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in Cardiology

Treatment of Hypertension in Patients with Coronary Artery Disease

Dyslipidemia

Hypertension

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EDITOR'S NOTE

The world of Medicine has made great advances since its early days. In recent years we have had the privilege of witnessing developments in understanding the pathogenesis of many of the diseases burdening humankind. It is frustrating, though, to realize that most of this up-to-date knowledge does not reach its natural recipients, who are physicians in each specialty working in daily practice. Thus, we believe that the need for an informative journal is obvious and self-explanatory.

For this reason, CCM will fill the gap in continuing medical education to benefit every day clinical practice, by publishing this innovative series of Current Views. In every issue, readers will find a review article and several summary articles. ***Current Views in Cardiology*** was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the CCM editorial team based on an ongoing review of the international literature, and articles are selected for review and citation on the basis of their relevance to clinical practice.

Current Views in Cardiology provides specialists with an attractive means of continuing medical education that demonstrates the best of critical thinking and is a source of, and a catalyst for, new ideas and learning. The editors and medical advisors at CCM have made every effort to search the international literature to present the most current, interesting and cutting edge articles, in order to make ***Current Views in Cardiology*** a respected and useful tool for the daily practice of physicians with one aim: to provide a good service to their patients. For this issue, we have retrieved information from several well respected peer reviewed journals:

Am J Cardiol
Am J Hypertens.
Am J Med Sci.
Am J Physiol Renal Physiol.
Arch Neurol
Blood Press
BMC Cardiovasc Disord.
Cardiol J.
Circulation
Clin Pharmacol Drug Dev.
Clin Res Cardiol
Curr Med Res Opin.
Curr Opin Cardiol.
Front Cardiovasc Med.
Hypertension.
J Am Coll Cardiol.
J Clin Hypertens (Greenwich).
J Clin Invest.
J Hypertens.
JAMA
JAMA Cardiol.
N Engl J Med
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PLoS One.
Pol Arch Med Wewn.
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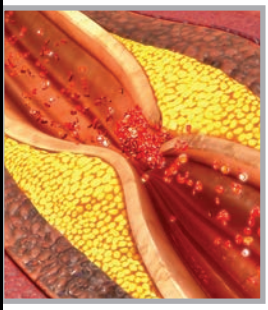
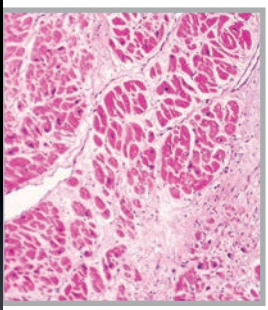
Feature Article

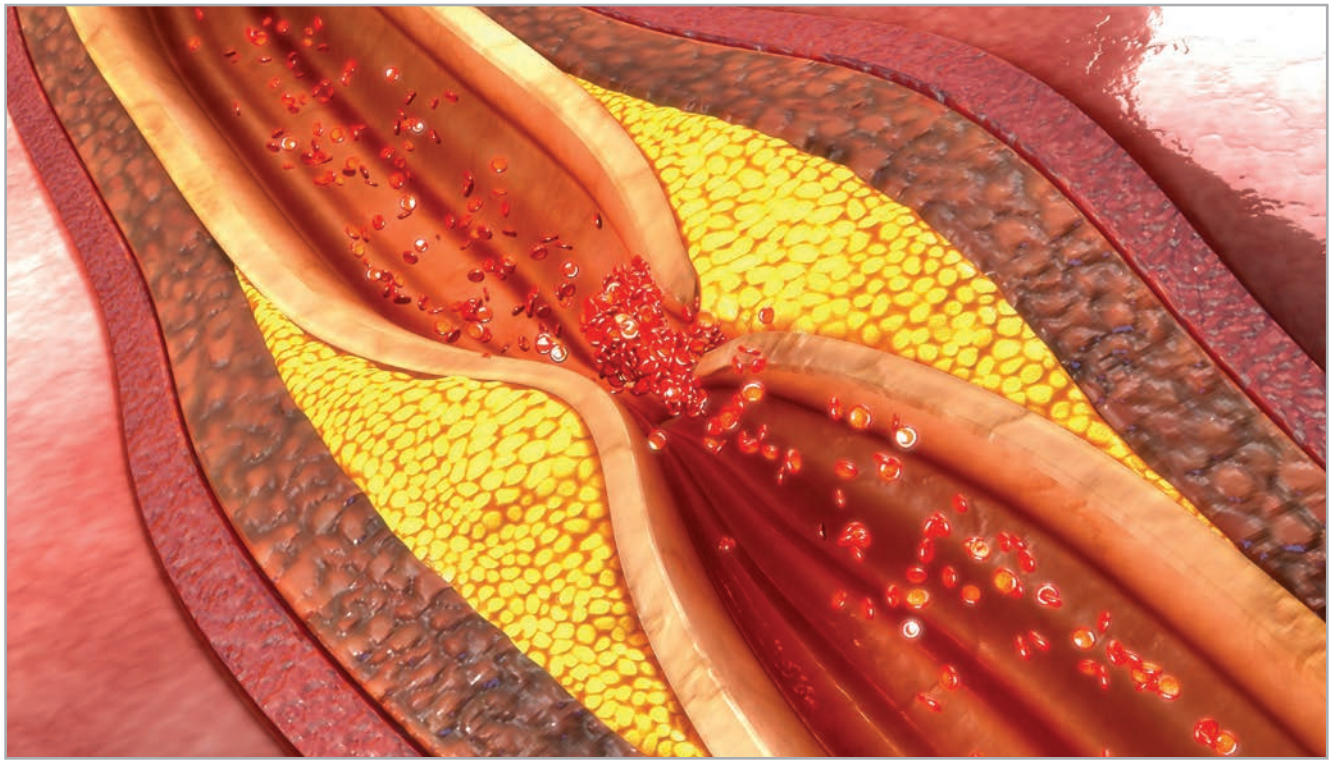


Dyslipidemia



Hypertension

Treatment of Hypertension in Patients with Coronary Artery Disease



Introduction

Arterial hypertension is the leading cause of death in the world affecting 1.4 billion worldwide. It is the most common cause for an outpatient visit to a physician, and the most easily recognized treatable risk factor for stroke, myocardial infarction, heart failure, peripheral vascular disease, aortic dissection, atrial fibrillation, and end-stage kidney disease. Despite this knowledge and unequivocal scientific proof that treating hypertension with medication dramatically reduces its attendant morbidity and mortality, hypertension remains untreated or undertreated in the majority of affected individuals in all countries, including those with the most advanced medical care systems. The 2017 American Heart Association/American College of Cardiology guideline has introduced the new threshold for diagnosis and treatment of hypertension to less than 130/80 mm Hg, while most other countries in the world have continued the old thresholds of less than 140/90 mm Hg in their guidelines. For this reason, hypertension remains one of the world's great public health problems. The asymptomatic nature of the condition impedes early detection, which requires regular BP measurement. Most cases of hypertension cannot be cured and thus blood pressure (BP) control requires lifelong treatment with prescription medications, which can be costly and may cause more symptoms than the

underlying disease process. Effective hypertension management requires continuity of care by a regular and knowledgeable medical provider as well as sustained active participation by an educated patient.[1]

Lowering BP in patients with hypertension reduces the risk of cardiovascular events and death, but the optimum target blood pressure remains unresolved. Randomized trials did not show a benefit of blood pressure targets of less than 140/90 mm Hg, and post-hoc analyses have suggested that the benefit of blood pressure-lowering treatment might even be reversed below a certain threshold, the so-called J-curve phenomenon. Conversely, a large meta-analysis of trials that randomly assigned participants to intensive versus less-intensive blood pressure-lowering treatment showed that intensive blood pressure-lowering was associated with decreased cardiovascular events, and the SPRINT trial showed that targeting a systolic blood pressure of less than 120 mm Hg in high-risk patients was associated with a reduction in blood pressure-related adverse outcomes, rather favoring a lower is better approach.[2]

These contradictory results leave clinicians with uncertainty as to the optimum blood pressure target in patients treated for hypertension. The concern for a J-curve phenomenon is particularly relevant for cardiac events, because the heart is perfused during diastole and its perfusion might be compromised at low diastolic blood pressure values, especially in patients with coronary artery disease, both because a coronary stenosis will lower perfusion pressure in the downstream territory and because auto-regulation is altered in these patients.[2]

Mechanisms of Hypertension and Coronary Artery Disease

Essential hypertension, which is defined as hypertension without a clear secondary cause, makes up the majority of cases. Two primary mechanisms have been proposed for essential hypertension: neurogenic and renogenic (or nephrogenic). The neurogenic model suggests that hypertension is the result of a chronic increase in sympathetic nervous system activity. This is in contrast to the renogenic model, which attributes blood pressure increase to renal origins either through decreased renal blood flow or through renal parenchymal disease.[3]

A variety of pathophysiological mechanisms contribute to the genesis of BP elevation and related target-organ damage, including coronary artery disease (CAD). These mechanisms include increased sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) activity; deficiencies in the release or activity of vasodilators, for example, nitric oxide and prostacyclin, and changes in the natriuretic peptide concentration; increased expression of growth factors and inflammatory cytokines in the arterial tree; hemodynamic effects; and structural and functional abnormalities in conductance and resistance arteries, particularly increased vascular stiffness and endothelial dysfunction. These neurohumoral pathways interact with genetic, demographic, and environmental factors (such as heightened exposure or response to psychosocial stress, excessive dietary intake of sodium, and inadequate dietary intake of potassium and calcium) to determine whether a person will develop hypertension and related CAD. Concomitant metabolic disorders, for example, diabetes mellitus, insulin resistance, and obesity, also lead to the production of vasoactive adipocytokines that promote vasoconstriction, endothelial dysfunction, inflammation, and increased oxidative stress in the vasculature, thus increasing both BP and cardiovascular disease (CVD) risk.[4,5,6]

Physiological Link between Hypertension and Coronary Artery Disease

Many of the physiological mechanisms involved in pathogenesis of hypertension also play a key role in the development of atherosclerosis in the epicardial coronary vessels as well as dysfunction in the microvessels. Increased sympathetic drive centrally via activation of the renin-angiotensin-aldosterone system (RAAS), increased oxidative stress and inflammatory cytokines, endothelial and microvascular dysfunction, and deficiency in vasodilators such as nitric oxide and prostacyclin are among the many

contributing factors. Endothelial dysfunction remains most pronounced in patients with vascular diseases such as CAD and hypertension. This includes an imbalance between bioavailable vasodilators (nitric oxide and prostaglandin E) and vasoconstrictors (endothelin and angiotensin II), as well as prothrombotic and antithrombotic mediators thereby contributing toward elevated blood pressure and athero-thrombotic risk. The increased sympathetic drive activates RAAS, increasing production of angiotensin II and aldosterone which have various downstream vasotoxic effects. Furthermore, injured endothelium releases inflammatory cytokines which potentiate oxidative stress and perpetuate vascular inflammation, thereby resulting in initiation and progression of CAD, as well as microvascular disease.[7]

Genetics

The pathophysiological mechanisms responsible for hypertension are complex and act on a genetic background. Primary hypertension involves multiple types of genes; some allelic variants of several genes are associated with an increased risk of developing primary hypertension and are linked in almost all cases to a positive family history.[4] This genetic predisposition, along with a host of environmental factors, such as high Na+ intake, poor sleep quality or sleep apnoea, excess alcohol intake and high mental stress, contribute to the development of hypertension. Finally, the probability of developing hypertension increases with aging, owing to progressive stiffening of the arterial vasculature caused by, among other factors, slowly developing changes in vascular collagen and increases in atherosclerosis.[4] Immunological factors can also play a major part, especially on the background of infectious or rheumatological diseases such as rheumatoid arthritis. The mosaic theory of hypertension describes its multifaceted pathophysiology.[4]

Genome-wide association studies have identified multiple genetic susceptibility variants, mostly single-nucleotide polymorphisms, for atherosclerotic disease. It has been suggested the polymorphisms of genes of the RAAS, particularly ACE, angiotensin II receptor type 1, and angiotensinogen, are implicated in the development of CAD and MI. The presence of hypertension further increases the risk of CAD and may explain why some individuals are more predisposed than others to developing coronary events. Some polymorphisms have also been implicated in the BP response to antihypertensive treatment. For example, genetic polymorphisms coding for the matrix metalloproteinases appear to modify CVD outcomes in hypertensive patients treated with chlorthalidone, amlodipine, or lisinopril.[8] In the future, determination of genetic variants may be of some use for selecting appropriate antihypertensive agents to reduce both BP and the risk for CAD. However, because CAD is polygenic and its causes are multifactorial, genetic studies explain only a small proportion of the heritability of the disease.[9]

Physical Forces and Hemodynamics

The elasticity and distensibility of arteries maintain a relatively constant blood pressure, despite the pulsating nature of the blood flow by every heartbeat. Arteries expand by receiving blood ejected from the heart during systole and expel it to the periphery during diastole to supply the peripheral circulation with a steady flow of blood during both cardiac cycles. However, as a hallmark of normal aging and apart from that also in association with many diseases compliance and distensibility of arteries decrease and the term “arterial stiffness” is used to qualitatively indicate these decreased elastic vessel wall properties. An increased arterial stiffness leads to a decreased buffer capacity of the arteries and an increase in pulse pressure (PP) and pulse wave velocity (PWV), causing an early return of the reflected waves and thereby an augmentation of late systolic pressure. As a consequence, the left ventricle has to generate an extra workload to overcome the augmented pressure, which is associated with an increased demand of oxygen and in the long-term development of left ventricular hypertrophy and heart failure. Insufficient arterial compliance furthermore transmits the increased pulsatile pressure deeper into the periphery and damages microvasculature of distal-end organ systems, especially in the kidney and the brain.[10]

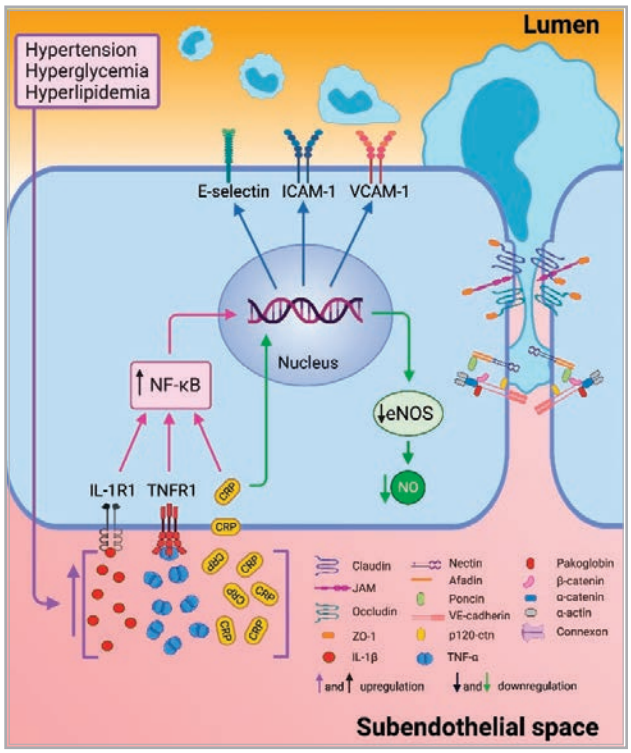
Studies using five different animal models of hypertension or vascular disorders, supported by the RFA-HL-10–027, showed that large artery stiffening preceded high blood pressure, consistent with the temporal sequence observed in several clinical studies. This concordance supports the notion that measurement of arterial stiffness may present opportunities for early detection of hypertension and better CV risk stratification.[11]

The most commonly used measure to assess arterial stiffness in humans is carotid-femoral pulse wave velocity (cf-PWV). The traditional view linking arterial stiffness (measured as increased cf-PWV) to hypertension noted that faster PWV produced faster reflection of the incident pulse wave, which resulted in an earlier reflected wave that returned to the central circulation before the end of systole, resulting in increased systolic BP. Although these mechanisms still hold true, later data have indicated the importance of two other factors, increased amplitude of the forward wave and increased characteristic impedance of the proximal aorta. When these specific factors are taken into account, the relative contribution of wave reflection to the observed age-dependent change in pulse pressure is only 4% to 11%.[12]

Endothelial Dysfunction

Endothelial dysfunction is generated when there is an imbalance in the production or bioavailability of endothelium-derived NO, generating a decreased vasodilator response and a prothrombotic and proinflammatory endothelium. During the inflammatory process induced by different risk factors as hypertension, oxidized LDL (oxLDL) and diabetes, there is an increase in the production of interleukin-1 (IL-1), interleukin-6 (IL-6), TNF-α and C-reactive protein (CRP) that generate the endothelial proinflammatory phenotype characterized by an increase in E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) expression. Therefore, there is a greater interest in the search for new biomarkers and therapeutic strategies that help to prevent endothelial dysfunction and reduce the risk of developing CAD and its complications.[13]

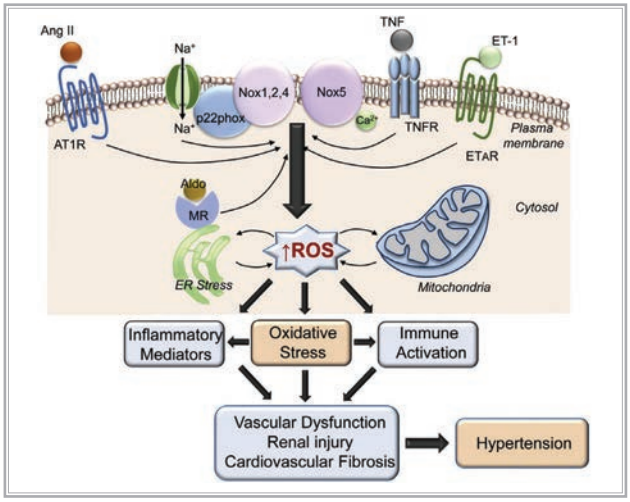
The role of ROS and increased oxidative stress is essential in endothelial dysfunction. ROS are reactive intermediates of molecular oxygen that act as important second messengers within cells; however, an imbalance between generation of reactive ROS and antioxidant defense systems represents the primary cause of endothelial dysfunction, leading to vascular damage in both metabolic and atherosclerotic diseases. In endothelial cells, NO is essential for vascular homeostasis. Reduction in NO bioavailability, resulting from reduced NO production and/or increased NO degradation by superoxide anion, marks the onset of endothelial dysfunction. Identification of new endothelial dysfunction-related oxidative stress markers represents a research goal for better prevention and therapy of CVD. New-generation therapeutic approaches based on carriers, gene therapy, cardiolipin stabilizer, and enzyme inhibitors have proved useful in clinical practice to counteract endothelial dysfunction.[13]



Endothelial inflammation. Endothelial dysfunction is triggered by different cardiovascular risk factors such as hypertension, hyperglycemia, and hyperlipidemia. These events increased production of interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and C reactive protein (CRP). Proinflammatory cytokines bind to their receptors and culminate in the activation of the nuclear transcription factor κB (NF-κB) that stimulate the transcription of selectin-E, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). CRP down-regulates endothelial nitric oxide synthase (eNOS) transcription and destabilizes eNOS mRNA, resulting in decreased nitric oxide (NO). Furthermore, the reorganization of actin filaments allows the opening of intercellular junctions through other signaling pathways. **From: Medina-Leyte, et al. 2021**

Oxidative Stress

There has been enormous progress in the understanding of cardiovascular, renal, and neural mechanisms involved in the pathophysiology of hypertension. Over the past decade, many new systems and factors have been identified as being important in the development of hypertension and hypertension-associated target-organ damage, including the immune system, inflammation, sex hormones, microRNAs, interstitial sodium, the microbiome, and environmental stressors. Common to these processes is oxidative stress with associated abnormal redox status and altered redox signalling. Oxidative stress acts as a common mediator of cell injury and inflammation in multiple systems that influence blood pressure regulation. Although the exact causes of oxidative stress in hypertension remain unclear, dysregulation of Noxs in cardiovascular, renal, immune, and neural cells seems to be important. The most significant consequence of oxidative stress is increased posttranslational oxidation of proteins and perturbed redox-dependent signalling. To fully understand the functional impact of oxidative stress in health and disease, it will be essential to know how proteins are differentially oxidised and activated. This will demand high-fidelity redox proteomics, which we believe is the next frontier in the unravelling of mechanism-specific targets in hypertension.[14]



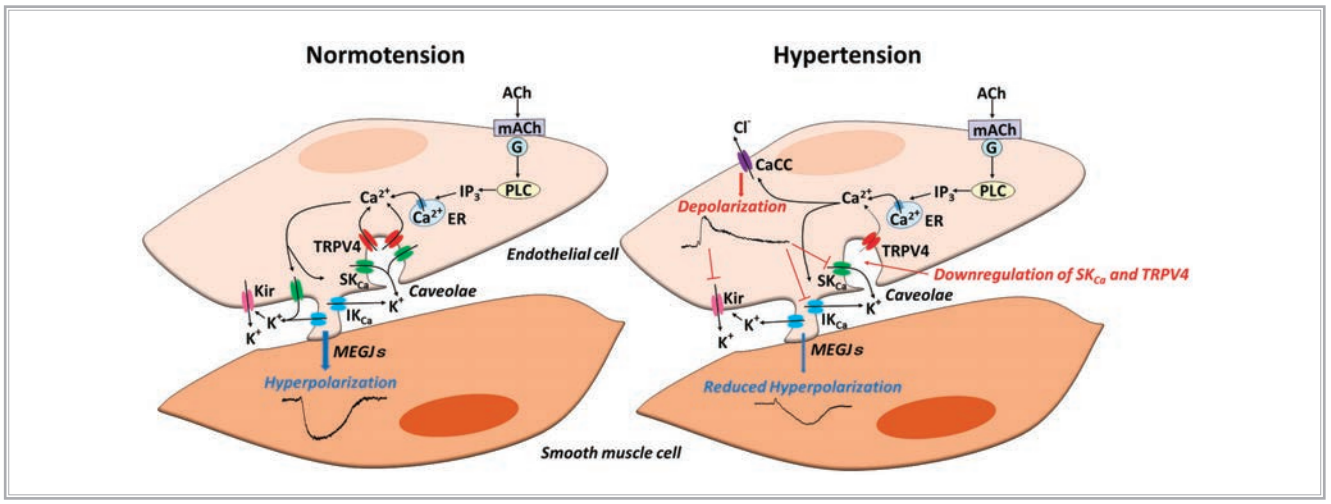
Oxidative stress as a unifying factor in hypertension. Prohypertensive factors, eg, angiotensin II (Ang II), endothelin-1 (ET-1), aldosterone (Aldo), and salt (Na), induce activation of NADPH oxidases (Noxs) that generate reactive oxygen species (ROS), which influence multiple systems involved in the pathophysiology of hypertension. AT1R, angiotensin II type 1 receptor, ER, endoplasmic reticulum, ETAR, endothelin-1 type A receptor; MR, mineralocorticoid receptor; TNF, tumour necrosis factor; TNFR, tumour necrosis factor receptor. **From: Touyz et al., 2020**

Humoral and Metabolic Factors

Many of the mechanisms that initiate and maintain hypertension also damage target organs, including the coronary arteries and the myocardium. Angiotensin II elevates BP and promotes target-organ damage, including atherosclerosis, by mechanisms that include direct effects on constriction and remodeling of resistance vessels, stimulation of al-

dosterone synthesis and release, enhancement of sympathetic outflow from the brain, and facilitation of catecholamine release from the adrenals and peripheral sympathetic nerve terminals. Aldosterone can mimic or potentiate the vasotoxic properties of angiotensin II and norepinephrine. Angiotensin II promotes cardiac and vascular smooth muscle cell hypertrophy directly via activation of the angiotensin II type 1 (AT1) receptor and indirectly by stimulating expression of a number of growth factors, cytokines, and adhesion molecules. AT1 receptor activation also contributes to endothelial damage and atherogenesis by inhibiting the mobilization of endothelial progenitor cells from the bone marrow, thus impairing endothelial regeneration and vascular repair processes.[15] There is also a link between RAAS activation and fibrinolysis. Angiotensin II induces the formation of plasminogen activator inhibitor-1 via an AT1 receptor–dependent effect on endothelial cells, whereas ACE downregulates tissue plasminogen activator production by degrading bradykinin, a potent stimulator of endothelial tissue plasminogen activator expression.

Calcium



Endothelial ion channels in normotension and hypertension. In normotension, in response to agonist stimulation of endothelial cells, a rise in intracellular Ca^{2+} occurs due to the release from intracellular Ca^{2+} stores and Ca^{2+} entry via transient potential vanilloid type 4 channel (TRPV4). A rise in intracellular Ca^{2+} subsequently generates endothelium-dependent hyperpolarization (EDH) through the activation of both small (SK_{Ca}) and intermediate conductance (IK_{Ca}) Ca^{2+}-activated K^+ channels. In some arteries, K^+ released from endothelial KCa channels activates endothelial Kir channels, which in turn amplifies EDH. EDH spreads to adjacent smooth muscle cells via myoendothelial gap junctions (MEGJs), resulting in vascular relaxation. In hypertension, alterations of endothelial ion channels additively reduce EDH; these alterations include downregulation of endothelial SK_{Ca} and TRPV4 channels, upregulation of endothelial Ca^{2+}-activated chloride channels (CaCCs), and functional loss of endothelial Kir channels. **From Goto, et al. 2018**

In vascular endothelial cells, both small and intermediate conductance Ca^{2+}-activated K^+ channels (SK_{Ca} and IK_{Ca}) are expressed, and there is a consensus that the activation of the SK_{Ca} and IK_{Ca} channels in the endothelium results in the generation of EDH in a number of vascular beds. Indeed, the involvement of both SK_{Ca} and IK_{Ca} channels in the generation of EDH has now been supported on the basis of the results from mice deficient in these channels. In addition, K_{Ca} channel-deficient mice show high blood pressure, suggesting that endothelial K_{Ca} channels play an important role in blood pressure regulation as well. Although large conductance Ca^{2+}-activated K^+ (BKCa) channels are present in the endothelial cells of some vascular beds, there is little evidence showing the involve-

ment of endothelial BKCa channels in the generation of EDH; or of the presence of endothelial BKCa channels in intact vessels.[16]

Changes in the function and/or expression of endothelial SK_{Ca} and IK_{Ca} channels during hypertension, in particular, those of SK_{Ca} channels, have been reported in various types of animal models of hypertension. Thus in mesenteric arteries of SHR and stroke-prone spontaneously hypertensive rats (SHRSP), the function and/or expression of SK_{Ca} channels are reduced and such reduction appears to underpin the impaired EDH-mediated responses in this vascular bed. A contribution of reduced SK_{Ca} channels' function and/or expression to impaired EDH-mediated responses has also been suggested in mesenteric arteries from angiotensin II-induced hypertensive rats, testosterone-induced hypertensive rats, and endothelial connexin mutant mice that exhibit hypertension.[16]

The dihydropyridine CCBs bind to the α1 subunit of the L-type channel and are highly selective for arterial/arteriolar tissues, including the coronary arteries, where they are vasodilators. The nondihydropyridine CCBs, including the phenylalkylamines (verapamil-like) and benzothiazepines (diltiazem-like), bind to different sites on the α1 subunit and are less selective for vascular tissue; they have negative chronotropic and dromotropic effects on sinoatrial and atrioventricular nodal conducting tissue and negative inotropic effects on cardiomyocytes. The nondihydropyridine CCBs have greater effects on the atrioventricular node than on the sinoatrial node and may predispose to high-degree atrioventricular block in patients with preexisting atrioventricular nodal disease or when given with other agents, for example, ß-blockers, that depress the atrioventricular node. Both CCB subclasses are indicated for the treatment of hypertension and angina pectoris. The antianginal effects of CCBs result from afterload reduction, that is, their ability to decrease SBP, as well as coronary vasodilation and, in the case of nondihydropyridine CCBs, heart rate slowing. CCBs are particularly effective in treating angina caused by coronary spasm, for example, the Prinzmetal variant or cold-induced angina.[17]

Treatment

To lower myocardial oxygen demands in patients with coronary artery disease, the antihypertensive regimen should reduce BP without causing reflex tachycardia. For this reason, a ß-blocker is often prescribed in conjunction with a dihydropyridine CCB such as amlodipine. ß-Blockers are indicated for patients with hypertension who have sustained a myocardial infarction and for most patients with chronic heart failure. ACEIs are indicated for almost all patients with left ventricular systolic dysfunction and may be considered after myocardial infarction even in the absence of ventricular dysfunction. Among patients with stable coronary artery disease, a cardioprotective effect of ACE inhibition has also been demonstrated in those with moderate cardiovascular risk profiles but not in those with lower risk profiles.

Blood Pressure Goals for Patients with Hypertension and CAD

Large-scale prospective studies have demonstrated that elevated blood pressure is associated with coronary artery disease (CAD). The prevalence of hypertension ranges from 30 to 70% in individuals with pre-existing CAD, and a previous study demonstrated that a 20 mm Hg rise in systolic blood pressure (SBP) or a 10 mm Hg rise in diastolic blood pressure (DBP) results in a twofold increase in the risk of mortality among patients with ischemic heart disease aged 40–69 years. Meanwhile, a reduction in SBP of 5 mm Hg can decrease the risk of death from cardiovascular disease (CVD) by 9%.[18]

In hypertensive patients with CAD, atherosclerotic lesions and arterial stiffness tend to be more severe, resulting in a lower DBP and increased pulse pressure. Patients who have undergone coronary revascularization seem to be more tolerant of lower DBP than those who had not, which may be partly explained by improved myocardial perfusion. When performed using the proper revascularization strategy for appropriate patients, coronary revascularization can offer survival benefits in CAD; however, there is a need for further research to define the optimal BP target and therapeutic benefit of intensive BP treatment in this population.[18]

Targets

- A blood pressure target of less than 140/90 mm Hg is recommended in most patients with CAD and hypertension.[19]
- A target of 130/80 mm Hg is reasonable in selected patients with CAD, including those with previous MI, stroke, or CAD risk equivalents.[19]

A. Recommendations for Hypertensive Patients with CAD[20]

- For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended.
- For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended.
- For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/ thiazide-like diuretic in selected patients.
- For patients with stable angina pectoris, but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a ß-blocker or CCB can be used as initial therapy.
- Short-acting nifedipine should not be used.
- When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is 60 mm Hg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy.

B. Recommendations for Patients with Hypertension who have had a Recent Myocardial Infarction[19]

- Initial therapy should include a ß-blocker as well as an ACE inhibitor (Grade A).
- An ARB can be used if the patient is intolerant of an ACE inhibitor (Grade A in patients with left ventricular systolic dysfunction).

- CCBs may be used in patients after myocardial infarction when ß-blocker are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography.

Nonpharmacological Interventions

Nonpharmacological interventions should be encouraged in all individuals with hypertension.[21] Exercise improves cardiac function, reduces BP and cardiac afterload by a variety of mechanisms, including reduced arterial stiffness. Research has shown that physical activity predicts the likelihood of CVS disease beyond that explained by the commonly measured cardiometabolic risk factors.[22] Although the mechanism is not entirely clear, evidence indicates that exercise improves coronary artery flow reserves in CHD patients[23] and pathophysiological mechanisms that are potentially important in generating CHD have been linked to physical activity.[24] Hence, regular exercise is recommended in all individuals with hypertension and CHD.

Studies have also shown that various lifestyle behaviors, including unhealthy diet, physical inactivity, and smoking, promote the development and clinical manifestations of CHD.[25] Therefore, lifestyle changes and adoption of healthful behaviors are equally important in the management of hypertension and CHD. Special attention should be given to weight loss, diet control, salt intake, alcohol consumption, smoking, and stress management.

Antihypertensive Drugs for the Secondary Prevention of Cardiovascular Events in Patients with CAD[7,19,20,26]

Thiazide and Thiazide-Type Diuretics

Thiazide diuretics and the thiazide-type diuretics chlorthalidone and indapamide are highly effective in reducing BP and preventing cerebrovascular events.

ß-*Blockers*

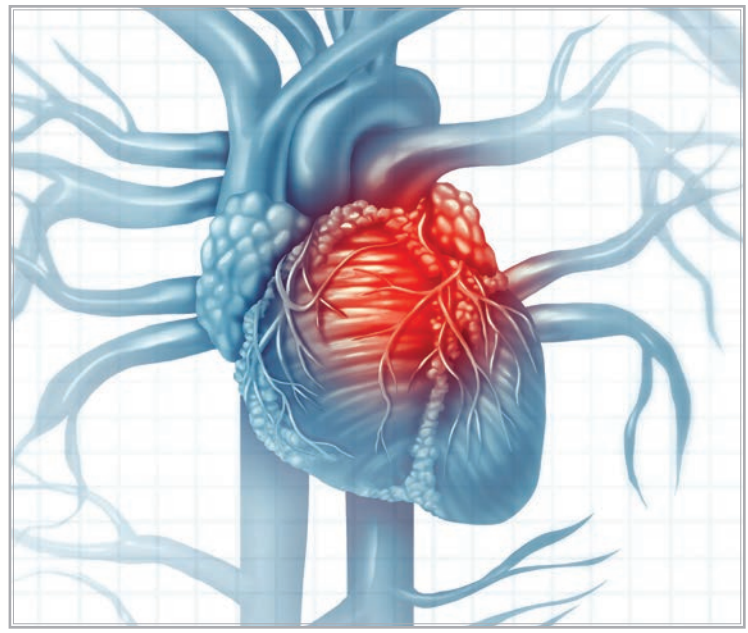
ß-Blockers make up a heterogeneous class of antihypertensive drugs with differing effects on resistance vessels and on cardiac conduction and contractility. ß-Blocker administration remains the standard of care in patients with angina pectoris, those who have had an myocardial infarction (MI), and those who have LV dysfunction with or without symptoms of HF unless contraindicated.

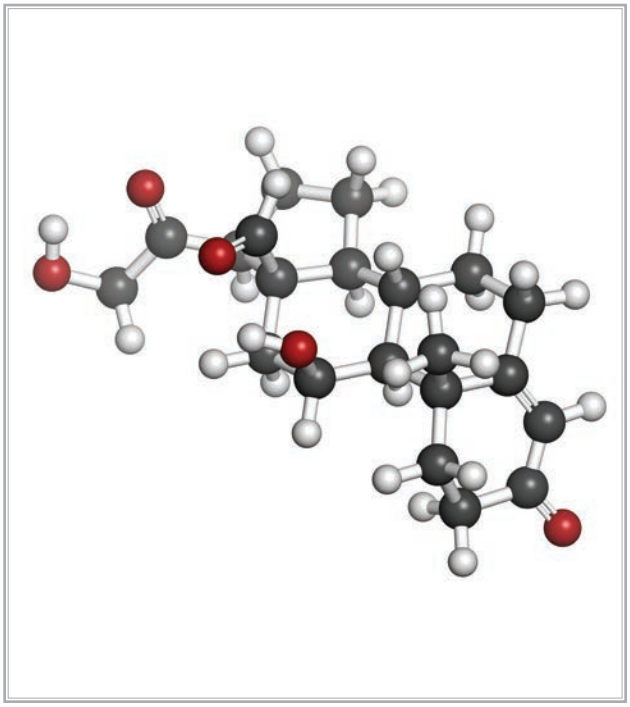
ACE Inhibitors

The ACE inhibitors are effective in reducing initial IHD events and are recommended for consideration in all patients after MI. They are proven to prevent and improve both heart failure (HF) and the progression of chronic kidney disease (CKD). When combined with thiazide diuretics, ACE inhibitors reduce the incidence of recurrent stroke. Major trials have addressed the use of ACE inhibitors in patients with IHD but without HF or known significant LV systolic impairment.

Angiotensin Receptor Blockers

Several angiotensin receptor inhibitors (ARBs) have been shown to reduce the incidence or severity of IHD events, the progression of renal disease in type 2 diabetes mellitus, and cerebrovascular events. ARBs are often considered to be an alternative therapy in individuals with cardiovascular disease who are intolerant of ACE inhibitors.





Aldosterone Antagonists

The aldosterone antagonists spironolactone and eplerenone lower BP alone or when added to other antihypertensive agents and have a protective effects in patients with chronic and advanced HF, in patients with LV dysfunction after MI, and in patients with chronic HF and mild symptoms.

Calcium Channel Blockers

CCBs form a heterogeneous class of agents that lower BP but have differing effects on cardiac conduction and myocardial contractility.

Direct Renin Inhibitors

The direct renin inhibitor aliskiren lowers BP alone or when added to other antihypertensive agents but has not been shown to have protective effects in patients with CVD, including HF.

Management of Hypertension in Patients with CAD and Stable Angina[7,19,20,26]

ß-*Blockers*

ß-Blockers are the drugs of first choice for the treatment of hypertension in patients with CAD that causes angina. They alleviate ischemia and angina primarily as a function of their negative inotropic and chronotropic actions. The decreased heart rate increases diastolic filling time for coronary perfusion. ß-Blockers also inhibit renin release from the juxtaglomerular apparatus. Cardioselective (ß1) agents without intrinsic sympathomimetic activity are used most frequently. Relative contraindications to their use include significant sinus or atrioventricular node dysfunction, hypotension, decompensated HF, and severe bronchospastic lung disease.

Peripheral artery disease (PAD) is rarely made symptomatically worse by the use of these agents, and mild bronchospastic disease is not an absolute contraindication. Caution is needed when brittle diabetic patients with a history of hypoglycemic events are treated because ß-blockers may mask the symptoms of hypoglycemia.

Calcium Channel Blockers

As a class, CCBs reduce myocardial oxygen demand by decreasing peripheral vascular resistance and lowering BP and increase myocardial oxygen supply by coronary vasodilation. CCBs or long-acting nitrates should be prescribed for the relief of symptoms when ß-blockers are contraindicated or cause unacceptable side effects in patients with stable angina. CCBs are added to, or substituted for, ß-blockers when BP remains elevated, when angina persists, or when drug side effects or contraindications mandate. Long-acting dihydropyridine agents are preferred over nondihydropyridines (diltiazem or verapamil) for use in combination with ß-blockers to avoid excessive bradycardia or heart block.

ACE Inhibitors

ACE inhibitors should be prescribed to all CAD patients with swtable angina who also have hypertension, diabetes mellitus, an LV ejection fraction ≤40%, or CKD unless contraindicated.

Angiotensin Receptor Blockers

ARBs are recommended for all patients with stable angina who also have hypertension, diabetes mel-

litus, LV ejection fraction ≤40%, or CKD and have indications for, but are intolerant of, ACE inhibitors. ARBs are indicated during hospitalization and at discharge for STEMI patients who are intolerant of ACE inhibitors and have HF or an ejection fraction <0.40. The combination of ACE inhibitors and ARBs has been used for the treatment of advanced or persistent HF in the convalescent or chronic phase after STEMI.

Diuretics

Thiazide diuretics and thiazide-like diuretics reduce cardiovascular events. It is a reasonable assumption that diuretics are as effective in the secondary as in the primary prevention of cardiovascular events.

Nitrates

Long-acting nitrates or CCBs can be prescribed for the relief of symptoms when ß-blockers are contraindicated or cause unacceptable side effects in patients with stable angina. Long-acting nitrates or CCBs in combination with ß-blockers should be prescribed for relief of symptoms when initial therapy with ß-blockers is unsuccessful in patients with stable angina. Nitrates should not be used with phosphodiesterase inhibitors of the sildenafil type. Hypertension does not affect the use of long-acting nitrates for the prevention of angina or of sublingual nitrate preparations for relief of an anginal attack. Conversely, nitrates have generally not been shown to be of use in the management of hypertension.

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Dyslipidemia

Current Perceptions and Practices in Lipid Management: Results of a European Society of Cardiology/ European Atherosclerosis Society Survey[1,2]

1. Koskinas KC, Catapano AL, Baigent C, Tokgozoglu L, Mach F. Current perceptions and practices in lipid management: results of a European Society of Cardiology/European Atherosclerosis Society Survey. Eur J Prev Cardiol. 2021 Jan 18:zwaa156.
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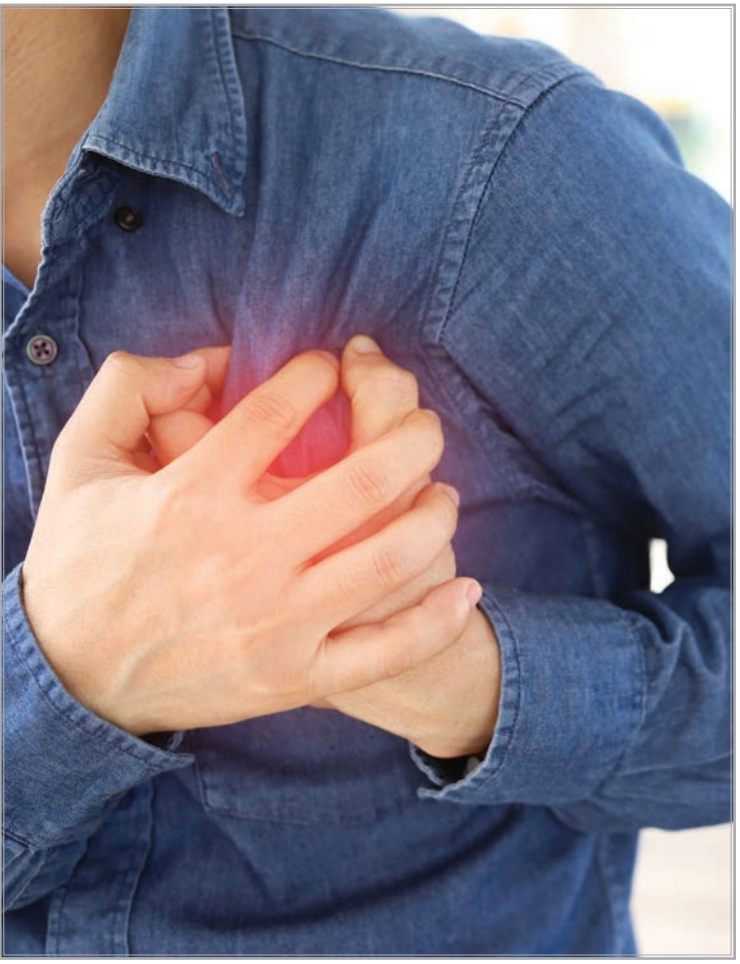
Koskinas et al sought to evaluate physicians' opinions and practices in lipid management by using a web-based survey by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). The survey was distributed to 70 696 individuals at two time points, before and after publication of the 2019 ESC/EAS dyslipidemia guidelines.[1]

Respondents (1271 in the first and 1056 in the second part) were most commonly cardiologists in Europe. More than 90% of participants reported that they regularly measure lipid levels and discuss lipid-lowering treatment with patients. More than 87% found the use of LDL-C goals useful or potentially useful, although it was acknowledged that recommended goals are frequently not achieved. Regarding the LDL-C goal according to the 2019 guidelines (<1.4 mmol/L for very high-risk patients), more than 70% of respondents felt that it is based on solid scientific evidence, but 31% noted that implementation should also consider available local resources and patient preferences. Statin intolerance was perceived as infrequent, affecting 1-5% of patients

according to most respondents but was the main reason for not prescribing a statin to secondary-prevention patients, followed by patient non-adherence. Although most respondents reported that 11-20% of secondary-prevention patients have an indication to add a non-statin medication, fewer patients (<10% according to most respondents) receive these medications.[1]



The 2019 the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Clinical Practice Guidelines on the Management of Dyslipidemias included updated material on LDL goals in high and very high-risk patients and showed increased focus on combination therapy.[2]

LDL goals in high and very high-risk patients

- Low-density lipoprotein (LDL) cholesterol levels should be lowered as much as possible to prevent cardiovascular disease, especially in high and very high-risk patients. It is recommended that very high-risk patients (in both primary and secondary prevention) should achieve both a goal LDL-C level of <55 mg/dL or <1.4 mmol/L **and** at least 50% reduction from baseline LDL-C levels. In high-risk patients, the LDL-C goal is <70 mg/dL or <1.8 mmol/L **and** at least 50% reduction from baseline LDL-C levels. These goals reinforce the view that the lower the LDL-C level, the better for prevention of CV outcomes in these very high-risk patients.[2]
- New to the guidelines is recognition that ACS patients are at very high risk of recurrent events. If patients experience a second vascular event within 2 years (not necessarily of the same type as the first event) on maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[2]

Increased focus on combination therapy

With recommendation of these new lower LDL-C goals in very high risk and high-risk patients, the ESC/EAS guidelines group have emphasised the importance of combination treatment, first with ezetimibe and then a PCSK9 inhibitor to achieve these targets. In patients with ACS, adding a PCSK9 inhibitor early after the event (if possible, during hospitalisation) should be considered. In these patients, if the LDL-C goal is not achieved after 4 - 6 weeks despite maximally tolerated statin therapy and ezetimibe, a PCSK9 inhibitor is recommended.[2]

The authors showed that the current ESC/EAS guidelines recommended LDL-C treatment goals enjoy a high level of acceptance. As reasons for suboptimal lipid-lowering therapy patient-related factors were mainly reported. This however, does not exclude physician inertia to intensify treatment as an additional contributing factor.[1]

Benefits of Statins in Elderly Subjects Without Established Cardiovascular Disease[3]

Savarese G, Gotto AM Jr, Paolillo S, D'Amore C, Losco T, Musella F, Scala O, Marciano C, Ruggiero D, Marsico F, De Luca G, Trimarco B, Perrone-Filardi P. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. J Am Coll Cardiol. 2013 Dec 3;62(22):2090-9.

Prevention of CV disease in the elderly is of increased importance, due to the population aging because of which, a large and increasing number of CV events (more than two-thirds) occur in elderly (age ≥65 years) subjects. In elderly patients with previous CV events, the use of statins is recommended by guidelines, whereas the benefits of these drugs in elderly subjects without previous CV events are still debated. Thus, Saravese et al designed a meta-analysis to assess whether statins reduce all-cause mortality and cardiovascular (CV) events in elderly people without established CV disease.

> In elderly subjects at high CV risk and without established CV disease, statins substantially reduce the incidence of MI and stroke in a short-term follow-up, with a favorable, albeit nonsignificant, trend for reduction in mortality.

The investigators included randomized trials comparing statins versus placebo and reporting all-cause and CV mortality, myocardial infarction (MI), stroke, and new cancer onset in elderly subjects (age ≥ 65 years) without established CV disease were included.

Eight trials enrolling 24,674 subjects (42.7% females; mean age 73.0 ± 2.9 years; mean follow up 3.5 ± 1.5 years) were included in analyses. Statins, compared with placebo, significantly reduced the risk of MI by 39.4% (relative risk [RR]: 0.606 [95% confidence interval (CI): 0.434 to 0.847]; p= 0.003) and the risk of stroke by 23.8% (RR: 0.762 [95% CI: 0.626 to 0.926]; p= 0.006). In contrast, the risk of all-cause death (RR: 0.941 [95% CI: 0.856 to 1.035]; p= 0.210) and of CV death (RR: 0.907 [95% CI: 0.686 to 1.199]; p= 0.493) were not significantly reduced. New cancer onset did not differ between statin- and placebo-treated subjects (RR: 0.989 [95% CI: 0.851 to 1.151]; p= 0.890).

In conclusion, the findings of this meta-analysis indicate that statins reduce the risk of MI and stroke in elderly subjects without established CV disease in a short-term follow-up, with a nonsignificant favorable trend toward reduction of mortality.

Defining the Place of Ezetimibe/Atorvastatin in the Management of Hyperlipidemia[4]

Ferreira AM, Marques da Silva P. Defining the Place of Ezetimibe/Atorvastatin in the Management of Hyperlipidemia. Am J Cardiovasc Drugs. 2017 Jun;17(3):169-181

Even though statins are unquestionably the mainstay of the pharmacological treatment of hypercho-

lesterolemia. However, even with the most effective agents, up to 40% of patients do not achieve desirable LDL-C levels because of:

- variability in individual response to statin therapy
- side effects of statins
- inability of some patients to attain desirable low-density lipoprotein cholesterol (ldl-c) levels (or percent ldl-c reductions) with statin monotherapy

Statin-ezetimibe combinations are a realistic treatment option for patients who do not achieve low-density lipoprotein cholesterol (LDL-C) targets while receiving statin monotherapy and for patients prone to dose-dependent statin side effects.

The IMPROVE-IT trial was the first to demonstrate a reduction in cardiovascular events with ezetimibe

Recently, combination therapy with atorvastatin plus ezetimibe was also associated with greater coronary plaque regression than atorvastatin alone.

Statin-ezetimibe combinations are a potentially advantageous therapeutic option for high-risk patients who need additional lowering of low-density lipoprotein cholesterol (LDL-C).

These combinations may overcome some of the limitations of statin monotherapy by blocking both sources of cholesterol.

A fixed-dose combination with atorvastatin, one of the most extensively studied statins, was approved and launched in several countries, including the USA. Depending on atorvastatin dose, this combination provides LDL-C reductions of 50-60%, triglyceride reductions of 30-40%, and high-density lipoprotein cholesterol (HDL-C) increases of 5-9%. In the EZ-PATH study adding ezetimibe to atorvastatin 40 mg/day resulted in significantly greater reductions in LDL-C and significantly more pts achieving LDL-C<70 mg/dl.

Studies comparing the lipid-lowering efficacy of the atorvastatin-ezetimibe combination with the alternatives of statin dose titration or switching to a more potent statin, consistently showed that combination therapy provided greater LDL-C reduction, translating into a greater proportion of patients achieving lipid goals. Simvastatin-ezetimibe combinations have been shown to reduce the incidence of major atherosclerotic events in several clinical settings to a magnitude that seems similar to that observed with statins for the same degree of absolute LDL-C lowering. The atorvastatin-ezetimibe combination has also been shown to induce the regression of coronary atherosclerosis measured by intravascular ultrasound in a significantly greater proportion of patients than atorvastatin alone.

Atorvastatin-ezetimibe combinations are generally well tolerated. Previous concerns of a possible increase in the incidence of cancer with ezetimibe were dismissed in large trials with long follow-up periods. In this paper, the authors examine the rationale for an atorvastatin-ezetimibe combination, review the evidence supporting it, and discuss its potential role in the management of dyslipidemia. In any case, the IMPROVE-IT trial results and the availability of an atorvastatin–ezetimibe combination are certainly welcome, since they extend the number of potential therapies we have to offer our patients as options to prevent cardiovascular events.

Statin Associated Lower Cancer Risk and Related Mortality in Patients with Heart Failure[5]

Ren QW, Yu SY, Teng TK, Li X, Cheung KS, Wu MZ, Li HL, Wong PF, Tse HF, Lam CSP, Yiu KH. Statin associated lower cancer risk and related mortality in patients with heart failure. Eur Heart J. 2021 Jun 22:ehab325

Ren et al identified 87,102 patients with incident heart failure between 2003 and 2015. Of these, 64% were 75 years and older, 48% were men, and 51% had hypertension. Over one-third of patients (35%) had coronary artery disease.

In total, 36,176 patients used statins while 50,926 were statin nonusers.

Over a median follow-up period of 4.1 years (404,924 person-years), 12.7% of patients were diagnosed with cancer, and 4.4% of patients had cancer-related mortality. The most common types of cancers were colorectal, stomach, lung, and liver/biliary system.

Median age at cancer diagnosis was 79.7 years, with a median time to diagnosis from the heart failure index date of 3.8 years. Propensity-matched statin users had a lower risk of developing cancer, with a 5-year cumulative cancer incidence of 7.9% among those who used statins, and a 10.4% rate among nonusers. The 10-year cumulative incidence rates were 11.2% and 13.2% among statin users and nonusers, respectively.

The 10-year cancer mortality was 3.8% and 5.2% in statin users and nonusers. Statin use was significantly associated with a lower adjusted risk of cancer-related death compared with nonusers (subdistribution hazard ratio [SHR], 0.74; 95% CI, 0.67-0.81). The 10-year all-cause mortality was 60.5% and 78.8% among statin users and nonusers, and the use of statins was significantly associated with a lower adjusted all-cause mortality risk (hazard ratio [HR], 0.62; 95% CI, 0.61-0.64).

Crude 10-year cumulative cancer incidence among statin users with atherosclerotic disease did not differ; absolute risk difference was 0.07%. Corresponding incidence among lipid control groups was 10.3%, 10.5%, and 10.8% in low-density lipoprotein (LDL) <1.8, 1.8 to 2.6, and >2.6 mmol/L. Following multivariable adjustment, cancer incidence in statin users was not related to statin indication or time-weighted LDL control.

The inverse relationship between statin use and cancer risk was duration dependent; risk of cancer was significantly lower with statin use of 4 to 6 years (adjusted SHR, 0.82) and was lowered further with long-term statin use of more than 6 years (adjusted SHR, 0.78).

Similar results demonstrating duration response were found in the association between statin use and cancer-related death. The risk of cancer-related death was significantly lower in statin use from 4 to 6 years and 6 or more years (adjusted SHR, 0.67 and 0.61) vs with short-term statin use.

Sensitivity analysis results were consistent after the exclusion of patients with a history of alcohol abuse or smoking. Cox regression HR for cancer risk was 0.83.

Study limitations include a lack of data on familial cancer history as a risk factor, no data on left ventricular ejection fraction, and potential residual confounders.

This study demonstrated that incident cancer was not uncommon [and] notably, statin use was associated with a reduced risk of cancer and cancer-related mortality. The findings have major clinical implications to reduce the associated burden in HF. The potential protective effect of statin on the development of cancer merits evaluation in future randomized studies.

Evaluating the Efficacy and Safety of Atorvastatin + Ezetimibe in a Fixed-Dose Combination for the Treatment of Hypercholesterolemia[6]

Ma YB, Chan P, Zhang Y, Tomlinson B, Liu Z. Evaluating the efficacy and safety of atorvastatin + ezetimibe in a fixed-dose combination for the treatment of hypercholesterolemia. Expert Opin Pharmacother. 2019 Jun;20(8):917-928.

Cardiovascular disease is a major cause of morbidity and mortality throughout the world and hypercholesterolemia is one of the key risk factors. Statins are the first line treatment to reduce atherogenic lipids and there is substantial and robust evidence with atorvastatin for reduction of cardiovascular events and mortality. Ezetimibe can be combined with any dose of atorvastatin for incremental lipid-lowering effects.

In this review, the authors summarized the pharmacokinetics, pharmacodynamics and clinical efficacy of the components and the combination of ezetimibe and atorvastatin. Clinical benefits have

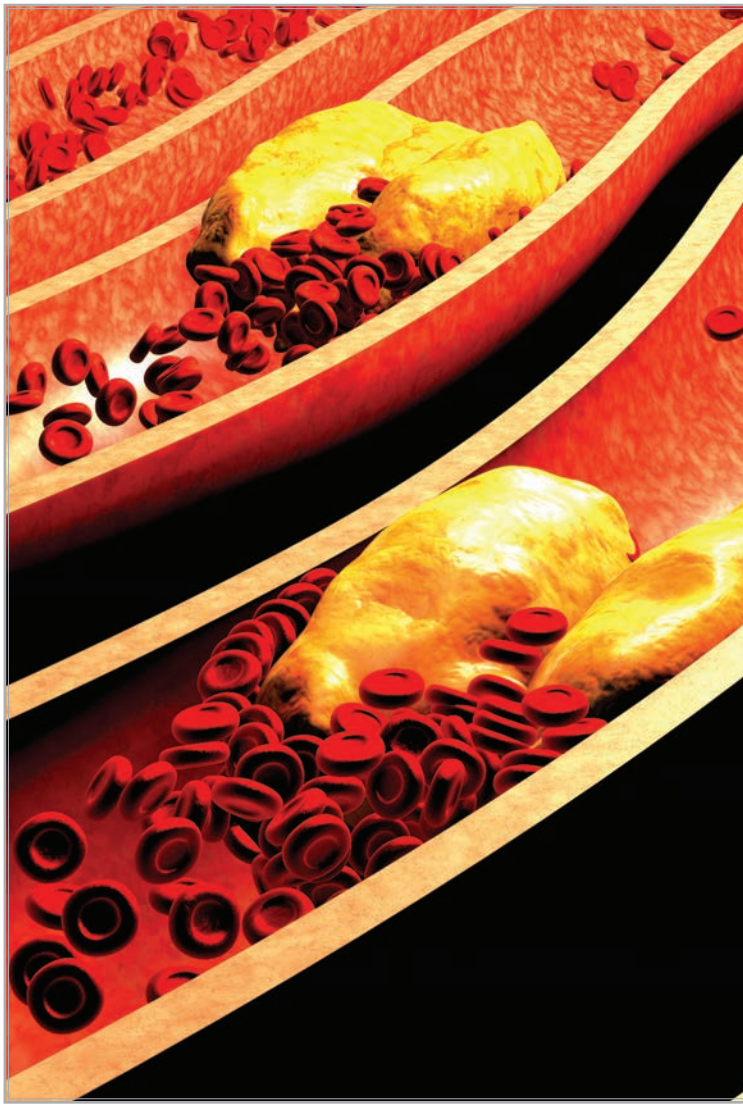
been seen with ezetimibe combined with simvastatin but studies of its combination with atorvastatin are generally limited to the effects on lipid parameters where the addition of ezetimibe to atorvastatin is generally more effective than titrating the atorvastatin dose. Although there are no cardiovascular outcomes studies with the combination of ezetimibe and atorvastatin, the greater reduction in atherogenic lipids can be assumed to have greater benefits in reducing cardiovascular events. The ezetimibe-atorvastatin combination is very effective in this respect and well tolerated. Fixed-dose combinations improve medication adherence and this combination should be useful for patients who cannot reach their lipid targets with maximally tolerated statin doses.

Rosuvastatin Corrects Oxidative Stress and Inflammation Induced by LPS to Attenuate Cardiac Injury by Inhibiting the NLRP3/TLR4 Pathway[7]

Source: Ren G, Zhou Q, Lu M, Wang H. Rosuvastatin corrects oxidative stress and inflammation induced by LPS to attenuate cardiac injury by inhibiting the NLRP3/TLR4 pathway. Can J Physiol Pharmacol. 2021 Feb 27.

The aim of this study was to evaluate whether rosuvastatin was effective in attenuating cardiac injury in lipopolysaccharide(LPS)-challenged mice and H9C2 cells and identify the underlying mechanisms, focusing on the NLRP3/TLR4 pathway. Cardiac injury, cardiac function, apoptosis, oxidative stress, inflammatory response and the NLRP3/TLR4 pathway were evaluated in both in vivo and in vitro studies. LPS-induced cardiomyocytes injury was markedly attenuated by rosuvastatin treatment. Apoptosis was clearly ameliorated in myocardial tissue and H9C2 cells cotreated with rosuvastatin. In addition, excessive oxidative stress was present, as indicated by increases in MDA content, NADPH activity and ROS production and decreased SOD activity after LPS challenge. Rosuvastatin improved all the indicators of oxidative stress, with a similar effect to NAC (ROS scavenger). Notably, LPS-exposed H9C2 cells and mice showed significant NLRP3 and TLR4/NF-κB pathway activation. Administration of rosuvastatin reduced the increases in expression of NLRP3, ASC, pro-caspase-1, TLR4, and p65 and decreased the contents of TNF-α, IL-1ß, IL-18 and IL-6, with a similar effect as MCC950 (NLRP3 inhibitor).

In conclusion, inhibition of the inflammatory response and oxidative stress contributes to cardioprotection of rosuvastatin on cardiac injury induced by LPS, and the effect of rosuvastatin was achieved by inactivation of the NF-κB/NLRP3 pathway.



Anti-Inflammatory Effects of Rosuvastatin Treatment on Coronary Artery Ectasia Patients of Different Age Groups[8]

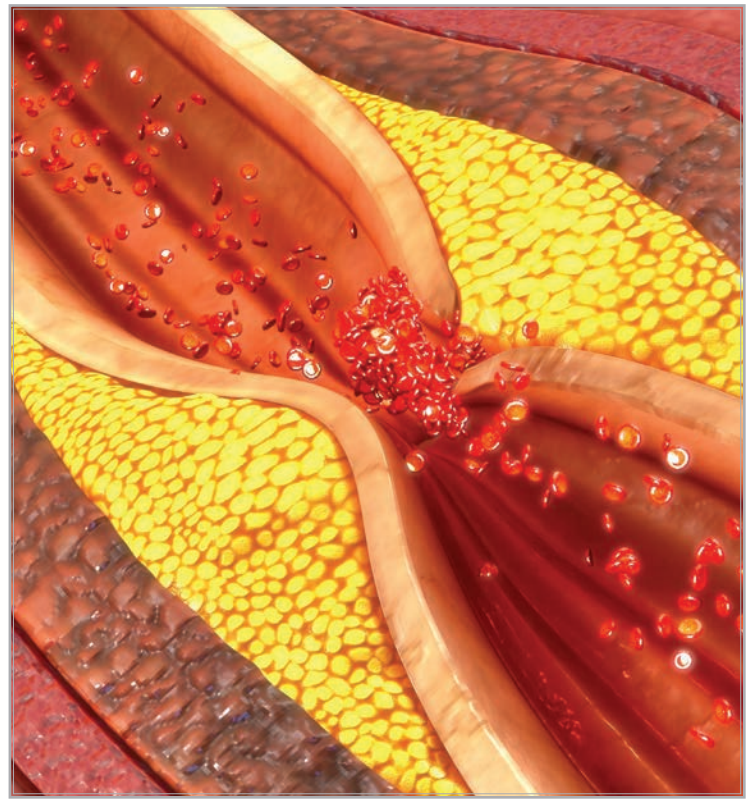
Source: Fan CH, Hao Y, Liu YH, Li XL, Huang ZH, Luo Y, Li RL. Anti-inflammatory effects of rosuvastatin treatment on coronary artery ectasia patients of different age groups. BMC Cardiovasc Disord. 2020 Jul 11;20(1):330.

Coronary artery ectasia (CAE) is an angiographic finding of abnormal coronary dilatation. Inflammation plays a major role in all phases of atherosclerosis.

Potential risk factors for CAE include an imbalance between matrix metalloproteinases (MMPs) and tissue inhibitor metalloproteinases (TIMPs), angiotensin-converting enzyme genotypes, a lower HDL cholesterol level, a higher low-density lipoprotein (LDL)/HDL ratio, elevated homocysteine levels, cocaine usage, smoking, vascular trauma, and diabetes. Conventionally, CAE has been considered a variant of coronary atherosclerosis and an important clinical complication in interventional cardiology with increased thrombogenic potential of the ectatic arteries. CAE is closely related to myocardial infarction. However, there are currently no standard treatment guidelines specified for CAE. Anti-inflammatory and endothelium-protective effects of rosuvastatin have been suggested to improve the symptoms in patients with coronary artery disease. Rosuvastatin is a selective hydroxy methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor widely used for coronary atherosclerotic heart disease. The liver is the main target organ of rosuvastatin, wherein it lowers cholesterol levels and increases the number of LDL receptors on the surface of liver cells, thereby improving lipid metabolism by promoting LDL absorption and inhibiting hepatic synthesis of very-low-density lipoprotein (VLDL). Statin therapy can exert pleiotropic effects in atherosclerotic processes, such as regulating inflammatory responses, endothelial function, and thrombus formation based on the reduction in LDL-C levels. Rosuvastatin can also stabilize or reverse atherosclerotic plaques by suppressing MMP expression and protecting the vascular endothelium against inflammation. However, there is no conclusive evidence of therapeutic efficacy or optimal timepoint for rosuvastatin therapy in CAE patients in different age groups.

Fan et al investigated the relationship between CAE and serum high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) levels to test our hypothesis that patient age is associated with the efficacy of anti-inflammatory therapy for CAE.

The authors conducted a prospective analysis of 217 patients with CAE treated at the Department of Cardiology, Shanghai East Hospital, Ji'an Campus and the Baoshan People's Hospital, from January 1, 2015 to July 30, 2019. Baseline data of patients, including sex; age; and history of hypertension, hyperlipidemia, and diabetes, were collected from patient medical records. Study participants were grouped by age as follows: CAE-A (n = 60, age ≤ 50 years), CAE-B (n = 83, 50 years <age ≤ 70 years), and CAE-C (n = 74, age > 70). Additionally, there was a control (NC) group (n = 73) with normal coronary arteries.



All patients received oral rosuvastatin therapy (10 mg, QN quaque nocte) when they were diagnosed with CAE and maintained good follow-up, with a loss rate of 0.0% at the end of the 6-month follow-up. The NC group received regular symptom-relieving treatments and rosuvastatin therapy. Of these four groups, the inflammatory markers, hs-CRP and IL-6, were significantly higher in patients with CAE than in the NCs ($p < 0.05$). Post-hoc tests showed that hs-CRP and Il-6 levels had significant differences between the CAE-A and CAE-C groups ($p= 0.048$, $p= 0.025$). Logistic regression analysis showed that hs-CRP (OR = 1.782, 95% CI: 1.124-2.014, $p= 0.021$) and IL-6 (OR = 1.584, 95% CI: 1.112-1.986, $p= 0.030$) were independent predictors of CAE. The inflammatory markers were higher in the CAE-A group than in the CAE-B group and higher in the CAE-B group than in the CAE-C group. Follow-up after 6 months of rosuvastatin therapy showed a significantly greater reduction in hs-CRP and IL-6 levels in the CAE-A group than in the CAE-B group, which again were greater in the CAE-B group than in the CAE-C group.

In this study, the efficacy of rosuvastatin in CAE patients in different age groups was investigated and compared. The findings may be explained by higher inflammatory marker levels in younger patients than in older patients; thus, the same dose of rosuvastatin could be more likely to produce a greater anti-inflammatory effect. Moreover, a smaller percentage of younger people had never taken rosuvastatin before. Older patients had a higher proportion of rosuvastatin history because of arteriosclerosis, hyperlipidemia, and stroke, among other health complications. Therefore, the lipid-lowering effect of rosuvastatin may be more potent, which boosts its anti-inflammatory effects in young patients. The Cholesterol Treatment Trialists' Collaboration reported that the efficacy of statin therapy was lower in older patients than in younger patients. Furthermore, younger individuals have a higher basal metabolism level with regard to lipid synthesis and degradation; therefore, younger CAE patients could be more sensitive to rosuvastatin treatment. After rosuvastatin treatment, hs-CRP and IL-6 levels of the CAE-A group were reduced to levels comparable to those of the NC group, while those of the CAE-C group were only partially reversed, indicating that the inflammatory status of younger CAE patients was more severe but reversible, while that of older CAE patients was comparatively mild, persistent, and irreversible.

In conclusion, younger CAE patients had higher inflammatory marker levels than older CAE patients. The greatest efficacy of anti-inflammatory treatment was found in younger CAE patients, suggesting that rosuvastatin should be prescribed at the time of CAE diagnosis, especially in younger patients.

2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults[9]

Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, Francis GA, Genest J, Grigoire J, Grover SA, Gupta M, Hegele RA, Lau D, Leiter LA, Leung AA, Lonn E, Mancini GBJ, Manjoo P, McPherson R, Ngui D, Pichı ME, Poirier P, Sievenpiper J, Stone J, Ward R, Wray W. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. Can J Cardiol. 2021 Mar 26:S0828-282X(21)00165-3.

The 2021 dyslipidemia guidelines provide updated recommendations based on important new evidence. The concept of lipid/lipoprotein treatment thresholds for intensifying lipid-lowering therapy with non-statin agents is introduced, and secondary prevention patients demonstrated to derive the largest benefit from intensification of therapy are identified. There are new recommendations for when to use non-HDL-C or ApoB be instead of LDL-C as the preferred lipid screening parameter, and for the role lipoprotein(a) to improve risk stratification and management.

The 2021 guidelines primary panel selected clinically relevant questions and produced updated recommendations, on the basis of important new findings that have emerged since the 2016 guide-

lines. In patients with clinical atherosclerosis, abdominal aortic aneurysm, most patients with diabetes or chronic kidney disease, and those with low-density lipoprotein cholesterol ≥ 5 mmol/L, statin therapy continues to be recommended. The panel introduced the concept of lipid/lipoprotein treatment thresholds for intensifying lipid-lowering therapy with nonstatin agents, and have identified the secondary prevention patients who have been shown to derive the largest benefit from intensification of therapy with these agents. For all other patients, the panel emphasize risk assessment linked to lipid/lipoprotein evaluation to optimize clinical decision-making. Lipoprotein(a) measurement is now recommended once in a patient's lifetime, as part of initial lipid screening to assess cardiovascular risk. For any patient with triglycerides > 1.5 mmol/L, either non-high-density lipoprotein cholesterol or apolipoprotein B are the preferred lipid parameter for screening, rather than low-density lipoprotein cholesterol. The panel provide updated recommendations regarding the role of coronary artery calcium scoring as a clinical decision tool to aid the decision to initiate statin therapy. There are new recommendations on the preventative care of women with hypertensive disorders of pregnancy. Health behaviour modification, including regular exercise and a heart-healthy diet, remain the cornerstone of cardiovascular disease prevention. These guidelines are intended to provide a platform for meaningful conversation and shared-decision making between patient and care provider, so that individual decisions can be made for risk screening, assessment, and treatment.

Primary Prevention

Statin-indicated conditions consist of all documented ASCVD conditions, as well as other high-risk primary prevention conditions in the absence of ASCVD, such as most patients with diabetes, those with chronic kidney disease, and those with an LDL-C ≥ 5.0 mmol/L. Screening should be repeated every 5 years for men and women aged 40-75 years using the modified FRS or Cardiovascular Life Expectancy Model (CLEM) to guide therapy to reduce major CV events. A risk assessment might also be completed whenever a patient's expected risk status changes.

Secondary Prevention Recommendations

- Use of high-intensity statin therapy in addition to appropriate health behaviour modifications for all secondary prevention CVD patients. For patients who do not tolerate a high-intensity statins, the maximally tolerated statin dose is recommended.
- Intensification of lipid-lowering therapy with a PCSK9 inhibitor (evolocumab or alirocumab)- with or without the additional use of ezetimibe- for secondary CV prevention patients shown to derive the largest benefit from PCSK9 inhibitor therapy in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) while receiving the maximally tolerated statin dose
- Intensification of lipid-lowering therapy with ezetimibe and/or PCSK9 inhibitor therapy for all secondary prevention CVD patients in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) while receiving the maximally tolerated statin dose.
- If ezetimibe is used initially and LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥0.7 g/L) PCSK9 inhibitor therapy is recommended.

Association of Blood Lipids, Atherosclerosis and Statin Use with Dementia and Cognitive Impairment after Stroke: A Systematic Review and Meta-Analysis[10]

Yang Z, Wang H, Edwards D, Ding C, Yan L, Brayne C, Mant J. Association of blood lipids, atherosclerosis and statin use with dementia and cognitive impairment after stroke: A systematic review and meta-analysis. Ageing Res Rev. 2020 Jan;57:100962.

Trial and observational evidence is conflicting in terms of the association of blood lipids, atherosclerosis and statin use with dementia and cognitive impairment in the general population. It is uncertain

whether the associations occur in stroke patients, who are at known higher risk of cognitive decline. This systematic review was to synthesize the evidence for these associations among stroke patients.

MEDLINE, EMBASE, the Cochrane Library and trial registries were searched. The authors included randomized controlled trials (RCTs) or observational cohort studies conducted among patients with stroke and reported on the association of blood lipids, atherosclerosis or statin use with dementia or cognitive impairment. Meta-analysis was conducted separately for crude and maximally adjusted odds ratios (ORs) and hazard ratios (HRs).

- Stroke patients are at known higher risk of cognitive decline.
- It is uncertain whether blood lipids, atherosclerosis and statin use are associated with dementia and cognitive impairment after stroke.
- This systematic review suggests that atherosclerosis may be an important risk factor for post-stroke dementia and cognitive impairment.
- Statins have a potential role in reducing the risk of post-stroke cognitive decline.

Of 18,026 records retrieved, 56 studies (one RCT and 55 cohort studies) comprising 38,423 stroke patients were included. For coronary heart disease, the pooled OR of dementia and cognitive impairment was 1.32 (95%CI 1.10-1.58, n = 15 studies, I^2 = 0%) and 1.23 (95%CI 0.99-1.54, n = 14, I^2 = 26.9%), respectively. Peripheral artery disease was associated with dementia (OR 3.59, 95%CI 1.47-8.76, n = 2, I^2 = 0%) and cognitive impairment (OR 2.70, 95%CI 1.09-6.69, n = 1). For carotid stenosis, the pooled OR of dementia and cognitive impairment was 2.67 (95%CI 0.83-8.62, n = 3, I^2 = 77.9%) and 3.34 (95%CI 0.79-14.1, n = 4, I^2 = 96.6%), respectively. For post-stroke statin use, the pooled OR of dementia and cognitive impairment was 0.89 (95%CI 0.65-1.21, n = 1) and 0.56 (95%CI 0.46-0.69, n = 3, I^2 = 0%), respectively. No association was observed for hypercholesterolemia. These results were mostly consistent with adjusted ORs or HRs, which were reported from limited evidence.

This review found some evidence of a link between atherosclerosis and dementia or cognitive impairment in people with stroke. Dementia and cognitive impairment are considered as potential consequences of atherosclerosis of extracranial or intracranial vessels, or as the independent but convergent disease processes of dementia and atherosclerosis sharing some major pathophysiological elements, such as cholesterol, inflammation and Apolipoprotein Ee4 (APOEe4) polymorphism. Alternatively, coronary heart disease and carotid stenosis may have direct causal links to cognitive impairment. Stroke patients with coronary heart disease are more likely to experience cardiac dysfunction, which has potentially detrimental effects on brain health. Embolization and hypoperfusion are considered as the main potential mechanisms of cognitive impairment in carotid stenosis. In line with the association between atherosclerosis and cognitive impairment, the authors observed that post-stroke statin use was associated with a lower risk of cognitive impairment, with a larger potential effect of higher dose and longer duration of statin use on post-stroke dementia prevention. On the other hand, they found a lack of association of blood lipids with post-stroke dementia or cognitive impairment.

In conclusion, atherosclerosis was associated with an increased risk of post-stroke dementia. Post-stroke statin use was associated with decreased risk of cognitive impairment. To confirm whether or not statins confer advantages in the post-stroke population in terms of preventing cognitive decline over and above their known effectiveness in reducing risk of further vascular events, further stroke trials including cognitive assessment and observational analyses adjusted for key confounders, focusing on key subgroups or statin use patterns are required.

Hypertension

Fixed-Combination Olmesartan/ Amlodipine Was Superior to Perindopril + Amlodipine in Reducing Central Systolic Blood Pressure in Hypertensive Patients with Diabetes[11]

Ruilope LM; SEVITENSION Study Investigators. Fixed-Combination Olmesartan/Amlodipine Was Superior to Perindopril + Amlodipine in Reducing Central Systolic Blood Pressure in Hypertensive Patients With Diabetes. J Clin Hypertens (Greenwich). 2016 Jun;18(6):528-35. doi: 10.1111/jch.12673. Epub 2015 Sep 23. PMID: 26395174.

RAS inhibitors have been found to be effective in preventing CV complications in diabetic patients. Because of the increased risk of CV events in hypertensive patients with diabetes, it is important to assess the effects of dual RAS-calcium channel blockade on arterial stiffness in these patients. The aim of this post hoc analysis from the Sevikar Compared to the Combination of Perindopril Plus Amlodipine on Central Arterial Blood Pressure in Patients With Moderate-to-Severe Hypertension (SEVITENSION) study was to assess the efficacy and tolerability of olmesartan (OLM) and amlodipine (AML) in reducing central systolic blood pressure (CSBP) compared with perindopril (PER) plus AML in hypertensive patients with type 2 diabetes.

Current treatment guidelines point out that the beneficial effects of RAS blockers on renal function make it reasonable to use an ACE inhibitor or an ARB in the management of hypertensive patients with diabetes.

Patients were randomized to OLM/AML 40/10 mg or PER/AML 8/10 mg for 24 weeks. The primary efficacy endpoint was the absolute change in CSBP from baseline to week 24, which was greater with OLM/AML (-13.72±1.14 mm Hg) compared with

PER/AML (-10.21±1.11 mm Hg). The between-group difference was -3.51±1.60 mm Hg (95% confidence interval, -6.66 to -0.36 mm Hg) and was within the noninferiority margin (2 mm Hg) as well as the superiority margin (0 mm Hg). In addition, OLM/AML was associated with a higher proportion of patients achieving blood pressure normalization. In hypertensive patients with diabetes, the fixed-dose combination of OLM/AML was superior to PER/AML in reducing CSBP, as well as other secondary endpoints.

This study shows that for hypertensive patients with diabetes, who have inadequately controlled BP on AML monotherapy, the dual combination of OLM/AML was noninferior and indeed superior to PER/AML in reducing CSBP. In addition, the noninferiority of OLM/AML to PER/AML was observed in a number of hemodynamic variables and in the proportion of patients with normalized BP.

The results from this subgroup analysis found that OLM/AML was noninferior to PER/AML in reducing CSBP in a subgroup of hypertensive patients with diabetes. Moreover, OLM/AML was found to have superior BP-lowering effects compared with PER/AML.

At the time of final examination, a higher proportion of patients treated with OLM/AML had normalized BP according to both the 2007 wESH/ESC guidelines for the management of arterial hypertension and the 2009 ESH guidelines reappraisal, compared with PER/AML.

Both treatments were well tolerated and diabetic patients showed no signs of having an additional risk for TEAE compared with the general population. Furthermore, OLM/AML was associated with a lower incidence of cough compared with PER/AML and a clinically relevant lower rate of discontinuations.

This analysis shows that a single-pill fixed-dose combination of OLM/AML 40/10 mg was associated with significant BP-lowering effects and demonstrates the importance of this type of dual-combination therapy in the treatment of higher-risk hypertensive patients with diabetes.

Management of Hypertension with a Fixed-Dose (Single-Pill) Combination of Bisoprolol and Amlodipine[12]

Gottwald-Hostalek U, Sun N, Barho C, Hildemann S. Management of Hypertension With a Fixed-Dose (Single-Pill) Combination of Bisoprolol and Amlodipine. Clin Pharmacol Drug Dev. 2017 Jan;6(1):9-18.

Hypertension is currently one of the greatest global health care challenges. Although many effective drugs are available, combinations of 2 or more medications are often required to meet clinical targets. Combination therapy has several advantages over monotherapy: lower doses of each drug can be used to achieve therapeutic goals; lower doses may lead to fewer adverse events, facilitating patient adherence; and using multiple drugs with different modes of action may be more effective in treating multifactorial diseases, including hypertension. Adherence is an important consideration when requiring patients to self-administer multiple medications; as the number of concurrent medications increases, patient adherence tends to decrease. Recent evidence suggests that fixed-dose combinations (FDCs) may be more effective than free-dose combinations, as they provide all necessary medications in a single convenient tablet/single-pill combination. Among combinations of hypertension medications, a ß-blocker such as bisoprolol with a

calcium channel blocker such as amlodipine is an effective combination therapy for hypertension, with distinct and complimentary modes of action. With advantages over free-dose combinations, the FDC of bisoprolol/amlodipine is thus an effective and convenient treatment for hypertension, allowing more patients to achieve their therapeutic goals, while potentially reducing the burden of hypertension on health care systems.

Benefits of a Fixed-Dose Combination of Bisoprolol and Amlodipine in the Treatment of Hypertension in Daily Practice: Results of More than 4000 Patients[13]

Czarnecka D, Koch EM, Gottwald-Hostalek U. Benefits of a fixed-dose combination of bisoprolol and amlodipine in the treatment of hypertension in daily practice: results of more than 4000 patients. Curr Med Res Opin. 2015 May;31(5):875-81.

Clinical trial results show that a very large proportion of patients receiving antihypertensive treatment from primary care physicians do not achieve the recommended BP levels. Many patients require more than one antihypertensive drug for successful BP control in a regimen encompassing different pharmacologic mechanisms of action.

A combination of a beta-blocker such as bisoprolol with a calcium channel blocker such as amlodipine is an established option for successful drug treatment of patients with high BP.

The study objective was assessing patient adherence to a fixed-dose combination (FDC) of bisoprolol and amlodipine in daily practice in patients who had been switched from the free to the fixed-dose combination prior to recruitment.

The non-investigational study was carried out in Poland. Patients over 18 years of age with essential hypertension were recruited if they had already been switched from a free combination to the FDC at least 4 weeks prior to recruitment. Exclusion criteria included pregnancy, lactation, any contraindication to the FDC, and other antihypertensive treatment. Adherence was measured by tablet count (tablets taken divided by tablets prescribed, times 100) and defined as follows: excellent >90%, good 76-90%, moderate 51-75%, bad ≤50%. Other patient data, clinical findings and laboratory values were recorded upon availability at study start, after 3 months (voluntary) and after 6 months.

Data of 4288 patients (mean age: 59 years; gender: 50% each) were documented. The average daily doses of the FDC were 5.8 mg bisoprolol and 6.4 mg amlodipine. These doses differ only slightly from those of the free combination. After 3 months' treatment with the FDC, a dose increase was carried out in 113 patients for bisoprolol and in 126 for amlodipine. After 6 months of FDC treatment, 82% of the participants of the study showed excellent adherence and for a further 15% the adherence could be considered good. This strong adherence may have led to the observed reduction in systolic and diastolic blood pressure of 11% (Cohen's D efficient size 1.23). In addition, pulse pressure decreased from 58.8 mm to 52.2 mm. Also in diabetic patients (21% of the cohort), further reduction of systolic blood pressure values could be achieved (mean before 150 mm, after 133), wherein the initial differences compared to patients without diabetes had disappeared. The pulse rate also changed from 75 b/min to 68 b/min under the FDC.

The results of this study demonstrate that systematic adherence with treatment instructions contributes to a clinically relevant improvement in BP control in these patients too. The high acceptance of the FDC by the patient was also shown by the fact that 97% of patients preferred the FDC over the free combination at study end.

These study results suggest that high adherence rates under a FDC of bisoprolol and amlodipine may lead to better BP control and, thus, to risk reduction for cardiovascular events. The implementation of an observational study with such a high number of patients provides a wide range of information for daily practice and enables us to draw conclusions about the relationships between the drug's effect and additional factors

Final Report of a Trial of Intensive versus Standard Blood-Pressure Control[14]

Source: SPRINT Research Group, Lewis CE, Fine LJ, Beddhu S, Cheung AK, Cushman WC, Cutler JA, Evans GW, Johnson KC, Kitzman DW, Oparil S, Rahman M, Reboussin DM, Rocco MV, Sink KM, Snyder JK, Whelton PK, Williamson JD, Wright JT Jr, Ambrosius WT. Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2021 May 20;384(20):1921-1930.

Targeting a systolic blood pressure of less than 120 mm Hg in patients at increased cardiovascular risk resulted in fewer major adverse cardiovascular events and lower all-cause mortality than a target of less than 140 mm Hg, according to the final report of a major study.

The Systolic Blood Pressure Intervention Trial (SPRINT) randomly assigned 9,361 participants at increased risk for cardiovascular disease but did not have diabetes or previous stroke to an intensive treatment target of systolic blood pressure less than 120 mm Hg or a standard treatment target of less than 140 mm Hg. The primary outcome was a composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes. The final report considered additional primary outcome events occurring through the end of the intervention period of Aug. 20, 2015, as well as analyzed post-trial observational follow-up data through July 29, 2016. Results appeared in this study, May 20 at the New England Journal of Medicine.

At a median of 3.33 years of follow-up, the intensive group had a lower rate of both the primary outcome (1.77% per year vs. 2.40% per year; hazard ratio [HR], 0.73; 95% CI, 0.63 to 0.86) and all-cause mortality (1.06% per year vs. 1.41% per year; HR, 0.75; 95% CI, 0.61 to 0.92). Serious adverse events of hypotension, electrolyte abnormalities, acute kidney injury or failure, and syncope were significantly more frequent in the intensive-treatment group than the standard group. When trial and post-trial follow-up data were combined (3.88 years in total), similar patterns were found for treatment benefit and adverse events. However, rates of heart failure no longer differed between the groups.

During a post-trial observational period, the achieved blood-pressure differential between the treatment groups was attenuated, and more frequent heart failure was noted in the intensive-treatment group. The updated findings from the intervention period in our trial confirm the significant benefits of intensive blood-pressure control for the primary composite outcome, the components of the primary outcome (myocardial infarction, heart failure, and death from cardiovascular causes), a post hoc composite outcome that excluded heart failure, and all-cause mortality.

Among patients who were at increased cardiovascular risk, targeting a systolic blood pressure of less than 120 mm Hg resulted in lower rates of major adverse cardiovascular events and lower all-cause mortality than targeting a systolic blood pressure of less than 140 mm Hg, both during receipt of the randomly assigned therapy and after the trial. Rates of some adverse events were higher in the intensive-treatment group.

In this final report of the main outcomes of the SPRINT trial, involving patients at increased risk for cardiovascular events, intensive treatment to lower blood pressure was associated with lower rates of fatal and nonfatal cardiovascular events and death from any cause than standard treatment.

However, some adverse events occurred more frequently with the lower blood-pressure target. During a post-trial observational period, the achieved blood-pressure differential between the treatment groups was attenuated, and more frequent heart failure was noted in the intensive-treatment group.

Myocardial Strain in Hypertension: A Meta-Analysis of Two-Dimensional Speckle Tracking Echocardiographic Studies[15]

Source: Tadic M, Sala C, Carugo S, Mancia G, Grassi G, Cuspidi C. Myocardial strain in hypertension: a meta-analysis of two-dimensional speckle tracking echocardiographic studies. J Hypertens. 2021 May 28. doi: 10.1097/HJH.0000000000002898. Epub ahead of print. PMID: 34054054.

Available evidence on systolic dysfunction in systemic hypertension, as assessed by left ventricular (LV) mechanics, is still based on single studies. The role of myocardial strain and GLS as a new, more sensitive marker of cardiac organ damage in hypertension is currently supported by several single studies. Given the importance of this topic we have performed an updated meta-analysis aimed at providing comprehensive information on systolic function, as assessed by GLS, in systemic hypertension.

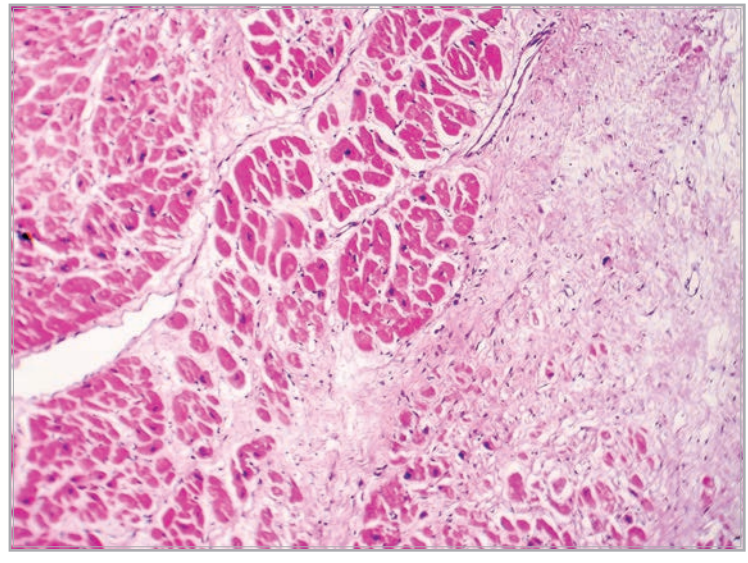
Thus, Tadic et al performed a systematic meta-analysis of two-dimensional speckle-tracking studies in order to provide an updated comprehensive information on this issue.

The PubMed, OVID-MEDLINE, and Cochrane library databases were analyzed to search English language articles published from the inception up to 31 December 2020. Studies were identified by using MeSH terms and crossing the following search items: 'myocardial strain', 'left ventricular mechanics', 'speckle tracking echocardiography', 'systolic dysfunction', 'hypertensive heart disease', 'systemic hypertension', 'essential hypertension'.

Data from 4276 individuals (2089 normotensive controls and 2187 mostly uncomplicated hypertensive patients) were included. Left ventricular (LV) mass index, relative wall thickness, left atrial volume index and E/e' ratio were significantly higher in hypertensive patients than in normotensive controls. LV ejection fraction did not differ in the two pooled groups (SMD -0.048 ± 0.054, 95% CI -0.20 to 0.10, p= 0.30), whereas LV global longitudinal strain (GLS) was significantly impaired in the hypertensive group (SMD: 1.07 ± 0.15, 95% CI 0.77-1.36, $p < 0.0001$). Similar findings were obtained in a sub-analysis restricted to 15 studies in which mean age was similar in cases and controls (SMD 1.21 ± 0.23, 95% CI 0.76-1.67, p= 0.002).

The results showed that GLS was significantly lower in hypertensive patients than in normotensive controls and this was the case even when the confounding effect of age was removed by comparing age-matched patients. Compared with controls, hypertensive patients also had significantly higher LVMI, RWT, LAVI, and E/e' ratio. This showed that LV structural and functional remodeling, mainly diastolic dysfunction, occurred together with GLS changes.

Even though average GLS among hypertensive patients was reduced in comparison to normotensive controls, GLS still remained in the normal range or in a grey zone, depending on the normal values proposed from the different guidelines - greater than -18% or greater than -20%, respectively.



In conclusion, this meta-analysis suggests that GLS assessment unmasks systolic dysfunction undetected by conventional ejection fraction in the uncomplicated hypertension setting and that this parameter should be incorporated into routine work-up aimed to identify hypertension-mediated cardiac damage.

Is Hypertensive Left Ventricular Hypertrophy a Cause of Sustained Ventricular Arrhythmias in Humans?[16]

Nadarajah R, Patel PA, Tayebjee MH. Is hypertensive left ventricular hypertrophy a cause of sustained ventricular arrhythmias in humans? J Hum Hypertens. 2021 Jun;35(6):492-498. doi: 10.1038/s41371-021-00503-w. Epub 2021 Mar 5. PMID: 33674703; PMCID: PMC8208890.

Sudden cardiac death (SCD) is most commonly secondary to sustained ventricular arrhythmias (VAs). This review aimed to evaluate if left ventricular hypertrophy (LVH) secondary to systemic hypertension in humans is an isolated risk factor for ventricular arrhythmogenesis. Animal models of hypertensive LVH have shown changes in ion channel function and distribution, gap junction re-distribution and fibrotic deposition.

The aim of this review was to assess whether systemic hypertension in combination with LVH is an independent risk factor for VAs in those without established CAD. Nadarajah et al hypothesized that hypertensive heart disease on its own does not contribute to the risk of VAs or SCD. The authors therefore reviewed the published literature on hypertension and VAs and critically appraised the data to determine whether hypertensive LVH on its own causes VAs.

Clinical data has consistently exhibited an increase in prevalence and complexity of non-sustained VAs on electrocardiographic monitoring. However, there is a dearth of trials suggesting progression to sustained VAs and SCD, with extrapolations being confounded by presence of co-existent asymptomatic coronary artery disease (CAD). Putatively, this lack of data may be due to the presence of more homogenous distribution of pathophysiological changes seen in those with hypertensive LVH versus known pro-arrhythmic conditions such as HCM and myocardial infarction.

The pathophysiological changes found in animal models of hypertensive LVH, including cellular changes (ion channels) and abnormalities in inter-cellular conduction (fibrosis and gap junction re-distribution), provide a putative basis for ventricular arrhythmogenesis in this population. Clinical data in humans has shown an increased prevalence and complexity of VAs in hypertensive LVH patients but there is a lack of confirmatory trial data suggestive of progression to sustained VAs that can cause SCD. This may be due to the more homogenous distribution of pathophysiological changes seen in hypertensive LVH when compared with known pro-arrhythmic disorders such as HCM and myocardial infarction where there is myocardial disarray and/or fibrosis.

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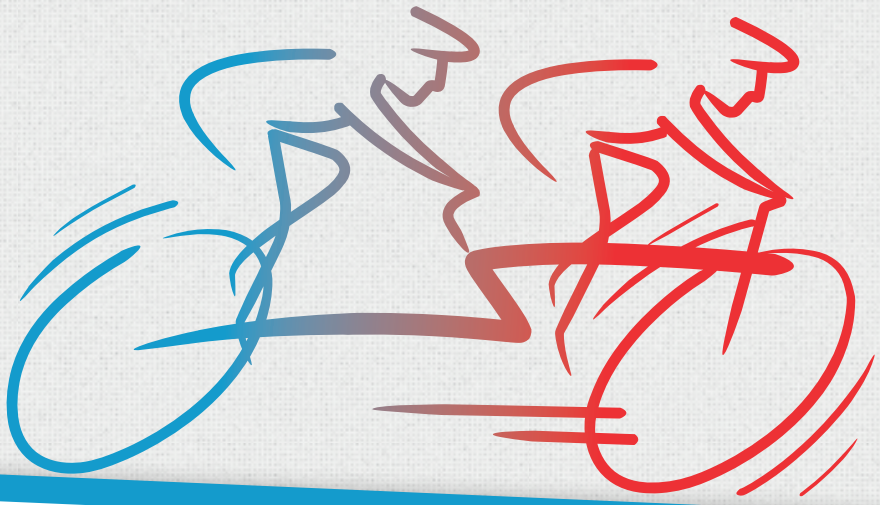
AMODUO

bisoprolol fumarate + amlodipine



Bisoprolol/amlodipine
5mg *10mg*

Bisoprolol/Amlodipine
10mg *5mg*

Bisoprolol/Amlodipine
5mg *5mg*

Bisoprolol/Amlodipine
10mg *10mg*

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