficacy and Previous Antihypertensive Treatment

In order to gain a better comparison of the efficacy of the two antihypertensive drugs, additional analysis were performed by evaluating BP reduction at the end of the 12 weeks of double-blind period in subgroups of patients who had received previous treatments with drugs belonging to the classes of ACE-inhibitors or ARBs. As shown in Fig. 8, olmesartan seemed to provide a superior BP response, both in terms of SBP or DBP, independently of the kind of previous antihypertensive treatment, whether it was based on an ACE-inhibitor or an ARB. However, in the case the patient had been previously treated with an ACE-inhibitor, the better performance of olmesartan appeared more evident and statistically significant. Corresponding results were obtained by analysis of 24-h BP reductions, despite the low size of the samples (Fig. 8).

A further analysis was performed on the basis of the number of previous antihypertensive drugs assumed by each patient. Even in this case, BP reductions tended to be greater after treatment with olmesartan than with ramipril (Fig. 9). A result of particular notice is that olmesartan appeared to be significantly superior to ramipril in the subgroup of patients that were previously treated with two or more drugs (Fig. 9). Thus, according to these findings, olmesartan taken as monotherapy was able to provide a more effective BP reduction in comparison with ramipril even in patients that were less susceptible to an adequate blood pressure response to previous multiple antihypertensive treatment.

Table 2: Baseline-adjusted changes in SBP and DBP and percentage of normalized and normalized plus responder patients after 12 weeks of treatment with olmesartan medoxomil 10–40 mg (n = 712) or ramipril 2.5–10 mg (n = 714) for the pooled intention-to-treat population divided by age subgroups.

Age (years)	SBP (mmHg)			DBP (mmHg)		
	O (10–40 mg)	R (2.5–10 mg)	*p*	O (10–40 mg)	R (2.5–10 mg)	*p*
65–69 (n = 597)	18.4 (13.6)	14.8 (13.7)	0.001	10.1 (8.8)	8.2 (9.1)	0.011
70–79 (n = 706)	16.6 (14.6)	15.4 (15.2)	0.312	9.6 (8.3)	8.7 (8.5)	0.158
>80 (n = 123)	18.3 (16.7)	14.5 (14.8)	0.184	11.3 (8.7)	6.1 (9.3)	0.002
Age (years)	**Normalized patients**			**Normalized plus responder patients**		
	O (10–40 mg)	R (2.5–10 mg)	*p*	O (10–40 mg)	R (2.5–10 mg)	*p*
65–69 (n = 597)	161 (54.0)	121 (40.5)	<0.001	220 (73.8)	185 (61.9)	0.002
70–79 (n = 706)	175 (44.7)	148 (41.7)	0.415	240 (68.4)	229 (64.5)	0.276
>80 (n = 123)	33 (52.4)	25 (41.7)	0.234	48 (76.2)	34 (56.7)	0.022

SBP and DBP reductions are reported as mean (SD). Normalized and normalized plus responder patients are expressed as n (% of the total) for each subgroup. The p value refers to the statistical significance of the between-treatment differences

Table 3: Baseline-adjusted changes in SBP and DBP and percentage of normalized and normalized plus responder patients after 12 weeks of treatment with olmesartan medoxomil 10–40 mg (n = 712) or ramipril 2.5–10 mg (n = 714) according to gender of the pooled intention-to-treat population.

	SBP (mmHg)			DBP (mmHg)		
	O (10–40 mg)	R (2.5–10 mg)	*p*	O (10–40 mg)	R (2.5–10 mg)	*p*
Males (n = 717)	17.8 (14.4)	14.9 (14.7)	0.006	10.0 (8.5)	7.8 (8.8)	0.001
Females (n = 709)	17.1 (14.5)	15.3 (14.4)	0.096	9.9 (8.5)	8.7 (8.9)	0.074
	Normalized patients			**Normalized plus responder patients**		
	O (10–40 mg)	R (2.5–10 mg)	*p*	O (10–40 mg)	R (2.5–10 mg)	*p*
Males (n = 717)	175 (49.3)	147 (40.6)	0.019	262 (73.8)	227 (62.7)	0.001
Females (n = 709)	176 (49.3)	147 (41.8)	0.044	246 (68.9)	221 (62.8)	0.086

SBP and DBP reductions are reported as mean (SD). Normalized and normalized plus responder patients are expressed as n (% of the total) for each subgroup. The p value refers to the statistical significance of the between-treatment differences

Drug Efficacy in Special Subgroups of Patients

Comparison of the antihypertensive activity of treatment with olmesartan medoxomil or ramipril was also performed by further dividing the study population according to gender or by age subgroups. Overall, the study population was composed of 597 patients aged 65–69 years (41.9 %), 706 patients aged 70–79 years (49.5 %) and 123 patients over 80 years (8.6 %). Men were slightly more prevalent than women (50.3 vs. 49.7 %). The distribution among the two randomized treatment groups was similar.

Mean changes in SBP and DBP and percentage of normalized and normalized plus responder patients at the end of the 12 weeks of treatment, on the basis of age and gender subgroups, are summarized in Tables 2 and 3.

According to these results, olmesartan appeared to effectively reduce BP in each category of age and gender, with statistically significant differences in respect to ramipril which were prevalently observed in the subgroups of patients aged 65–69 and over 80 years (Table 2), and in men (Table 3).

Most patients in the two studies were affected by both systolic and diastolic hypertension, while about a quarter of the pooled population (n = 349 out of 1,426) included patients with isolated systolic hypertension, i.e. SBP ≥140 mmHg and DBP <90 mmHg: of these, 162 subjects were treated with olmesartan and 187 with ramipril.

Separated analysis performed according to the type of arterial hypertension showed that in the group of patients with systo-diastolic hypertension both SBP and DBP could be more effectively reduced after 12 weeks of treatment with olmesartan, whereas no significant between-treatment difference was observed in the group with isolated systolic hypertension (Table 4), as previously reported in the Italian study [66]. Similar results were also obtained as concerned 24-h SBP and DBP monitoring at the end of the 12 weeks of treatment (not shown).

Accordingly, among patients with systolic and diastolic hypertension, a minor percentage was treated with the maximal drug dose under olmesartan than under ramipril ($p < 0.01$), while the frequency of utilization of the maximal doses was similar for both drugs in the group of patients with isolated systolic hypertension. However, for subjects with isolated systolic hypertension, drug doses tended to be generally lower, with an average of 25.1 mg and 6.6 mg, respectively for olmesartan and ramipril, in comparison with mean doses of 27.8 mg for olmesartan and 7.6 mg for ramipril that were used for treating patients with systolic-diastolic hypertension.

Tolerability

Pooling together data from the two studies, a total of 105 out of 712 patients (14.7 %) under olmesartan and 96 out of 714 patients (13.4 %) under ramipril reported adverse events (AEs) during the 12-week period of double-blind treatment. The proportion of subjects experiencing an AE related to the drug treatment was comparable in the two groups (2.9 % olmesartan vs. 3.2 % ramipril).

A total number of 134 AEs for olmesartan and 131 for ramipril was observed in the course of the 12 weeks, with no significant between-treatment difference. The majority of these events, about 60 %, were of mild intensity, while 33.2 % were classified as moderate and only a small proportion (6.4 %) were of severe intensity. Overall 67 out of 265 AEs (25.3 %) were judged as drug-related (33 under olmesartan and 34 under ramipril). The most common drug-related AEs were cough (above all in the ramipril group), headache, dizziness and asthenia. On the whole, the number of patients withdrawn from the study after an AE during the double-blind period was of 37, of which 21 in the olmesartan group (2.9 %) and 16 in the ramipril group (2.2 %).

It is interesting to note that, when evaluating the efficacy of treatment as a function of safety, the presence of a drug-related AE in patients under olmesartan was associated with a lower BP response, particularly for SBP (mean reduction of 8.0 vs. 17.8 mmHg for patients without drug-related AE), whereas a similar SBP reduction was observed after 12 weeks of treatment with ramipril independently of the presence or not of drug-related AEs (14.4 vs. 15.1 mmHg). However, an adequate statistical analysis could not be performed due to the reduced sample of patients, respectively 21 for olmesartan and 23 for ramipril, reporting adverse events correlated to treatment.

Table 4: Mean office SBP and DBP at randomization and after 12 weeks of treatment, and baseline-adjusted reductions at the end of the 12 weeks of treatment with olmesartan medoxomil or ramipril, for the pooled intention-to-treat population classified according to the type of arterial hypertension.

	Systo-diastolic hypertension			Isolated systolic hypertension		
	O (10–40 mg) (n = 550)	**R (2.5–10 mg) (n = 527)**	***p***	**O (10–40 mg) (n = 162)**	**R (2.5–10 mg) (n = 187)**	***p***
Baseline SBP (mmHg)	158.3 (9.9)	157.5 (9.9)		153.1 (9.4)	154.3 (9.7)	
SBP after 12 weeks of treatment	139.9 (14.4)	142.1 (15.3)		138.7 (15.8)	140.1 (14.0)	
Mean reduction (95 % confidence intervals)	18.2 (19.4/17.1)	15.6 (16.7/14.4)	0.002	14.7 (16.8/12.5)	13.9 (15.9/11.9)	0.618
Baseline DBP (mmHg)	94.6 (4.4)	94.2 (4.2)		82.6 (4.5)	82.9 (5.2)	
DBP after 12 weeks of treatment	83.0 (7.9)	84.2 (8.2)		78.4 (7.1)	79.7 (7.8)	
Mean reduction (95 % confidence intervals)	11.5 (12.2/10.9)	10.2 (10.8/9.5)	0.005	4.3 (5.4/3.2)	3.1 (4.2/2.1)	0.141

SBP and DBP values are reported as mean (SD). The P-value refers to the statistical significance of the between-treatment differences

Open-Label Phase of the Clinical Study

At the end of the double-blind phase, a subgroup of 284 patients taking olmesartan medoxomil at the full dosage of 40 mg continued an open-label follow-up for additional 36 weeks. During this open phase, almost a third of the population (n = 83) was treated with olmesartan 40 mg as monotherapy, while the majority of patients followed a combination therapy with olmesartan 40 mg plus HCTZ 12.5–25 mg daily (for non-diabetic patients) or olmesartan 40 mg plus zofenopril 7.5–30 mg daily (for diabetic patients).

In the course of the 36-week follow-up a further BP decrease was obtained, with mean reductions of 25.5 mmHg for SBP and 13.8 mmHg for DBP. At the end of the study average SBP and DBP were respectively of 134.8 and 78.9 mmHg. The rate of normalization was 65.1 %, while the proportion of normalized plus responder patients reached 84.2 % of the population.

A total of nine patients (3.2 %) reported a drug-related adverse event during the open-label period, without significant differences between the group under olmesartan as monotherapy or in combination with other drugs. Serious adverse events occurred in five patients, corresponding to 1.8 % of the study population.

Conclusions

Drug therapy with angiotensin receptor antagonists may represent a valuable and indicated alternative to ACE-inhibitors for the management of hypertension in older people. Pooled analysis of two randomized, double-blind, controlled parallel-group studies, including totally over 1,400 subjects over 65 years, allowed a wide-range comparison between the efficacy and safety of the ARB olmesartan medoxomil and the ACE-inhibitor ramipril. Evidence summarized in this review supports the use of olmesartan for an effective, prolonged and well-tolerated BP control in elderly patients with essential systo-diastolic or isolated systolic hypertension. In particular, olmesartan appeared superior to ramipril in providing a sustained and more homogeneous BP control throughout the 24-h dosing interval. Post-hoc analyses in subgroups of patients classified according to the presence of metabolic syndrome, on the basis of renal function or the CV risk level, confirmed that olmesartan could give comparable, and in some cases greater, BP responses to those achieved with the ACE-inhibitor. Consequently, in agreement with these results, olmesartan could be considered as an effective option among first line drug treatments in elderly hypertensive patients. However, future randomized, large, prospective studies are required to verify whether olmesartan may be as effective as or even superior to ramipril in improving the risk of cardiovascular events, beyond BP control, as demonstrated for ramipril by the HOPE Study [54].

Evidence summarized in this review supports the use of olmesartan for an effective, prolonged and well-tolerated BP control in elderly patients with essential systo-diastolic or isolated systolic hypertension. In particular, olmesartan appeared superior to ramipril in providing a sustained and more homogeneous BP control throughout the 24-h dosing interval.

Acknowledgments: The present study was supported by a grant from Laboratori Guidotti, Malesci Istituto Farmacobiologico and Menarini International Operations Luxembourg.

Conflict of interest: S.O., E.M., J.M.M. and M.V. have occasionally received grants for lectures by the manufacturers of olmesartan or ramipril. M.V. has been consultant in scientific advisory boards of Daiichi Sankyo. P.F. is Medical Director of Laboratori Guidottti.

Appendix and References available on request Healthcare.India@springer.com

Source: Stefano Omboni, Ettore Malacco, Jean-Michel Mallion, Paolo Fabrizzi, Massimo Volpe. Olmesartan vs. Ramipril in Elderly Hypertensive Patients: Review of Data from two Published Randomized, Double-blind Studies. High Blood Press Cardiovasc Prev. 2014; 21(1):1–19. DOI 10.1007/s40292-013-0037-9.

A Patient with Apparent Resistant Hypertension

Carlos Aguiar[1]

This paper describes a case of a 44-year-old male discharged on a fixed combination of valsartan/hydrochlorothiazide (HCTZ) 160/125 mg/day after presenting to the emergency room with paraesthesia of the upper left limb and recording a BP of 190/110 mmHg. He had a number of other CV risk factors. After specialist assessment, the patient's antihypertensive regimen was switched to a fixed-dose combination of olmesartan/HCTZ in the morning and a fixed-dose combination of olmesartan/amlodipine in the evening. Repeat ABPM 6 weeks later showed better BP control than previous ABPM.

Carlos Aguiar (✉)
ctaguiar@sapo.pt

[1] Cardiology Department, Hospital de Santa Cruz, Carnaxide, Portugal

Introduction

A 44-year-old Caucasian male patient presented to the emergency room in November 2013 complaining of paraesthesia of the upper left limb. At this time, seated BP was 190/110 mmHg, which decreased to 140/90 mmHg with diazepam + captopril. He was discharged on valsartan/HCTZ 160/12.5 mg once daily.

The patient had a number of CV risk factors, including a 20-cigarette/day smoking habit, a 6-year history of HTN, high cholesterol, abdominal obesity and lack of regular physical activity. He also had mild obstructive sleep apnoea (apnoea-hypopnoea index 7.5/h). The patient's father had HTN, was a smoker, and had died from intracerebral haemorrhage (ICH) at age 64 years, and his mother had HTN, dyslipidaemia and type 2 diabetes mellitus (T2DM).

Approximately 1 month later the patient visited his family physician.

Physical examination revealed the following:

- BP: 150/100 mmHg,
- weight: 88 kg,
- height: 165 cm,
- BMI 32.3 kg/m^2,
- waist circumference: 115 cm,
- resting pulse: 80 beats/min,
- normal heart auscultation; no carotid or abdominal murmurs,
- no signs of heart failure.

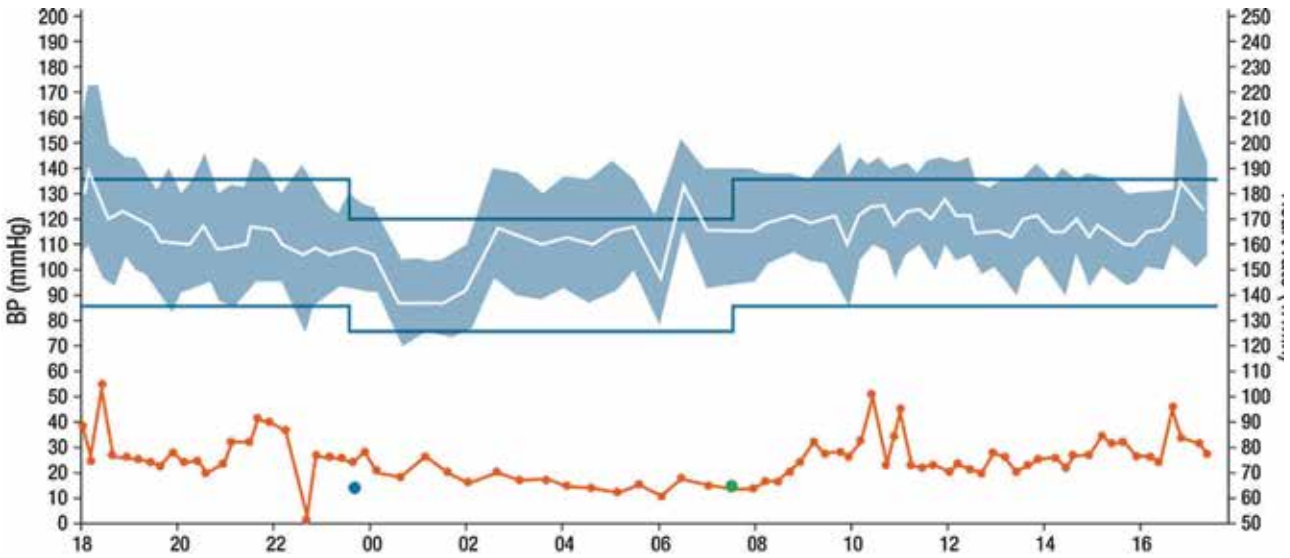


Fig. 1: Patient's 24 h ambulatory BP monitoring (ABPM) after 3 weeks treatment with valsartan, hydrochlorothiazide and carvedilol.

A resting ECG showed sinus rhythm, complete right bundle branch block (RBBB) with left anterior fascicular block (LAFB), QRS 126 ms, and probable left ventricular hypertrophy (LVH).

One week later, laboratory rest results were as follows:

- haemoglobin: 16.2 g/dL,
- haematocrit: 49.5 %,
- fasting plasma glucose: 89 mg/dL,
- fasting lipids: total cholesterol; 243 mg/dl, HDL-cholesterol, 50 mg/dL; LDL-cholesterol, 164 mg/dL; triglycerides, 145 mg/dL,
- electrolytes: sodium, 143 mEq/L; potassium, 3.9 mEq/L,
- uric acid: 4.6 mg/dL
- renal function: creatinine, 0.9 mg/dL; eGFR, 92 mL/min/1.73 m^2,
- urine analysis unremarkable,
- albuminuria: 11.6 mg/24 h,
- normal liver function tests,
- normal thyroid function.

On the same day, an echocardiogram showed normal left ventricular (LV) dimensions, mild hypertrophy (LV mass index 130 g/m^2 and LV relative wall thickness 0.42), preserved LV ejection fraction (LVEF), normal regional wall motion, grade 1 diastolic dysfunction, mild dilatation of the left atrium (36 mL/m^2) and the ascending aorta (42 mm), normal right atrial (RA) and right ventricular (RV) dimensions; normal systolic function; and normal heart valves.

What is the Patient's Risk of Developing T2DM?

Based on the common tools used in Europe for assessing risk of fatal cardiovascular disease and type 2 diabetes—for example the SCORE Risk charts and the FINnish Diabetes RIsk Score—this patient has a high 10-year risk of both CV death and of developing T2DM [1, 2].

A couple of weeks later the patient returned to his family physician. Given his high overall CV and diabetes risks, add-on treatment with carvedilol 25 mg once daily in the morning and atorvastatin 10 mg once daily in the evening were prescribed. The initial goal was to reduce CV risk by lowering LDL-cholesterol. The important role of lifestyle modifications, including a healthy diet and regular exercise was discussed with the patient, but he felt unable to adhere to those recommendations because of frequent traveling and excessive workload. The benefits of lowering LDL-cholesterol as primary prevention in high-risk patients with HTN have been demonstrated [3], with a target LDL-cholesterol level 100 mg/dL [4, 5].

After another 3 weeks, the patient underwent 24-h ABPM (Fig. 1). ABPM may also be a useful tool. 24-h ABPM has been shown to be useful in obstructive sleep apnoea, where multiple risk factors and HTN are common and, therefore, accurate diagnosis of HTN and evaluation of BP control are of particular importance. Complex treatment regimens are often

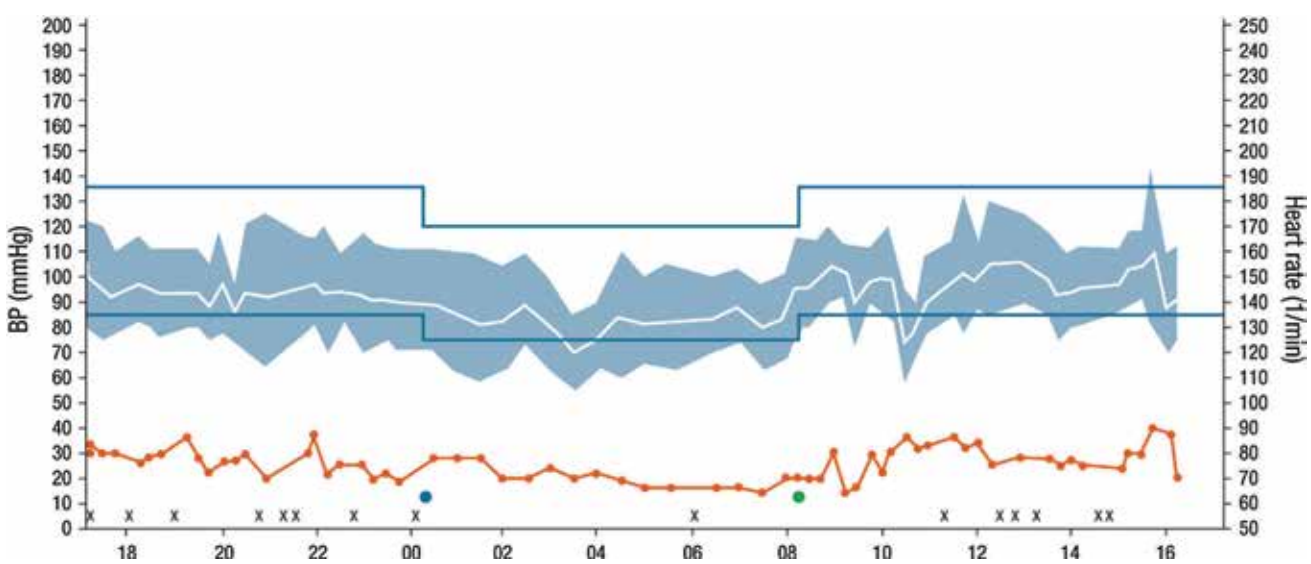


Fig. 2: Patient's 24 h ambulatory BP monitoring after 6 weeks treatment with olmesartan, amlodipine and hydrochlorothiazide.

Table 1: Patient's 24-h ambulatory BP monitoring data before and after treatment modification.

Parameters	Treatment	
	Valsartan + HCTZ + carvedilol	Olmesartan + amlodipine + HCTZ
Mean 24 h SBP/DBP (mm/Hg)	137/96	112/76
Mean awake SBP/DBP (mm/Hg)	139/97	115/79
Mean asleep SBP/DBP (mm/Hg)	127/88	102/65
Nocturnal SBP dip (%)	8.5	10.8
Nocturnal DBP dip (%)	9.4	17.7

required to achieve 24-h BP control in such patients. ABPM is also useful for the assessment of treatment response, and is superior to office BP for determining the effects of antihypertensive therapy on the nocturnal BP dip [6].

Is This a Case of Treatment-Resistant HTN?

HTN is defined as resistant when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and 2 other drugs belonging to different classes at adequate doses fails to lower systolic and diastolic BP to <140 and <90 mmHg, respectively [7]. HTN is not truly resistant if elevated office BPs are due to white-coat HTN, improper BP measurement or lack of adherence to medication; the term pseudoresistant HTN should be used to define such cases. Accordingly, TRH should be considered apparent until pseudoresistance has been excluded by 24-h ABPM, proper office BP measurement and confirmation of adherence to medication. These criteria make the distinction between true TRH and pseudoresistant HTN [8]. The estimated prevalence of apparent TRH has been reported to range from 5 to 30 % of the overall hypertensive population, but the prevalence of true TRH is probably less than 10 % [7].

True TRH is associated with high risk of CV and renal events, and may have any of a number of causes [7]:

- lifestyle factors (obesity, large weight gain, excessive alcohol consumption, high sodium intake) that may counteract the BP-lowering effect of antihypertensives via systemic vasoconstriction, sodium and water retention and, for obesity, the sympatho-stimulating effect of insulin resistance and increased insulinaemia,
- chronic intake of vasopressor or sodium-retaining substances,
- obstructive sleep apnoea (nocturnal hypoxia, chemoreceptor stimulation and sleep deprivation may have long-lasting vasoconstrictor effects),
- undetected secondary forms of HTN,
- advanced and irreversible organ damage (particularly renal dysfunction).

The use of fixed-dose combinations improves adherence to medication, because of reducing the number of pills taken daily, and hence improves BP control. This approach is particularly relevant in the setting of treatment resistant hypertension, and has been facilitated by the availability of different fixed-dose combinations of the same two or three BP-lowering drugs.

The efficacy of an antihypertensive drug regimen may be optimized by selecting appropriate combinations of different drugs. Of the 53,530 patients enrolled in the REACH registry, 6790 (12.7 %) had TRH; 6.2 % were on 3 antihypertensives, 4.6 % were on 4, and 1.9 % were receiving ≥5 agents. Patients with TRH were more likely to be younger, female, have more comorbidities (e.g., diabetes, chronic kidney disease (CKD), hypercholesterolaemia, obesity, heart failure, coronary arterial disease (CAD) or polyvascular disease), and had an increased risk of CV death, MI, stroke, non-fatal stroke, and hospitalisation for heart failure (HF). Patients with TRH more often were taking a β-blocker than a CCB [9]. The 2013 ESH/ESC Guidelines recommend use of a RAAS inhibitor in the presence of LVH, microalbuminuria, diabetic nephropathy, CKD, metabolic syndrome, diabetes, or prior MI, HF or peripheral arterial disease (PAD), whereas a CCB is preferred in patients with LVH, isolated systolic HTN, metabolic syndrome, PAD, and/or black ethnicity [7].

The patient was referred to a HTN clinic. During specialist assessment he had a seated BP of 140/100 mmHg and a heart rate of 72 beats/min. Antihypertensive therapy was modified by discontinuing valsartan/HCTZ and carvedilol and prescribing OLM/HCTZ 20/25 mg once daily in the morning and OLM/AML 20/5 mg once daily in the evening (since the triple combination is not yet available in Portugal, which also applies for several other European countries). Another ABPM was performed 6 weeks later and showed good BP control (Fig. 2).

Patient's ambulatory BP monitoring parameters before and after treatment modification are reported in Table 1.

The use of fixed-dose combination improves adherence to medication, because of reducing the number of pills taken daily, and hence improves BP control [7]. This approach is particularly relevant in the setting of TRH, and has been facilitated by the availability of different fixed-dose combinations of the same two or three BP-lowering drugs. In a retrospective analysis of data from a large US healthcare database, treatment adherence and persistence were significantly improved when triple antihypertensive therapy with olmesartan, amlodipine and hydrochlorothiazide was taken in a single pill combination of all three agents, compared to two pills with one containing two of these drugs, and was worst when taken as three separate pills [10]. Treatment simplification through such an approach may be particularly relevant in the setting of apparent TRH.

Acknowledgments: The authors wish to thank Renata Perego, Nicola Ryan and Raelene Simpson, independent medical writers, who provided editorial assistance on behalf of Springer Healthcare Communications. This assistance was supported by the Menarini group.

Conflict of interest: Dr. Aguiar received speaker fees and honoraria for advisory board activities from Menarini, Daiichi Sankyo, Novartis, and Bial-Portela; the activities conducted with the support of the Menarini group do not constitute a conflict of interest in relation to the contents of this article.

Disclaimer: Please refer to the approved SmPC for the correct use of the drugs mentioned in this article.

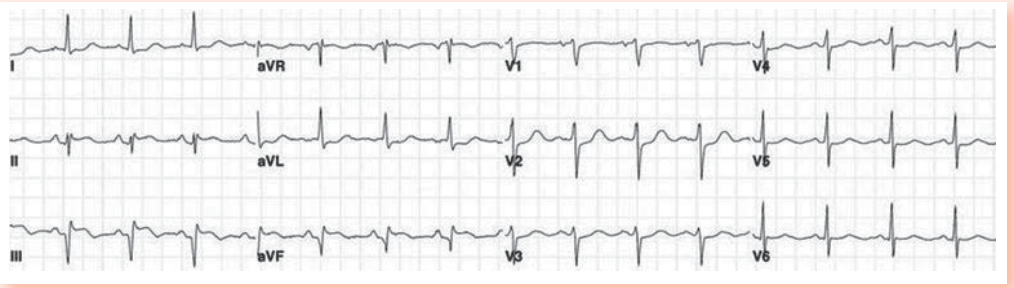
References available on request
Healthcare.India@springer.com

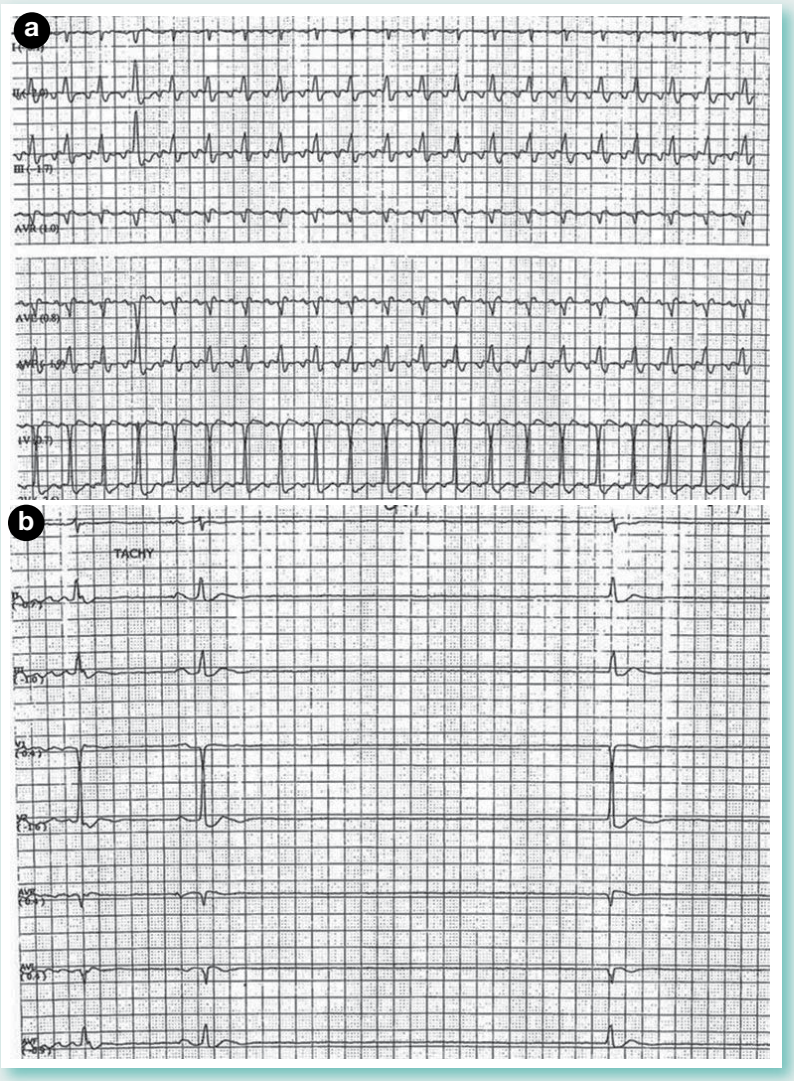
Source: Carlos Aguiar. Patient Cases 2. A Patient with Apparent Resistant Hypertension. High Blood Press Cardiovasc Prev. 2015; 22 (S1):19–22. DOI 10.1007/s40292-015-0111-6.

Top Ten Electrocardiographic (ECG) Abnormalities Not to Miss

ST Elevation Myocardial Infarction

Twelve-lead electrocardiogram of a 64-year-old female who presented with the acute onset of epigastric pain. The electrocardiogram shows ST segment elevation in leads II, III, and aVF. A Q wave is also seen in leads III and aVF.



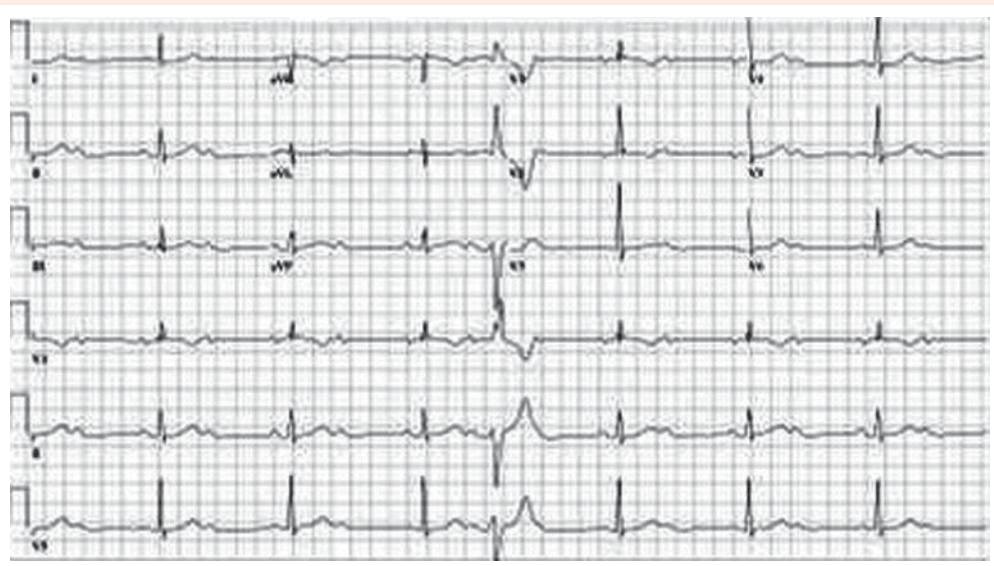


Sinus Node Dysfunction (Sick Sinus Syndrome)

(**a**) Twelve-lead electrocardiogram of an 84-year-old female who presented with altered mental status. Atrial flutter with 2:1 atrioventricular conduction is seen. (**b**) 12-lead electrocardiogram showing flutter termination. A 4.9-s period of asystole is noted before ventricular activity resumes. The patient had multiple sinus pauses during sinus rhythm. These rhythms are typical of Tachy–Brady syndrome and are characteristic of sick sinus syndrome.

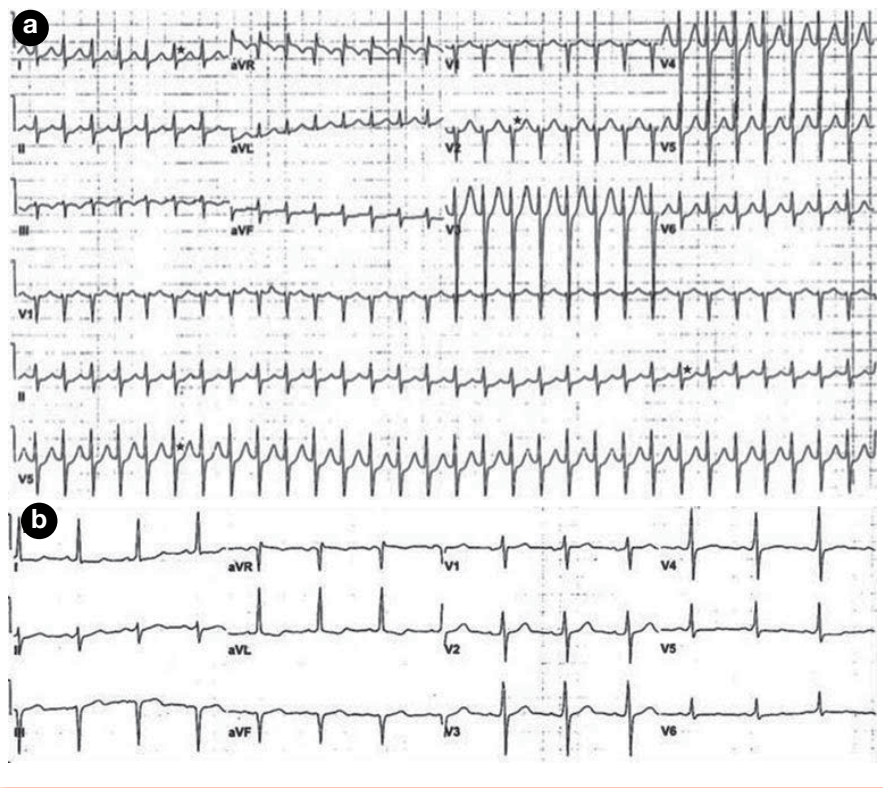
Atrioventricular Block

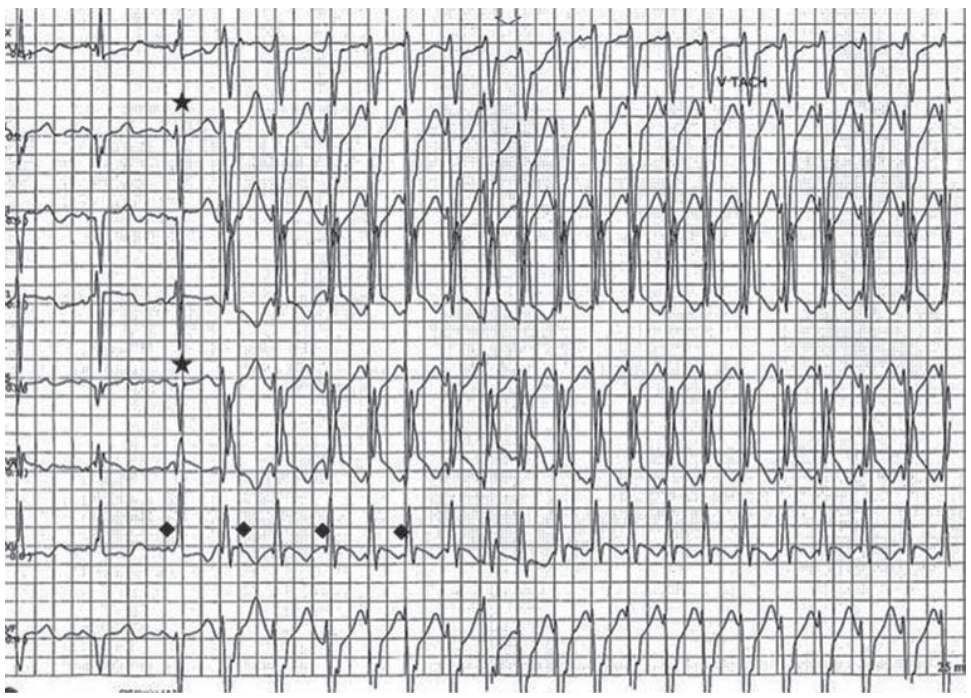
Twelve-lead electrocardiogram of a 76-year-old female who presented with dizziness showing normal sinus rhythm with 2:1 conduction to the ventricles. Differentiating atrioventricular (AV) nodal from infranodal conduction delay is very important in patients with 2:1 AV block. In this case, evaluation of the PR and QRS durations can be useful. Long PR intervals with narrow QRS complexes usually indicate AV nodal conduction delay, while normal PR intervals with wide QRS complexes suggest an infranodal block.



Wolff–Parkinson–White Syndrome

(**a**) Twelve-lead electrocardiogram of a 49-year-old male who presented with palpitations and dizziness. A short RP tachycardia can be seen determined by the location of the P waves (★). (**b**) Baseline electrocardiogram of the patient showing normal sinus rhythm with short PR interval and delta waves (best seen in leads I, V_4, and V_5) that are suggestive of Wolff–Parkinson–White.



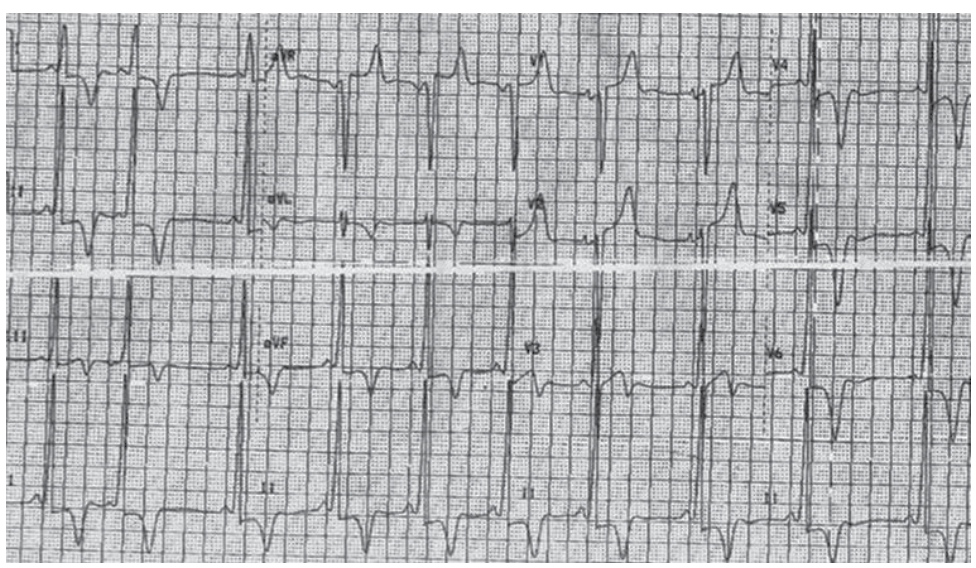


Wide QRS Complex Tachycardia

Telemetry monitoring of a 59-year-old female admitted with heart failure exacerbation that shows wide complex tachycardia. Narrow complex beats (★) are seen preceding the onset of the wide complex tachycardia with different QRS morphology than the sinus rhythm. These fusion beats preceded by P waves are diagnostic of ventricular tachycardia. AV dissociation is also seen (♦).

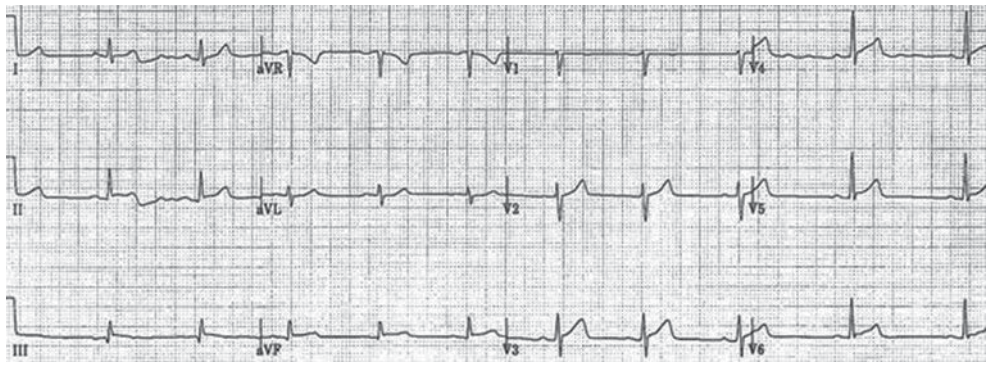
Hypertrophic Cardiomyopathy

Twelve-lead electrocardiogram of a previously healthy 16-year-old boy recorded prior to elective oral surgery. There is normal sinus rhythm at a rate of 73 bpm with a normal mean frontal plane QRS axis, QRS, and QTc intervals. High-voltage QRS complexes associated with short PR intervals and inverted T waves in leads II, III, aVF, and V_4–V_6 were noted and were suggestive of left ventricular hypertrophy (LVH). In the absence of a history of hypertension, this is diagnostic of hypertrophic cardiomyopathy.



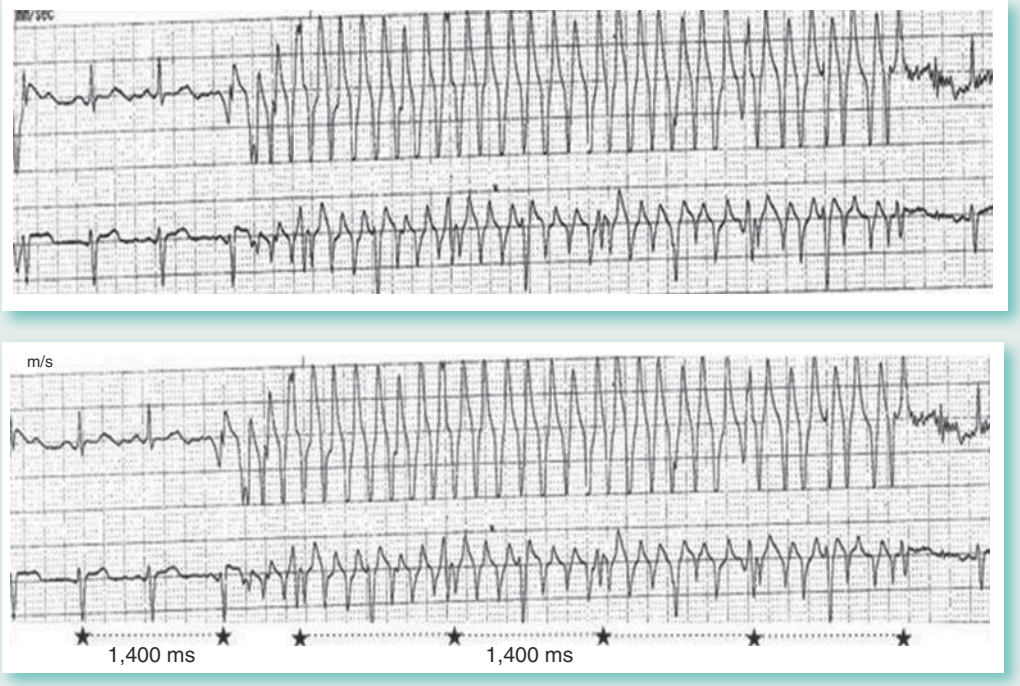
Early Repolarization

Twelve-lead electrocardiogram of a 39-year-old male who presented with palpitations. This ECG was taken after cardioversion from ventricular tachycardia. Leads II, III, aVF, and V_3–V_6 reveal concave ST segment and J point elevations. The differential diagnosis of the J point elevations includes early repolarization, acute pericarditis, ventricular hypertrophy, and myocardial ischemia. On the ECG, acute pericarditis is usually seen as diffuse ST segment elevation. LVH usually presents as ST segment elevation in leads V_1–V_3 with QRS complex voltages that adhere to the criteria for LVH. According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, ST elevation reflecting myocardial ischemia or infarction is less likely in the presence of a concave (as is seen on this ECG) rather than a convex ST segment. Thus, this patient was diagnosed with early repolarization syndrome associated with sudden cardiac death (SCD) based on his strong family history and presentation with ventricular tachycardia (VT).



Artifact

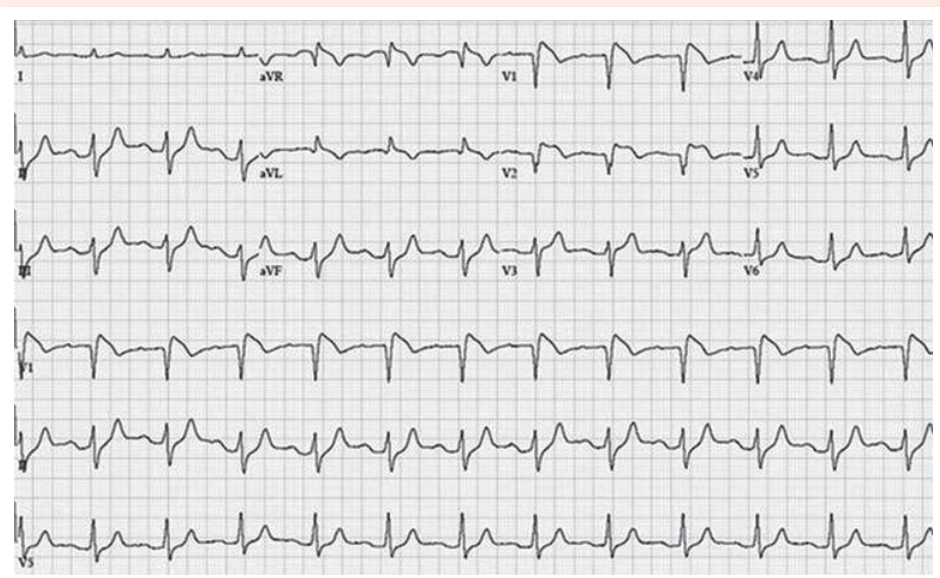
Rhythm strip (leads II and V1) showing wide complex tachycardia in a 44-year-old male who presented with chest pain.



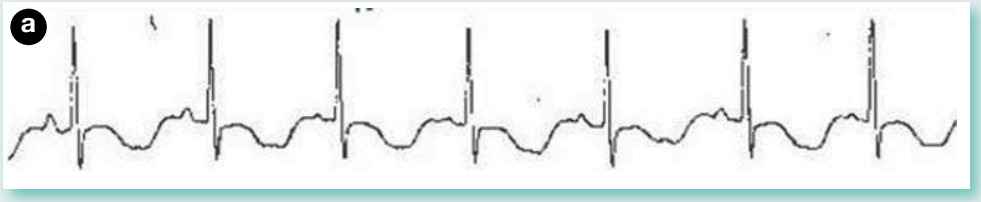
Evaluation of the rhythm strip shows notches in the middle of the wide complex tachycardia (★) that represent sinus QRS complexes. This is diagnostic of recording artifact.

Brugada Syndrome

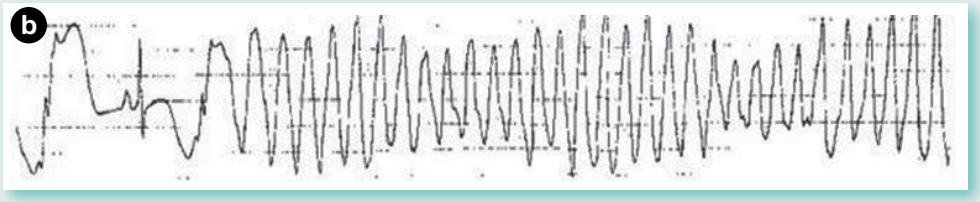
Post-defibrillation 12-lead electrocardiogram of a 61-year-old who presented with syncope. There is sinus bradycardia at a rate of 54 bpm with a normal mean frontal plane QRS axis. His PR and QTc intervals are 194 and 443 ms, respectively. There are ST segment elevations in leads V_1 and V_2 that, together with the clinical presentation and absence of structural heart disease and CAD, are consistent with a diagnosis of Brugada syndrome.



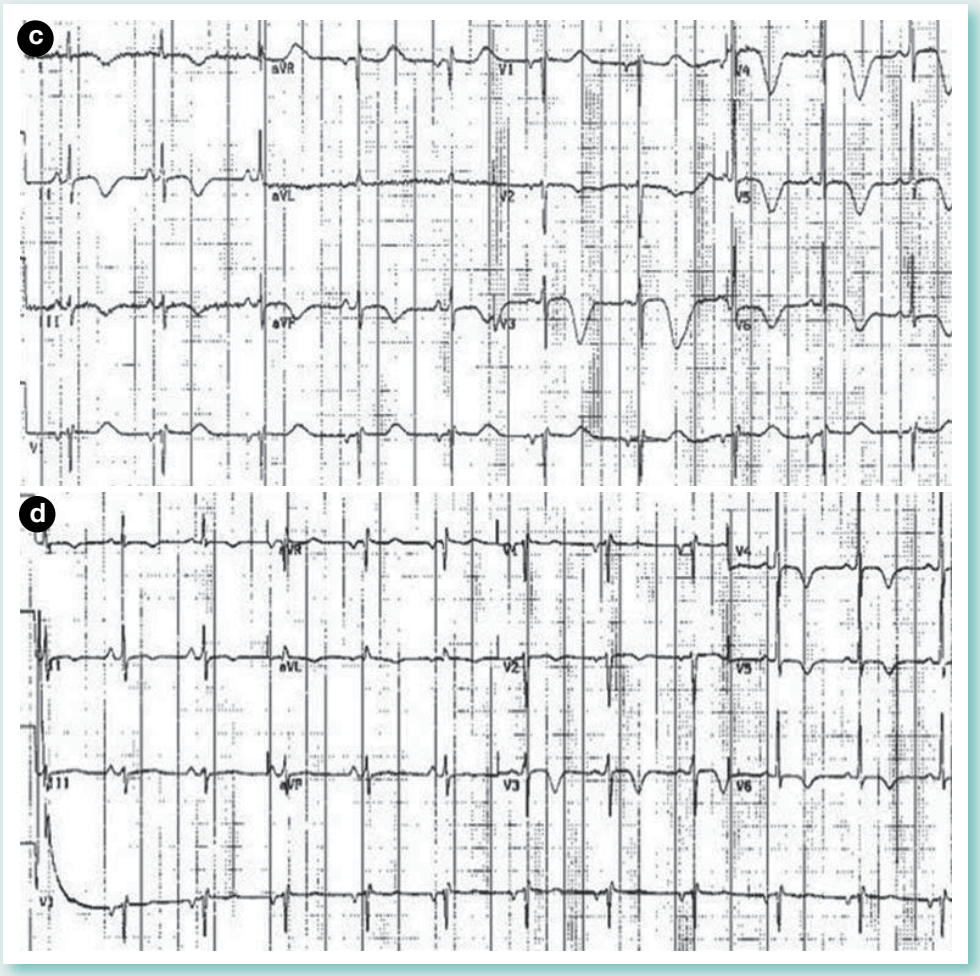
Long QT Syndrome



Lead II rhythm strip recorded in the intensive care unit of a 52-year-old female who was admitted to the hospital for treatment of community-acquired pneumonia. The QTc interval is prolonged (greater than half R–R) and is associated with broad and notched T waves. These findings are consistent with long QT syndrome (LQTS).



Rhythm strip of lead II showing polymorphic ventricular tachycardia (torsades de pointes) recorded a few hours after the rhythm strip in Fig. (**a**).



She was cardioverted to normal sinus rhythm and treated with intravenous isoproterenol and lidocaine to shorten the QT interval. Serum calcium, magnesium, and potassium levels were within normal limits. She was diagnosed with haloperidol-induced LQTS. She had dramatic prolongation of her QT interval after stopping the lidocaine infusion (**c**) that normalized with an additional intravenous bolus (**d**).

Source: Lea El Hage, Nitish Badhwar, Nora Goldschlager. Top Ten Electrocardiographic (ECG) Abnormalities not to Miss. In: K. Stergiopoulos, D.L. Brown (eds). Evidence-Based Cardiology Consult. 1st ed. London: Springer-Verlag; 2013, pp 133-148. DOI 10.1007/978-1-4471-4441-0_11. © Springer-Verlag London 2014.

May 2018

Springer Healthcare

This edition is created in India for free distribution in India.

This edition is published by Springer (India) Private Limited, (a part of Springer Science+Business Media)
Registered Office: 7th Floor, Vijaya Building, 17, Barakhamba Road, New Delhi 110 001, India.
Phone: 91 (0) 11 4575 5888 | www.springerhealthcare.com

Part of the Springer Nature group

Printed and Bound by: Parksons Graphics Pvt. Ltd., Mumbai.

Uncontrolled BP leads to parallel CV & renal disease progression - A Cardio Renal Continuum[1]

Set the Goal... with

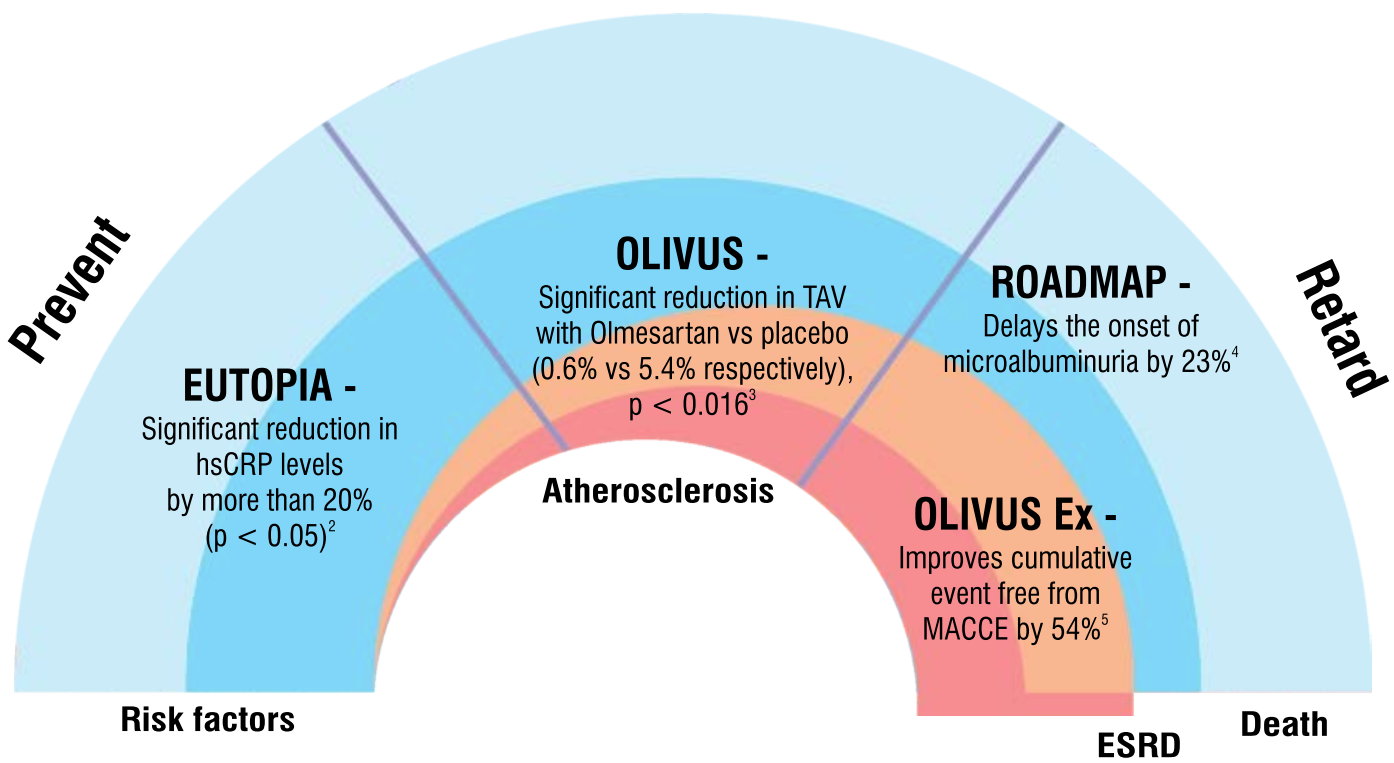
ONCE-A-DAY

Olmezest® 10 20 40

Olmesartan Medoxomil 10 / 20 /40 mg

EFFICACY
SUSTAINABILITY
CONSISTENCY

Get the Results across the Continuum



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

1. Ruilope, L. M. Nat. Rev. Cardiol. 9, 267–275 (2012); 2. Circulation. 2004;110:1103-1107, Mean follow up of 12 weeks 3. J. Am. Coll. Cardiol. 2010;55;976-982, mean follow up of 14 months
4. J Am Heart Assoc. 2014;3:e000810 doi: 10.1161/JAHA.114.000810, mean follow up of 3.2 years 5. Atherosclerosis 220 (2012) 134–138, 4 year clinical outcomes from OLIVUS

AZURA
Life Sciences
a SUN PHARMA division

8334862
J2113961