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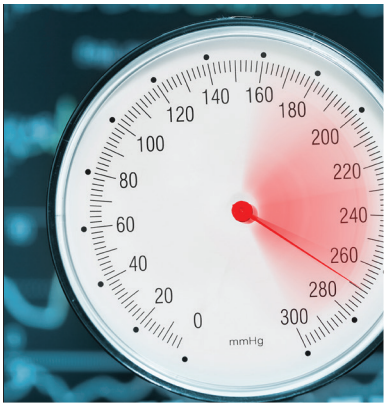
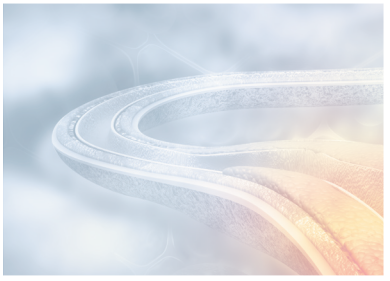
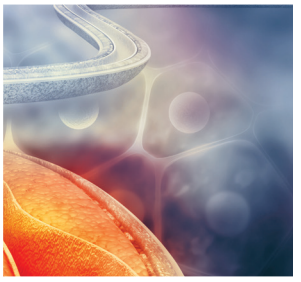


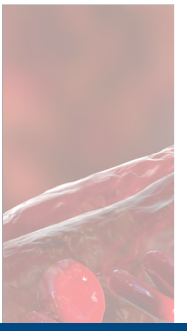


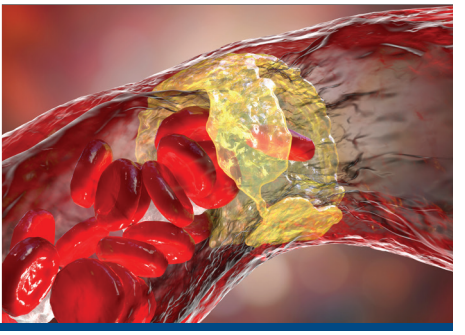


Hypertensive Crisis

Hypercholesterolemia

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.
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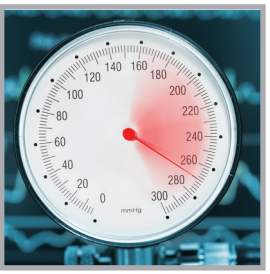


Feature Article

Dyslipidemia

Hypertension

Hypertensive Crisis

Introduction

The term *hypertensive crisis* generally is inclusive of two different diagnoses, *hypertensive emergency* (HE) and *hypertensive urgency*. Distinguishing between the two is important because they require different intensities of therapy. It should be noted that older and less specific terminology, such as "malignant hypertension" and "accelerated hypertension," should no longer be used. The important thing to remember is that there is no absolute value of BP that separates the two syndromes. Instead, the most important distinction is whether there is evidence of impending or progressive end-organ damage, which defines an emergency, or other symptoms that are felt referable to the BP.[1]

Definitions

Current hypertension Guidelines have suggested to replace the term "hypertensive crisis" with 'hypertensive emergencies' or 'hypertensive urgencies'. Both the European Society of Hypertension and the American Society of Hypertension have defined a 'hypertensive emergency' as a condition characterized by an acute and severe elevation of BP associated to a new onset or worsening organ damage (OD). The degree of BP elevation suggested by these Guidelines for the definition of hypertensive emergencies is > 180 mmHg for systolic (SBP) or 120 mmHg for diastolic BP (DBP), respectively.[2]

Hypertensive urgency and hypertensive emergency should be distinguished from a hypertensive pseudocrisis, which is characterized by a transient elevation of the blood pressure during painful or emotional events, such as headache, rotational dizziness, anxiety, or panic syndrome. The treatment of a hypertensive urgency consists of a gradual reduction of blood pressure using oral medication, whereas in a hypertensive emergency, intravenous therapy is

indicated for a faster reduction in blood pressure. As to hypertensive pseudocrisis, the treatment is focused on symptoms, and the subject is little explored in the literature on hypertensive crisis.[3]

Presentation

A *hypertensive emergency* is an acute, marked elevation in blood pressure (usually significantly >99th percentile for age and gender) that is associated with signs of target-organ damage. These can include pulmonary edema, cardiac ischemia, neurologic deficits, acute renal failure, aortic dissection, and eclampsia. This activity reviews the cause and pathophysiology of hypertensive emergency and highlights the role of the interprofessional team in its management.[3,4]

Typical presentations include severe headache, shortness of breath, epistaxis, faintness, or severe anxiety. Clinical syndromes typically associated with HE include hypertensive encephalopathy, intracerebral hemorrhage, acute myocardial infarction (MI), acute heart failure, pulmonary edema, unstable angina, dissecting aortic aneurysm, or preeclampsia/eclampsia. In hypertensive emergencies presentations, there is evidence of impending or progressive target organ dysfunction and that the absolute value of the BP is not pathognomonic.[1]

- (1) Most commonly secondary to renal disease, catecholamine-producing tumors, endocrine syndromes, toxidromes, medication withdrawal, or elevated intracranial pressure (ICP).[5]
- (2) Presents with encephalopathy (e.g., headaches, vomiting, seizures, altered mental status), vision disturbance, congestive heart failure (e.g., dyspnea, peripheral edema, gallop rhythm), and acute kidney injury.[5]

Epidemiology and Clinical Profile

In a recent large multicenter Italian study, 4.6/1,000 cases—out of 333,407 patients—consecutively admitted to emergency department were diagnosed with hypertensive crises (n = 1,546). Out of 1,546 hypertensive cases, 25.3% of them (n = 391) being reported as hypertensive emergencies. Interestingly, 23% of the emergencies occurred in patients with unknown HTN (27.9% among men and 18.5% among women). Regarding symptoms, the majority (55.6%) of the hypertensive crisis patients reported non-specific symptoms like headache without neurological deficit, dizziness, vomits, palpitations, etc., even among emergency cases (49.3%). Moreover, heart-related symptoms (dyspnea, chest pain, arrhythmias, and syncope) were the less common symptoms in hypertensive crises (28.3%). Regarding hypertensive emergencies, the majority (30.9%) of the patients had acute pulmonary edema, 22% had stroke, and 17.9% had myocardial infarction. Less frequent diagnoses were acute aortic dissection (7.9%), acute renal failure, and hypertensive encephalopathy (4.9%). Also, patients with hypertensive emergencies had 34% higher odds of being male and 28% less odds of having non-specific symptoms compared with patients with hypertensive urgencies.[6,7]

Etiology

Hypertensive emergencies and urgencies can develop *de novo* in normotensive individuals, or can complicate underlying primary or secondary hypertension. In some hypertensive emergencies, an underlying condition is the clear cause of acute BP elevation. In acute glomerulonephritis, renal crisis in patients with systemic sclerosis, or renal artery stenosis, severe BP elevations are evoked through increased activity of the renin-angiotensin system (RAS). In pheochromocytoma, cocaine intoxication, or spinal cord injury, acutely elevated BP is the result of excess catecholamine release. In other patients, acute sustained elevations in BP itself are the etiologic factor, resulting in conditions such as hypertensive encephalopathy or severe hypertension with acute left ventricular failure and pulmonary edema. In some cases, however, it may be difficult to differentiate whether BP elevation is the cause or the result of a hypertensive emergency.[8]

Hypertensive Emergencies

Various inciting events can cause hypertensive emergencies. The majority of hypertensive emer-

gencies occur in patients already diagnosed with chronic hypertension. Noncompliance with antihypertensive medications and use of sympathomimetics are two of the more common causes. These lead to a rapid rise in blood pressure beyond the body's innate autoregulation capacity.[4]

Hypertensive Urgencies

The etiology of acute elevations is variable. Noncompliance with antihypertensive therapy, use of sympathomimetics, and thyroid dysfunction are among the many possible causes of hypertensive urgencies. Even anxiety and pain may cause acute elevations in blood pressure and require a different treatment strategy.[5]

Pseudohypertension, a falsely elevated blood pressure reading due to sclerotic or calcified arteries that do not collapse during inflation of a blood pressure cuff, is another possible cause of elevated blood pressure readings. Pseudohypertension should be considered in patients presenting without symptoms suggestive of end-organ dysfunction but with markedly elevated blood pressure despite seemingly aggressive management.[5,9]

Pathophysiology

The precise pathophysiology of the hypertensive crisis remains unclear. However, two different but interrelated mechanisms may play a central role in the pathophysiology of the hypertensive crisis. The first is the failure in autoregulatory mechanism in the vascular bed. The autoregulation system is a key factor in the pathophysiology of HTN and hypertensive crisis. Autoregulation is defined as the ability of the organs (brain, heart, and kidneys) to maintain a stable blood flow irrespective of alterations of perfusion pressure. If the perfusion pressure drops, the corresponding blood flow decreases temporarily, but it returns to normal values after the next few minutes. In case of autoregulation malfunction, if the perfusion pressure drops, this leads to decrease in blood flow and an increase in vascular resistance. In hypertensive crisis, there is a lack of autoregulation in vascular bed and blood flow and so an abrupt increase of BP and systemic vascular resistance can occur, which often leads to mechanical stress and endothelial injury.[6,10]

The second mechanism is the activation of renin–angiotensin system, leading to further vasoconstriction and thus generating a vicious cycle of continuous injury and subsequently ischemia, Besides these mechanisms, a prothrombotic state may play a key role in hypertensive crisis; a recent, albeit small, study showed that sP-selectin was significantly higher in patients with hypertensive crisis compared with normotensive controls regardless of the presence of retinopathy, which suggests that platelet activation is a relatively early finding in the pathophysiologic sequelae of hypertensive crisis.[12] (Figure1).

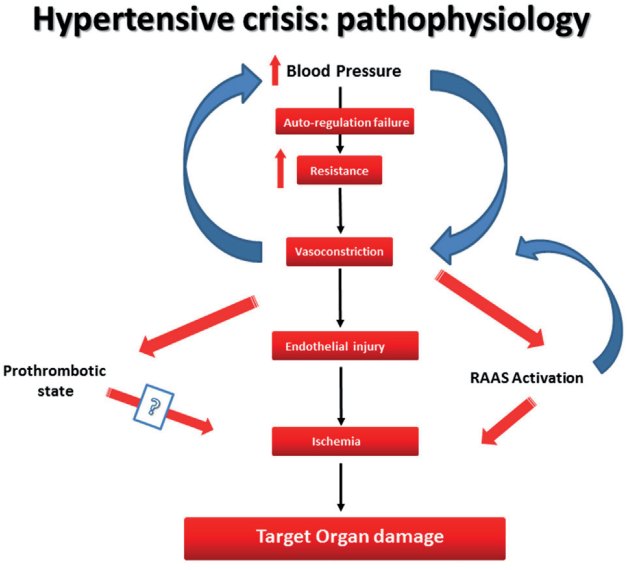


Figure 1: The pathophysiology of hypertensive crisis. (From Ref 6: Varounis C, et al. Front Cardiovasc Med. 2017)

Risk Factors for Hypertensive Crisis

Comorbid cardiac, renal, and cerebral comorbidities (coronary artery disease, congestive heart failure, cerebrovascular disease, and chronic kidney disease) increase the risk of hypertensive crisis. The risk of hypertensive crisis is higher in patients with unhealthy alcohol and recreational drug use. Systolic and diastolic blood pressure are marginally higher in patients with hypertensive emergency compared to patients with hypertensive urgency.

Since these differences are small and not clinically significant, clinicians should rely on other symptoms and signs to differentiate between hypertensive urgency and hypertensive emergency. The risk of hypertensive emergency is higher in older adults. The co-existence of diabetes, hyperlipidemia, and chronic kidney disease increases the risk of hypertensive emergency.[13]

Diagnostic Evaluation

The primary goal of the diagnostic process is to differentiate a true hypertensive emergency from a hypertensive urgency, because of the different therapeutic approaches. The second goal is rapid assessment of the type and severity of ongoing target organ damage. In some hypertensive emergencies, the history (e.g., acute head trauma, preeclampsia, scleroderma) or overt symptoms and signs (e.g., chest/back pain, dyspnea, throbbing abdominal mass) may guide the diagnosis; whereas in other cases (e.g., severe hypertension with altered mental status), the evaluation must be more comprehensive.[6]

The diagnostic approach begins with the patient's history, with attention to duration, severity, and treatment of preexisting hypertension and associated conditions. BP measurements should be performed in both arms (if possible, in both sitting and standing positions) and a leg. A careful examination and assessment of cardiac, pulmonary, peripheral vascular, and neurologic systems with assessment of mental status should follow, along with a thorough funduscopic (ophthalmoscopic) examination for hemorrhages, exudates, and papilledema.[6]

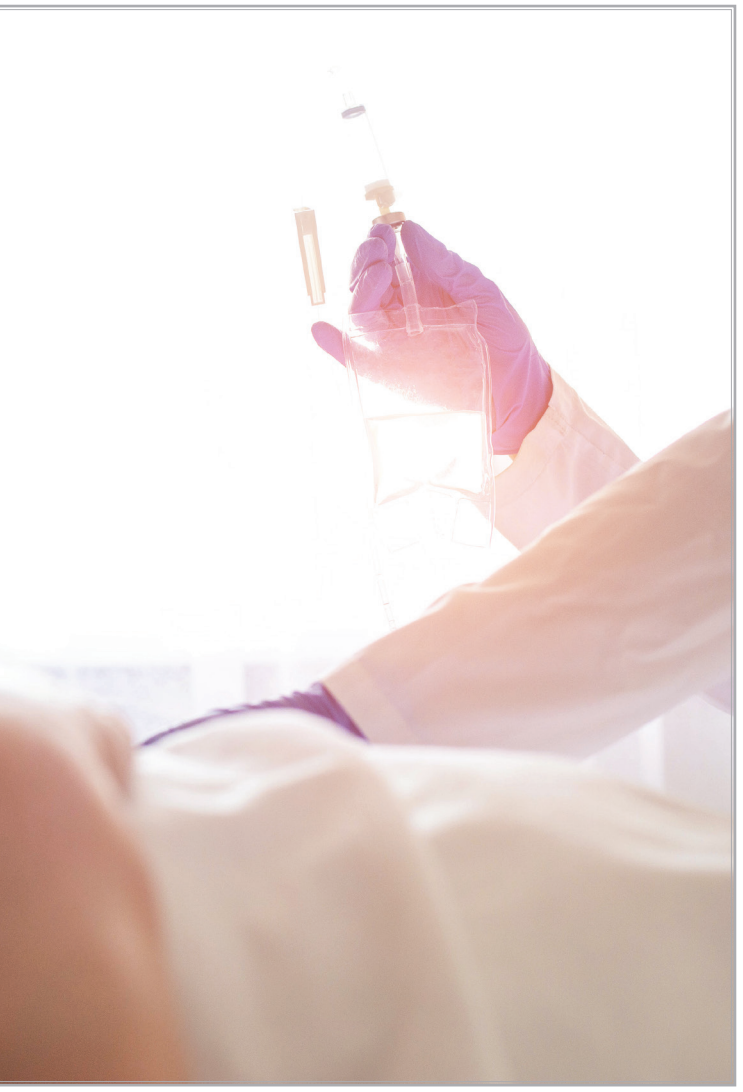
The expected exam findings vary depending on the specific target organ most affected. With cardiac dysfunction, rales may be heard on lung auscultation, jugular venous distention or peripheral edema may be noted, and extra heart sounds may be apparent. In the event of a very rapid onset of hypertension, often seen with sympathomimetic abuse, marked dyspnea in the absence of peripheral edema due to flash pulmonary edema may be encountered.[3]

Neurologic dysfunction may result in altered mental status, blurry vision, ataxia or other cerebellar dysfunction, aphasia, or unilateral numbness or weakness. A careful neurologic exam that includes a cranial nerve exam, strength, and sensation testing, as well as cerebellar tests and gait testing should be done. The eye exam may reveal papilledema as well as exudates and flame-shaped hemorrhages.[3] Signs of heart failure such as elevated jugular venous distention, rales on lung auscultation, or a gallop on heart auscultation indicate that the patient may be actively experiencing a hypertensive emergency rather than urgency. A detailed neurologic exam including cerebellar testing is also important to rule out central nervous system impairment. Finally, fundoscopy showing papilledema may be a significant finding mandating more aggressive therapy.[4] Acute renal failure may also result in signs of pulmonary edema or peripheral edema.[3]

Laboratory and Ancillary Data

The evaluation for hypertensive emergencies also depends on the symptoms and signs present. Once

it is determined that a true hypertensive emergency is present or likely, labs such as metabolic panels, urinalysis, B-natriuretic peptide, and cardiac enzymes may be useful. An electrocardiogram (ECG) is recommended in any patient suspected of having cardiac ischemia. If there are any focal neurologic findings, a computed tomography (CT) scan of the brain should be performed. A chest x-ray may prove to be useful in patients with shortness of breath. A chest x-ray may also show widening of the mediastinum in the setting or aortic dissection, but this is a relatively insensitive marker, and CT angiography of the chest and abdomen should be obtained to rule out or confirm a dissection and to determine the extent of the intimal tear.[1,3,14]



Cardiac Manifestations of Hypertensive Emergencies

Cardiac manifestations of HE include acute coronary syndromes, acute cardiogenic pulmonary edema, and aortic dissection. The latter deserves special attention because it has much higher short-term morbidity and mortality, requires more urgent and rapid reduction in BP, and also requires specific inhibition of the reflex tachycardia often associated with BP-lowering agents. It is recommended that patients with aortic dissection have their systolic BP (SBP) reduced to at least 120 mm Hg within 20 minutes, a much more rapid decrease than is recommended for other syndromes associated with HE.[1]

Central Nervous System Manifestations of Hypertensive Emergencies

Neurologic emergencies associated with HE include subarachnoid hemorrhage, cerebral infarction, intraparenchymal hemorrhage, and hypertensive encephalopathy. Patients with hemorrhage and infarction usually have focal neurologic findings and may have corresponding findings on head CT or magnetic resonance imaging (MRI) of the brain. Hypertensive encephalopathy is more difficult to diagnose; symptoms may include severe headache, vomiting, drowsiness, confusion, visual disturbances, and seizures; coma may ensue. Papilledema is often present on physical examination.[1]

Renal Manifestations of Hypertensive Emergencies

Renal failure can both cause and be caused by HE. Hypertensive renal failure typically presents as nonoliguric renal failure, often with hematuria.[1]

Pregnancy-Related Issues with Hypertensive Emergency

Preeclampsia is a syndrome that includes hypertension, peripheral edema, and proteinuria in women after the 20th week of gestation. Eclampsia is the

more severe form of the syndrome, with severe hypertension, edema, proteinuria, and seizures. Unlike other forms of acute hypertension, intravenous magnesium is a key component of BP management in eclampsia.[1]

Management

Although therapy with parenteral antihypertensive agents may be initiated in the ED, patients with a hypertensive emergency should be admitted to an ICU for continuous BP monitoring, clinical surveillance, and continued parenteral administration of an appropriate agent. Specific BP levels do not determine the severity and the emergency of the situation because the autoregulatory structural and functional changes may vary among individuals, such that some may develop target organ damage at lower BP.[15]

- a. Rule out increased intracranial pressure before instituting antihypertensive treatment given critical need to maintain cerebral perfusion.[4]
- b. Goal is to reduce BP by ≤ **25%** in the **first 8 hours,** then gradual normalization over the next **24 to 48 hours.**[4]

While the specific target organ that is affected may dictate some specifics of treatment, rapid lowering of blood pressure is the mainstay of therapy for hypertensive emergencies. The goal would be to lower the mean arterial pressure by 20% to 25% within the first 1 to 2 hours. Several agents can be used, but the unifying characteristics are that they are rapidly acting and easily titratable. For this reason, oral medications, such as clonidine and nifedipine, play no role in the immediate management of a hypertensive emergency. Intravenous vasoactive drips such as labetalol, esmolol, nicardipine, and nitroglycerin are typically effective options.[3,16]

The key feature about management is that if there is no evidence of organ damage, then the blood pressure reduction should be gradual over a few days. On the other hand, severe hypertension in pregnancy demands immediate treatment. Female patients who become pregnant should be prescribed nifedipine, methyldopa or labetalol during pregnancy; these women should not be treated with ACE inhibitors or ARBs. During the acute event, IV hydralazine or oral nifedipine can be used to lower blood pressure.[3]

Current Guidelines

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommendations for hypertensive crises and emergencies include the following:[17]

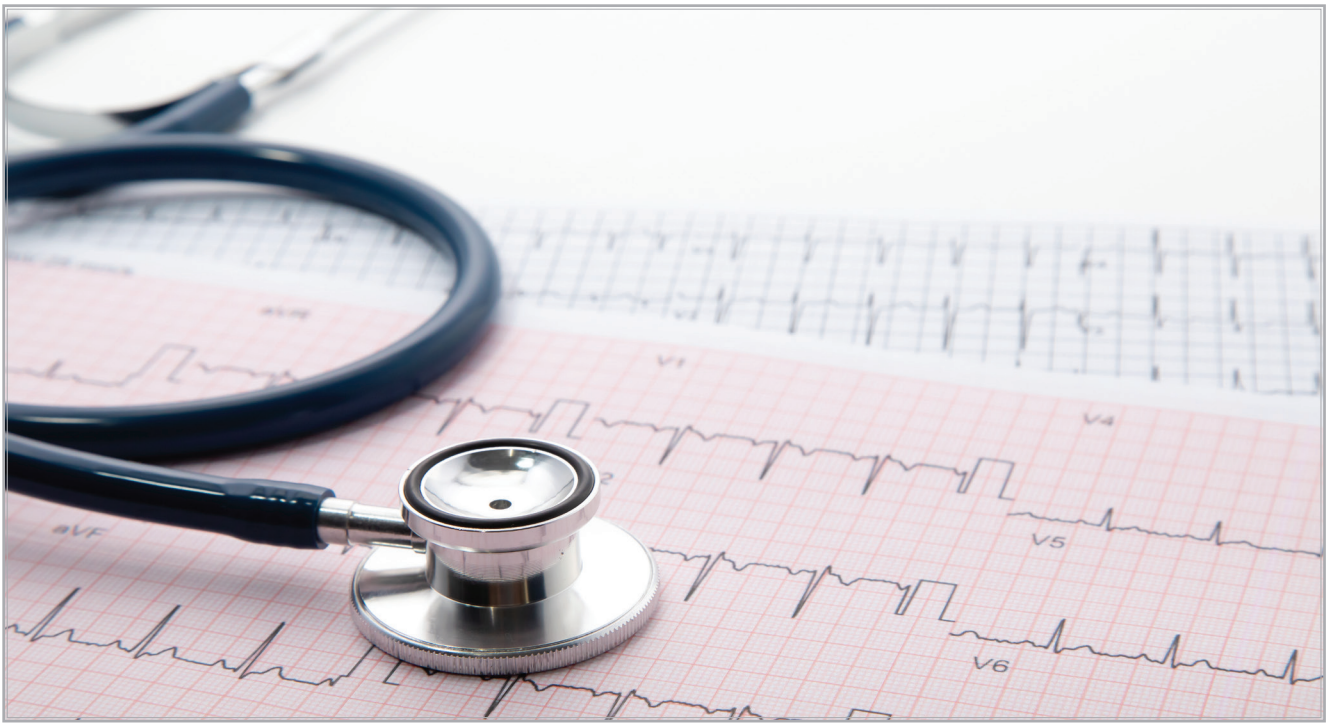
- Admit adults with a hypertensive emergency to an ICU for continuous monitoring of BP and target organ damage, as well as for parenteral administration of an appropriate medication.
- For adults with a compelling condition (ie, aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis), lower SBP to below 140 mm Hg during the first hour and to below 120 mm Hg in aortic dissection.

- For adults without a compelling condition, reduce the SBP to a maximum of 25% within the first hour; then, if the patient is clinically stable, lower the BP to 160/100 -110 mm Hg over the next 2-6 hours, and then cautiously to normal over the following 24-48 hours.

The treatment for hypertensive urgency is to ensure better long-term blood pressure control.[18] Emphasizing the need for compliance with medications and close primary care follow up is paramount. Patients without symptoms or signs of target organ damage have not been shown to benefit from aggressive antihypertensive therapy in the acute setting. Rapid lowering of blood pressure in these patients offers no benefit and carries the theoretical risk of causing relative hypotension and end-organ hypoperfusion, especially in those individuals who have longstanding severely elevated blood pressure. However, it may be beneficial to start these patients on oral antihypertensives with the goal of lowering the blood pressure slowly over 24 to 48 hours. Little data directly address what specific agent is ideal in this situation. More importantly, close follow-up within a week with a primary care provider should be scheduled to ensure improved blood pressure control and to initiate or titrate medications as needed.

Conclusions

- **A hypertensive emergency is hypertension that causes target-organ damage; it requires intravenous therapy and hospitalization.**
- **Target-organ damage includes hypertensive encephalopathy, preeclampsia and eclampsia, acute left ventricular failure with pulmonary edema, myocardial ischemia, acute aortic dissection, and renal failure.**
- **Do ECG, urinalysis, serum blood urea nitrogen and creatinine measurement, and head CT for patients with neurologic symptoms or signs.**
- **Reduce mean arterial pressure by about 20 to 25% over the first hour using a short-acting, titratable IV drug such as clevidipine, nitroglycerin, fenoldopam, nicardipine, or labetalol.**
- **It is not necessary to achieve "normal" blood pressure urgently (especially true in acute stroke).**



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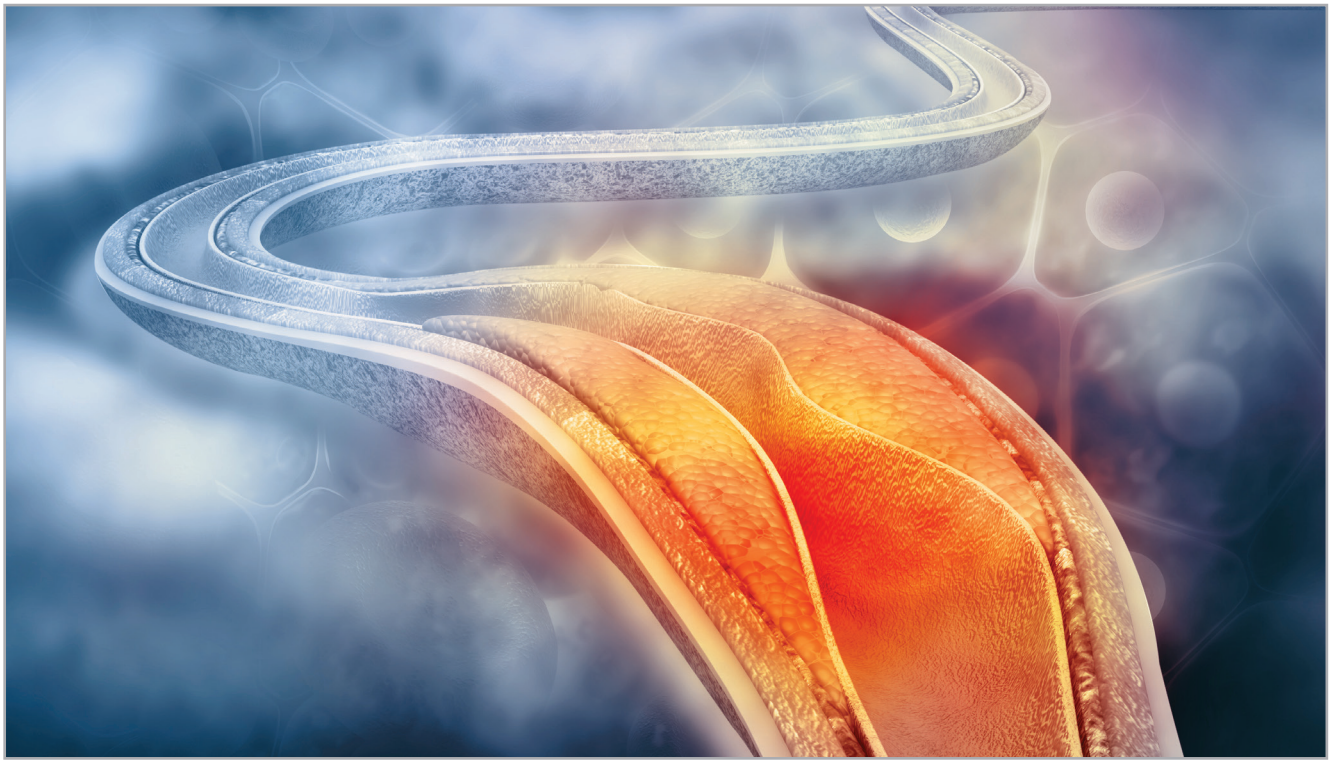
Hypercholesterolemia



Practical Guidance for Combination Lipid-Modifying Therapy in High- and Very-High-Risk Patients: A statement from a European Atherosclerosis Society Task Force[1]

Averna M, Banach M, Bruckert E, Drexel H, Farnier M, Gaita D, Magni P, Mδrz W, Masana L, Mello E Silva A, Reiner Z, Ros E, Vrablik M, Zambon A, Zamorano JL, Stock JK, Tokgωzoğlu LS, Catapano AL. Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force. Atherosclerosis. 2021 May;325:99-109.

This European Atherosclerosis Society (EAS) Task Force provides practical guidance for combination therapy for elevated low-density lipoprotein cholesterol (LDL-C) and/or triglycerides (TG) in high-risk and very-high-risk patients. The aim of this guidance is to offer a practical way to implement the 2019 European Society of Cardiology/EAS guidelines for the management of dyslipidemias.

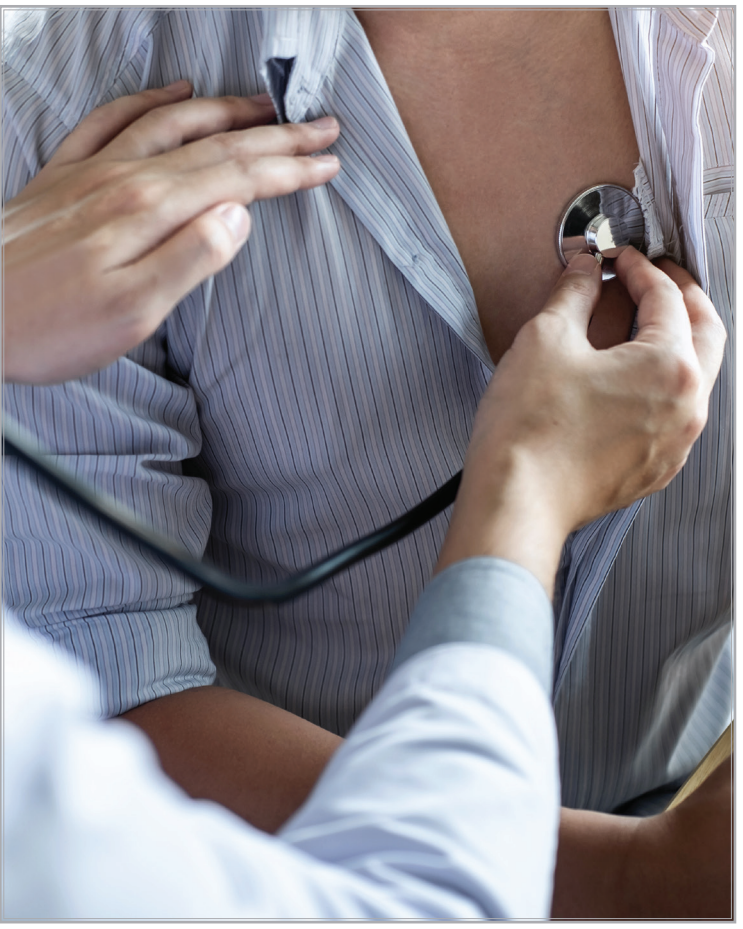
As for the key highlights of new document, most noteworthy is the recommendation to prescribe a combination of statins with ezetimibe to patients with a low baseline probability of achieving their LDL cholesterol targets on statin monotherapy as first choice, without prior attempts to use a statin alone. In particular, for patients with atherosclerotic CVD, whose LDL goal is < 1.4 mmol/L, the co-administration of a high-intensity statin and ezetimibe is suggested already at LDL cholesterol levels ≥ 2.6 mmol/L. After that, a PCSK9 inhibitor may be added if LDL-C levels remain high.

Statin-ezetimibe combination treatment is the first choice for primary prevention familial hypercholesterolemia patients as well.

A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor may be added if LDL-C levels re-

main high. In high and very-high-risk patients with mild to moderately elevated TG levels (>2.3 and < 5.6 mmol/L [>200 and < 500 mg/dL) on a statin, treatment with either a fibrate or high-dose omega-3 fatty acids (icosapent ethyl) may be considered, weighing the benefit versus risks. Combination with fenofibrate may be considered for both macro- and microvascular benefits in patients with type 2 diabetes mellitus.

In conclusion, this Task Force statement provides evidence-based practical guidance for the use of guideline-recommended combination lipid-modifying therapy in high and very-high-risk patients to prevent ASCVD events. Integration of these approaches into routine practice has the potential to improve the implementation of guideline-recommended management of high LDL-C and TG levels, and ultimately to favorably impact the trajectory and burden of ASCVD.



The Effect of Rosuvastatin on Cardiogenic Cerebral Infarction[2]

Wu B, Wang Y, Li W, Dong R, Dun C. The effect of rosuvastatin on cardiogenic cerebral infarction. Am J Transl Res. 2021 Aug 15;13(8):9444-9450.

Cerebral infarction is seen commonly in clinics, and it can be assigned into different types. Cardiogenic cerebral infarction is considered the most common cerebral infarction and has a high morbidity and mortality. It is of great clinical significance to use effective drugs to minimize the cerebral infarction area as much as possible and to decrease the disability and mortality rates.

This study was performed to investigate whether rosuvastatin treatment is associated with a better curative effect for patients with cardiogenic cerebral infarction and its mechanisms. The results of this study provide the guidance and an experimental foundation for the clinical treatment of cardiogenic cerebral infarction.

Overall, 300 patients with cardiogenic cerebral infarction were recruited as the study cohort and randomly divided into an observation group and a control group. Routine treatment, including urinary kallikrein injections and bayaspirin tablets were given to the patients in the control group for one month. Rosuvastatin was given once a day in addition to the treatment the control group received to the patients in the observation group, also for one month. The two groups' treatment efficacies were compared. Also, the two groups' NIHSS and mRS scores, lipid and inflammatory factor levels, and their oxidative stress statuses were also compared.

The total effective rate in the observation group was significantly higher than it was in the control group (74.0% vs 84.7%, p=0.023). The NIHSS and mRS scores in the observation group were significantly lower than they were in the control group (all p<0.001). Compared with their levels after the treatment in the control group, the cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) levels in the observation group were significantly decreased and the high-density lipoprotein cholesterol (HDL-C) was significantly

increased (all $p<0.001$). Moreover, after the treatment, the inflammatory factors, such as the tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) levels, and the oxidative stress status, such as the oxidatively modified low density lipoprotein (ox-LDL) levels, were significantly lower than they were in the control group, but the superoxide dimutase (SOD) levels were significantly higher.

There are some limitations to this study, such as it being a single center study, its small sample size, and the absence of any long-term follow-up results, and so on. In the future, a large sample size, and a multi-center randomized controlled prospective study should be performed to further confirm the long-term effect of the different doses of rosuvastatin on patients with cardiogenic cerebral infarction.

However, in conclusion, the oral administration of rosuvastatin can significantly improve the treatment effect in patients with cardiogenic cerebral infarction and can enhance their neurological function recovery. This may be associated with the improvement of the patients' lipid levels, inflammatory factor levels, and oxidative stress statuses.

Lipid Management Across Europe in the Real-World Setting: A Rapid Evidence Review[3]

Barrios V, Soronen J, Carter AM, Anastassopoulou A. Lipid management across Europe in the real-world setting: a rapid evidence review. Curr Med Res Opin. 2021 Sep 14:1. doi: 10.1080/03007995.2021.1973396. Epub ahead of print.

The objective of this review was to provide a contemporary overview of recent real-world lipid-lowering therapy (LLT) practices and outcomes in patients with hypercholesterolemia/dyslipidemia at high/very high risk of atherosclerotic cardiovascular disease in Europe.

Barrios et al conducted a structured literature review of real-world studies which were performed between July 2015 and July 2020 and reported lipid management and outcomes using a rapid evidence synthesis. Outcomes included patient characteristics, LLT treatment practices, adherence and low-density lipoprotein cholesterol (LDL-C) goal attainment.

Fifty-three real-world observational studies in high/very high risk patients were selected after screening 5,664 records (n = 50 national [sample size range 38 to 237,279] and n = 3 multinational studies [sample size range 6,648 to 8,456]). Mean age ranged from 33 to 77 years; hypertension, diabetes and obesity were commonly reported comorbidities. Statins were the most common LLT; patients without familial hypercholesterolemia (FH) mostly received high or moderate intensity statins/LLT, while patients with FH mostly received high intensity statins/LLT. The proportion of patients receiving ezetimibe was low overall (ezetimibe + statin use in those with and without familial hypercholesterolemia [FH] range 5%-59% and 1%-22%, respectively). Overall, the use of PCSK9i therapy was limited. Adherence to LLT therapies was defined variably and ranged from 46%-92%. LDL-C goal attainment was suboptimal, irrespective of LLT (overall range in goal attainment with oral LLT was 2%-73% [FH: 2%-23%] and PCSK9i was 20%-65%).

In conclusion LDL-C control is suboptimal and the available LLT armamentarium, most importantly combination therapy, is being underutilized in high/very high risk patients leading to inadequate management of cardiovascular risk.

Comparing the Combination Therapy of Ezetimibe and Atorvastatin with Atorvastatin Monotherapy for Regulating Blood Lipids: A Systematic Review and Meta-Analysis[4]

Ai C, Zhang S, He Q, Shi J. Comparing the combination therapy of ezetimibe and atorvastatin with atorvastatin monotherapy for regulating blood lipids: a systematic review and meta-analyse. Lipids Health Dis. 2018 Oct 17;17(1):239.

Although there were many studies reporting the combination therapy of Ezetimibe and Atorvastatin's efficacy and Atorvastatin monotherapy's, the conclusions were controversial. Therefore, the purpose of this study was to compare the combination therapy of Ezetimibe and Atorvastatin (E+A) with Atorvastatin monotherapy (A) for regulating blood lipids in the clinical application dose, and summarize the results of comparisons. Subgroup analysis was used to explore whether different doses had impact on the comparison between combination therapy and monotherapy.

PubMed, Cochrane Library and Embase were searched for studies of the combination therapy of Ezetimibe and Atorvastatin and Atorvastatin monotherapy published up to October 20, 2017. Two investigators assessed the articles for eligibility and evaluated quality. The changed values and the efficacy of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), Total Cholesterol (TC) and Triglyceride (TG) indicators were the outcomes. Four doses of the comparisons were included: the combination therapy of Ezetimibe (10 mg) and Atorvastatin (10 mg) (E10 + A10) versus Atorvastatin (20 mg) monotherapy (A20); E10 + A10 vs. A10; E10 + A20 vs. A40; E10 + A40 vs. A80. Review manager software 5.1 was used for quality assessment and Stata version 12.0 software was used for statistical analysis.

Seventeen studies (11 publications) were included in the meta analysis. Compared with Atorvastatin monotherapy, the overall efficacy of combination therapy of Ezetimibe and Atorvastatin on lowering LDL-C (MD = - 15.38, 95% CI: -16.17 to - 14.60; I^2 = 26.2%, n = 17), TC (MD = - 9.51, 95% CI: -10.28 to - 8.74; I^2 = 33.7%, n = 17) and TG (MD = - 6.42, 95% CI: -7.78 to - 5.06; I^2 = 0%, n = 15) and raising HDL-C (MD = 0.95, 95% CI: 0.34 to 1.57; I^2 = 0%, n = 17) was significant. The efficacy of the comparison on HDL-C was largely significant for the different doses.

The results of this meta-analysis showed that the overall effectiveness of combination therapy of Ezetimibe and Atorvastatin was significantly better than Atorvastatin monotherapy on lowering LDL-C, TC and TG among all the four doses comparison (E10+A10/A20; E10+A10/A10; E10+A20/A40; E10+A40/A80). Besides, the authors also found a significant effect on raising HDL-C which was different with previous individual studies. Sensitivity analysis showed that the results remained relatively stable by excluding individual studies.

In conclusion, the overall efficacy and subgroup's efficacy of combination therapy of Ezetimibe and Atorvastatin on lowering LDL-C, TC and TG was significantly better than Atorvastatin monotherapy's. The overall and the E10+A10/A20 group's effectiveness of combination therapy on raising HDL-C were significantly.

High-Intensity Statins Benefit High-Risk Patients: Why and How to Do Better[5]

Grundy SM, Stone NJ, Blumenthal RS, Braun LT, Heidenreich PA, Lloyd-Jones D, Orringer CE, Saseen JJ, Smith SC Jr, Sperling LS, Virani SS. High-Intensity Statins Benefit High-Risk Patients: Why and How to Do Better. Mayo Clin Proc. 2021 Sep 14:S0025-6196(21)00434-1.

Review of the US and European literature indicates that most patients at high risk for atherosclerotic cardiovascular disease (ASCVD are not treated with high-intensity statins, despite strong clinical-trial evidence of maximal statin benefit. High-intensity statins are recommended for 2 categories of patients: those with ASCVD (secondary prevention) and high-risk patients without clinical ASCVD. Most patients with ASCVD are candidates for high-intensity statins, with a goal for low-density lipoprotein cholesterol reduction of 50% or greater. A subgroup of patients with ASCVD are at very high risk and can benefit by the addition of non-statin drugs (ezetimibe with or without bile acid sequestrant or bempedoic acid and/or a proprotein convertase subtilisin/kexin type 9 inhibitor). High-risk primary prevention patients are those with severe hypercholesterolemia, diabetes with associated risk factors, and patients aged 40 to 75 years with a 10-year risk for ASCVD of 20% or greater. In patients with a 10-year risk of 7.5% to less than 20%, coronary artery calcium scoring is an option; if the coronary artery calcium score is 300 or more Agatston units, the patient can be up-classified to high risk. If high-intensity statin treatment is not tolerated in high-risk patients, a reasonable approach is to combine a moderate-intensity statin with ezetimibe. In very high-risk patients, proprotein convertase subtilisin/kexin type 9 inhibitors lower low-density lipoprotein cholesterol levels substantially and hence reduce risk as well.

The strategy for use of maximal cholesterol-lowering therapy in high-risk patients, with emphasis on high intensity statins includes the addition of ezetimibe at 10 mg/d (± bile acid resin or bempedoic acidb) to achieve further LDL-C lowering if only moderate-intensity statins are tolerated.

If similar symptoms recur with a second statin, an alternative treatment strategy should be tried, eg: ezetimibe at 10 mg/d (± bile acid resin or bempedoic acid) with intermittent statin dosing can lower LDL-C substantially.

If patient is unable or unwilling to take statins, then an alternative strategy should be considered utilizing LDL-C-lowering drugs proven to reduce LDL-C and coronary events. PCSK9 inhibitors, possibly with ezetimibe, can be useful in such cases.

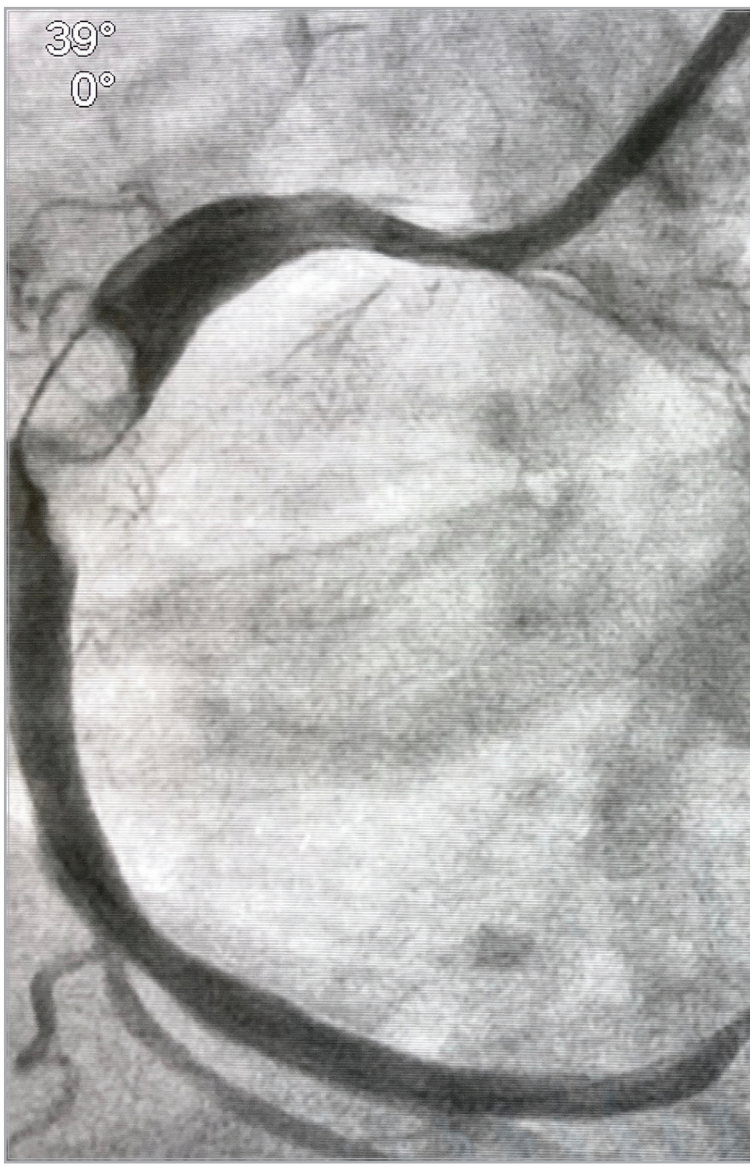
In conclusion, there is strong evidence that most patients at high risk for ASCVD benefit from substantial LDL-C lowering of 50% or more. Yet too often, such patients are unnecessarily undertreated with LDL-Celowering therapy. Many reasons exist for undertreatment, but ultimately, in high-risk patients, the clinician needs to discuss the value of maximal LDL-C lowering and utilize regular monitoring for efficacy and adherence. Enhanced lowering can be achieved preferably by use of a high-intensity statin or if preferred, a moderate-intensity statin plus ezitimibe with or without a bile acid sequestrant, or bempedonic acid. For patients with ASCVD who are completely intolerant of statins, strong consideration should be given to use of a PCSK9 inhibitor.

Impact of Statin Intensity on Adverse Cardiac and Cerebrovascular Events in Older Adult Patients with Myocardial Infarction[6]

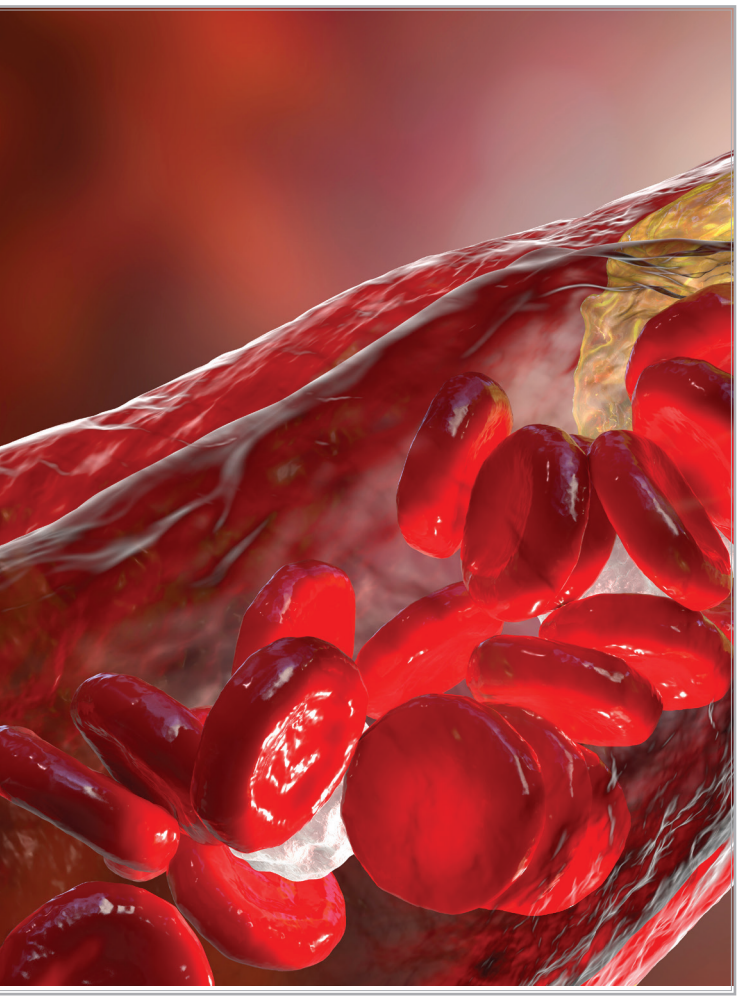
Moon IT, Kang SH, Lee W, Cho Y, Park JJ, Yoon YE, Oh IY, Yoon CH, Suh JW, Youn TJ, Chae IH, Choi DJ, Cho YS. Impact of statin intensity on adverse cardiac and cerebrovascular events in older adult patients with myocardial infarction. J Geriatr Cardiol. 2021 Aug 28;18(8):609-622.

There is a lack of evidence on the use of high-intensity statins for patients with MI at least 75 years old and whether a high-intensity statin is sufficiently effective for secondary prevention in comparison with low-to-moderate intensity statins. Therefore, Moon et al aimed to investigate the prescription intensities of statins in real-world practice and the long-term cardiac and cerebrovascular outcomes according to statin intensity in older adult patients with MI.

Consecutive patients with MI aged at least 75 years were analyzed retrospectively. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of all-cause death, MI, rehospitalization due to unstable angina, repeat revascularization, and ischemic stroke. The high-intensity group was compared to the low-to-moderate intensity group in the propensity score-matched cohort.



Average age of total 546 patients was 81 years. Among them, 84% of patients underwent percutaneous coronary intervention. The unadjusted seven-year MACCE rate differed by statin intensity (high-intensity statin group: 38%, moderate-intensity statin group: 42%, low-intensity statin group: 56%, and no-statin group: 61%, p=0.004). However, among these groups, many baseline characteristics were significantly different. Among the 74 propensity score-matched pairs, which lacked any significant differences in all baseline characteristics, the high-intensity group had a significantly lower rate of MACCE than the low-to-moderate intensity group (37% vs. 53%, p=0.047). Follow-up low-density lipoprotein cholesterol levels were significantly lower in the high-intensity group than that in the low-to-moderate intensity group (69.4 ± 16.0 mg/dL vs. 77.9 ± 25.9 mg/dL, p=0.026).



In this study, the frequency of prescription of high-intensity statin in older adult patients with MI increased annually during the study period. The high-intensity statin group showed significantly lower MACCE than that in the low-to-moderate intensity statin group in the propensity score-matched cohort. Furthermore, high-intensity statins effectively lowered total cholesterol and LDL-C compared to low-to-moderate intensity statins.

In conclusion, in older adult patients with MI, the use of high-intensity statin significantly reduced the occurrence of MACCE in comparison to low-to-moderate intensity for up to seven years of follow-up. It is anticipated that further large-scale prospective studies on statin intensity, especially in older adult patients, will confirm our results and reinforce statin treatment in older adult patients.

Efficacy of Intensive Lipid-Lowering Therapy with Statins Stratified by Blood Pressure Levels in Patients with Type 2 Diabetes Mellitus and Retinopathy: Insight from the EMPATHY Study[7]

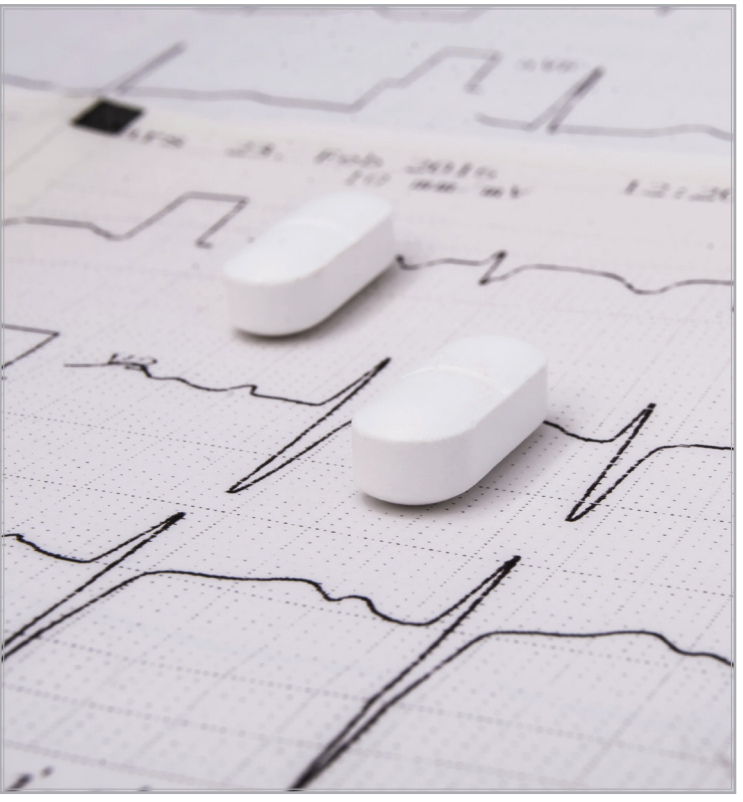
Shinohara, K., Ikeda, S., Enzan, N. et al. Efficacy of intensive lipid-lowering therapy with statins stratified by blood pressure levels in patients with type 2 diabetes mellitus and retinopathy: Insight from the EMPATHY study. Hypertens Res (2021). https://doi-org.rsm.idm.oclc.org/10.1038/s41440-021-00734-x

Intensive lipid-lowering therapy is recommended in individuals exhibiting type 2 diabetes mellitus (T2DM) with microvascular complications (as high-risk patients), even without known cardiovascular disease (CVD). However, evidence is insufficient to stratify the patients who would benefit from intensive therapy among them. Hypertension is a major risk factor, and uncontrolled blood pressure (BP) is associated with increased CVD risk.

Shinohara et al evaluated the efficacy of intensive vs. standard statin therapy for primary CVD preven-

tion among T2DM patients with retinopathy stratified by BP levels.

This analysis of the EMPATHY study was the first to investigate the efficacy of intensive vs. standard statin therapy for the primary prevention of CVD among T2DM patients with retinopathy stratified by baseline BP levels. Intensive statin therapy with a target LDL-C of <70 mg/dL significantly reduced the risk of composite CVD compared with standard statin therapy with a target LDL-C ranging from ≥100 to <120 mg/dL in T2DM patients with BP ≥ 130/80 mmHg but not in those with BP < 130/80 mmHg. The primary outcome in this study was the same as that in the original EMPATHY study and included renal events, whereas CVD, as commonly defined, does not include renal events. Therefore, in addition to the primary composite CVD outcome, the authors analyzed the hazard ratios for non-renal CVD and MACE in the intensive therapy group compared with the standard therapy group in each BP subgroup



The authors used the dataset from the EMPATHY study, which compared intensive statin therapy targeting low-density lipoprotein cholesterol (LDL-C) levels of <70 mg/dL and standard therapy targeting LDL-C levels ranging from ≥100 to <120 mg/dL in T2DM patients with retinopathy without known CVD. A total of 4980 patients were divided into BP ≥ 130/80 mmHg (systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 80 mmHg, n = 3335) and BP < 130/80 mmHg (n = 1645) subgroups by baseline BP levels. During the median follow-up of 36.8 months, 281 CVD events were observed. Consistent with previous studies, CVD events occurred more frequently in the BP ≥ 130/80 mmHg subgroup than in the BP < 130/80 mmHg subgroup (p<0.001). In the BP ≥ 130/80 mmHg subgroup, intensive statin therapy was associated with lower CVD risk (HR 0.70, p=0.015) than standard therapy after adjustment. No such association was observed in the BP < 130/80 mmHg subgroup. The interaction between BP subgroup and statin therapy was significant.

In conclusion, intensive statin lipid-lowering therapy with a target LDL-C level of <70 mg/dL was associated with a lower risk of composite CVD events than standard therapy with a target LDL-C of ≥100 to <120 mg/dL among the BP ≥130/80 mmHg subgroup of T2DM patients with diabetic retinopathy without known CVD. These associations were not observed in T2DM patients with BP< 130/80 mmHg. As per the results of this study, intensive statin therapy might not be equivalently effective among high-risk patients with hyperlipidemia and diabetic retinopathy, which further suggests that stratification based on whether T2DM patients have a baseline BP of ≥130/80 mmHg might be a novel and useful strategy for determining target LDL-C levels in statin lipid-lowering therapy for the primary prevention of CVD among T2DM patients with microvascular complications.

Hypertension

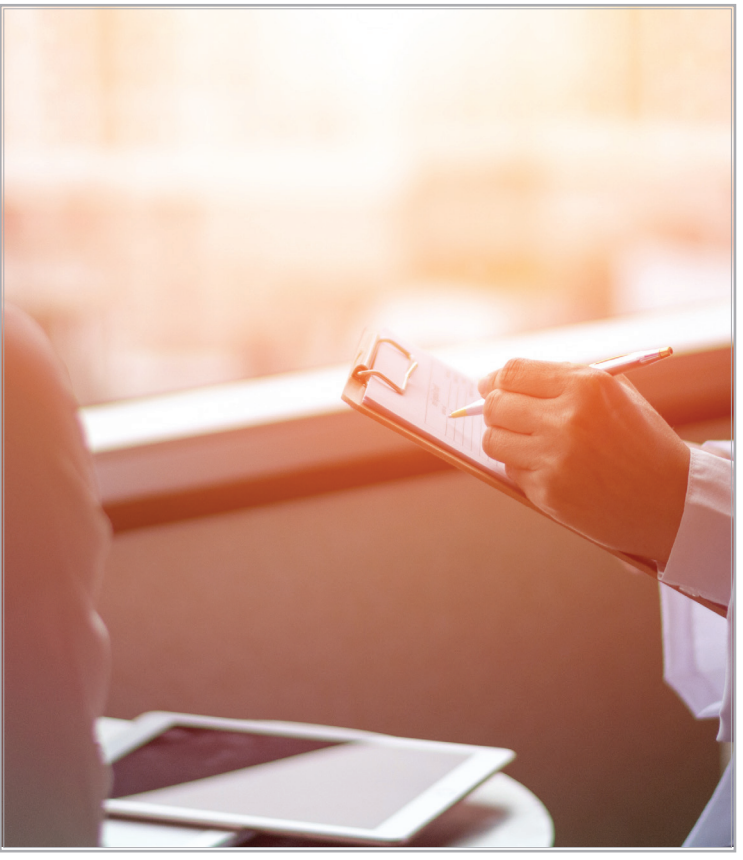
Olmesartan/Amlodipine: A Review of its Use in the Management of Hypertension[8]

Kreutz R. Olmesartan/amlodipine: a review of its use in the management of hypertension. Vasc Health Risk Manag. 2011;7:183-192.

Combination therapy is an effective strategy to increase antihypertensive efficacy in those patients with poor blood pressure (BP) control. The European guidelines on hypertension management recommends that it may be prudent to lower BP to values within the range of 130–139/80–85 mmHg in the majority of hypertensive patients, including those with diabetes. In these guidelines, both angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) are recommended for first-line therapy either as monotherapy or in combination. This article reviewed the rationale for fixed-dose combination therapy with the ARB olmesartan medoxomil and the CCB amlodipine.

In order to achieve BP targets, at least 75% of patients may require combination therapy, and European guidelines advocate this approach, particularly in those patients with a high cardiovascular risk. Evidence from large, randomized controlled trials, and the European hypertension treatment guidelines is supportive of the use of an angiotensin receptor blocker (ARB) with a calcium channel blocker (CCB). Fixed-dose combination formulations of olmesartan medoxomil, an ARB, and the CCB amlodipine are approved in several European countries for patients with essential hypertension. The olmesartan/amlodipine combination has demonstrated greater efficacy than its component monotherapies in reducing BP in patients with mild-to-severe hypertension. Significantly greater reductions in seated diastolic BP were observed between baseline and after eight

weeks of treatment with olmesartan/amlodipine, compared with equivalent doses of olmesartan or amolodipine monotherapy ($p < 0.001$), in the factorial Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure (COACH) trial. About 85% of the maximal BP reductions after the 8-week treatment period were already observed after two weeks. Uptitration as necessary, with or without hydrochlorothiazide, allowed the majority of patients to achieve BP control in a 44-week open-label extension treatment period to the COACH trial. The use of olmesartan/amlodipine allowed up to 54% of patients, with previously inadequate responses to amlodipine or olmesartan monotherapy, to achieve their BP goals. Data from post-registration studies using tight BP control and forced titration regimens have further demonstrated the high efficacy of olmesartan/amlodipine in achieving BP goal rates. Moreover, consistent reductions in BP were observed over the 24-hour dosing interval using ambulatory measurements.



In randomized, double-blind trials, olmesartan/amlodipine has demonstrated greater efficacy than the respective monotherapies in reducing BP, including a reduction within two weeks of initiation in the COACH trial, and achieving their BP goals, including over 24 hours, in patients with moderate-to-severe hypertension who had responded inadequately to olmesartan or amlodipine monotherapy. Up to 54% of patients who had failed to respond adequately to olmesartan or amlodipine monotherapy achieved their BP goal during eight weeks of treatment with olmesartan/ amlodipine. Uptitration of olmesartan/amlodipine provided additional BP reductions, allowing even more patients to achieve their BP goal, while the incidence of hypotension remained very low. Furthermore, treat-to-target studies have demonstrated the power of olmesartan/amlodipine-based treatment in achieving high BP goal rates. Olmesartan/amlodipine was generally well tolerated over short- and long-term therapy and this observation was not affected by uptitration. Peripheral edema was significantly less common with olmesartan/amlodipine 40/10 mg than with amlodipine 10 mg monotherapy. In Europe, a fixed-dose combined olmesartan/amlodipine formulation is available in three dosages (20/5, 40/5 and 40/10 mg), allowing flexible dosing and uptitration.

Risk of Atrial Fibrillation in Young Adults with Isolated Diastolic, Isolated Systolic, and Systolic-Diastolic Hypertension[9]

Lee SR, Han KD, Choi EK, Ahn HJ, Oh S, Lip GYH. Risk of Atrial Fibrillation in Young Adults With Isolated Diastolic, Isolated Systolic, and Systolic-Diastolic Hypertension. Hypertension. 2021 Sep 20:HYPERTENSIONAHA12117399. doi: 10.1161/HYPERTENSIONAHA.121.17399. Epub ahead of print. PMID: 34538103.

There is limited evidence regarding the risks of incident atrial fibrillation (AF) associated with stage 1 isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), and systolic-diastolic hypertension (SDH), especially among young adults.

Lee et al aimed to evaluate the association between early stage of hypertension and AF in young adults. From the Korean nationwide health screening database, 2 958 544 subjects aged 20 to 39 years who were not prescribed antihypertensive medication at the index examination in 2009 were included. Subjects were categorized into 8 groups according to the 2017 American College of Cardiology/American Heart Association blood pressure (BP) guidelines: normal BP, elevated BP, stage 1 IDH, stage 1 ISH, stage 1 SDH, stage 2 IDH, stage 2 ISH, and stage 2 SDH. The primary outcome was new-onset AF. During a median follow-up of 8.3 years, 7347 subjects had incident AF (0.3 per 1000 person-years). Compared with normal BP, stage 1 IDH (adjusted hazard ratio, 1.160 [95% CI, 1.086-1.240]) and stage 1 SDH (1.250 [1.165-1.341]) were associated with higher risks of incident AF, but not stage 1 ISH. Stage 2 IDH, ISH, and SDH were associated with higher risks of incident AF by 24%, 37%, and 61%, respectively. Stage 1 IDH and SDH were associated with higher risks of incident AF compared with normal BP. The risk of incident AF with stage 2 IDH was similar to that of stage 1 SDH.

Among young adults aged 20 to 39 years, stage 1 isolated diastolic hypertension and systolic-diastolic hypertension were associated with a higher risk of incident atrial fibrillation compared with those with normal blood pressure. The risk of incident atrial fibrillation with stage 2 isolated diastolic hypertension was similar to that of stage 1 systolic-diastolic hypertension.

The results of this study demonstrated the associations between BP categorized by the 2017 American College of Cardiology/American Heart Association (ACC/ AHA) classification and the risk of incident AF. The principal findings were as follows: (1) According to the 2017 ACC/AHA BP classification, a substantial proportion of young adults aged 20 to 39 years (42%) had hypertension; (2) not only stage 2 hypertension but also stage 1 IDH and stage 1 SDH were significantly associated with a higher risk of incident AF (16% and by 25%, respectively); (3) in subjects aged 20 to 29 years, stage 1 IDH and stage 1 SDH were consistently associated with higher risks of incident AF (22% and 33%, respectively); and (4) SB p<140 mm Hg and DB p<70 mm Hg may represent optimal targets to reduce the future risk of incident AF in young adults.

In conclusion, among young adults, stage 1 IDH and SDH were associated with a higher risk of incident AF compared with those with normal BP. The risk of incident AF with stage 2 IDH was similar to that of stage 1 SDH. Optimal BP control, including DBP, is associated with the lowest risk of new-onset AF, even among young adults.

Bisoprolol/Amlodipine Combination Therapy Improves Blood Pressure Control in Patients with Essential Hypertension Following Monotherapy Failure[10]

Gottwald-Hostalek U, Li L, Montenegro P. Bisoprolol/amlodipine combination therapy improves blood pressure control in patients with essential hypertension following monotherapy failure. Curr Med Res Opin. 2016 Oct;32(10):1735-1743. doi: 10.1080/03007995.2016.1205573. Epub 2016 Jul 4. PMID: 27334671.

Gottwald-Hostalek investigated the efficacy of a bisoprolol/amlodipine fixed-dose combination (FDC) in patients with essential hypertension who had not responded to bisoprolol or amlodipine monotherapy.

In an 18 week, multicenter, randomized, comparative phase III study (ClinicalTrials.gov identifier: NCT01977794), patients with blood pressure uncontrolled by bisoprolol or amlodipine monotherapy (5 mg OD) began treatment with bisoprolol/amlodipine FDC 5/5 mg OD. Patients with controlled blood pressure (BP) at week 6/12 continued at current FDC strength, and patients with uncontrolled BP received FDC dose uptitration (maximum dose: 10/10 mg). The primary efficacy endpoint was change in systolic blood pressure (SBP) at week 18 versus baseline (corresponding to SBP under monotherapy), and secondary endpoints included change from baseline in SBP after week 6/12 and percentage of BP-controlled patients at week 6, 12 and 18. Safety was assessed by number/types of adverse events (AEs).

Two hundred patients were randomized to treatment (100 with uncontrolled BP under bisoprolol and 100 under amlodipine monotherapy). Overall, 196 patients were eligible for analysis. The patient groups displayed similar mean SBP reductions from baseline by study end (bisoprolol monotherapy failure: 25.9 ± 12.82 mmHg reduction; amlodipine monotherapy failure: 24.7 ± 11.67 mmHg reduction; $p< 0.001$ for both). Overall mean SBP decreased by 25.3 ± 12.25 mmHg ($p< 0.001$). Mean heart rate reductions were also observed (bisoprolol monotherapy failure: 6.6 ± 9.67 bpm reduction; amlodipine monotherapy failure: 11.5 ± 8.65 bpm reduction; $p< 0.001$ for both). Most patients (83.2%) displayed BP control with bisoprolol/amlodipine 5/5 mg at 6 weeks. Treatment was well tolerated at all dose levels; treatment-related AEs (mostly of mild/moderate intensity) were reported by 52.5% of patients, with no severe or serious treatment-related AEs reported. As the study focused on hypertension, total cardiovascular risk was not assessed.

In conclusion, bisoprolol/amlodipine FDC therapy is associated with significant BP improvements in patients with essential hypertension following monotherapy failure.

Prevalence of Hypertension Mediated Organ Damage in Subjects with High-Normal Blood Pressure without Known Hypertension as well as Cardiovascular and Kidney Disease[11]

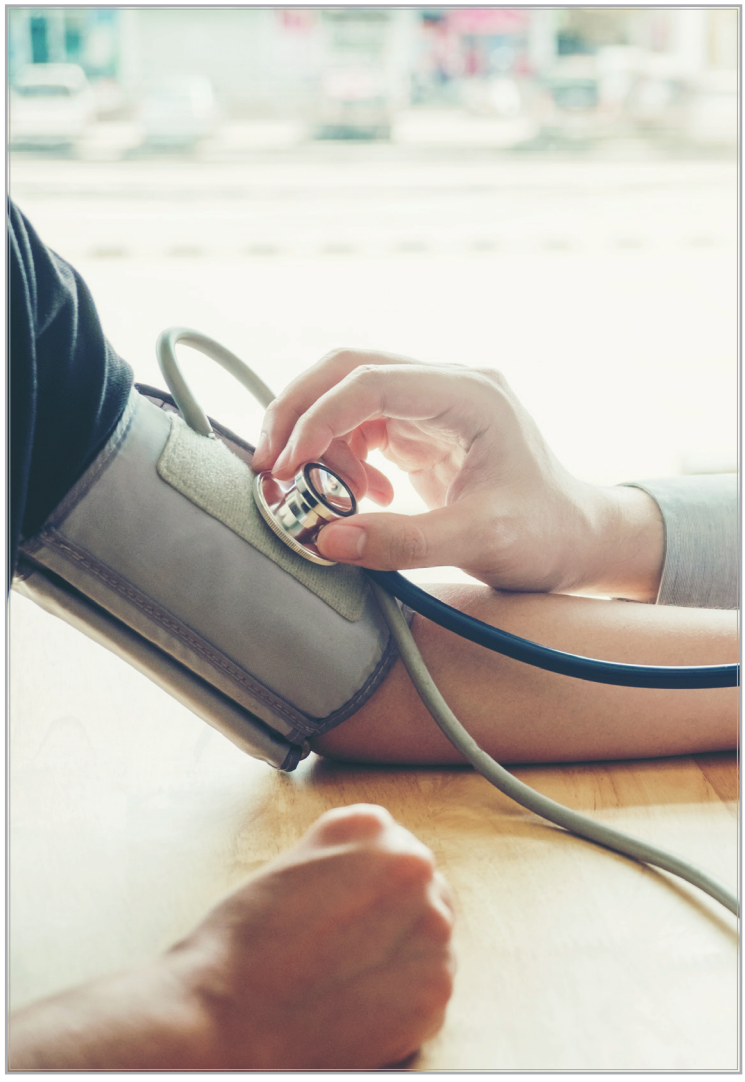
Maloberti, A., Rebora, P., Occhino, G. et al. Prevalence of hypertension mediated organ damage in subjects with high-normal blood pressure without known hypertension as well as cardiovascular and kidney disease. J Hum Hypertens (2021). https://doi-org.rsm.idm.oclc.org/10.1038/s41371-021-00604-6

In the American guidelines, individuals with SBP between 120 and 140 mmHg were previously defined as pre-hypertensives while currently they are split into the elevated BP group (SBP 120–129 mmHg) and the stage 1 hypertension (SBP 130–139 mmHg). Despite the differences in classification, similar indications were given with non-pharmacological therapies for both groups and pharmacological one when clinical atherosclerotic symptomatic CV diseases are present (similarly to ESH guidelines) or estimated CV is high for stage 1 hypertension group.

The prevalence of hypertension-mediated organ damage (HMOD) in those subjects have been previously evaluated with heterogeneous results. The purpose of this study was to assess the prevalence of HMOD in healthy subjects with high-normal BP comparing them with subjects from the same population with BP values that are considered normal (<130/85 mmHg) or indicative of hypertension (≥140/90 mmHg).

Seven hundred fifty-five otherwise healthy subjects were included. HMOD was evaluated as pulse wave velocity (PWV), left ventricular mass index (LVMI), and carotid intima-media thickness (IMT) and plaque. When subjects were classified according to BP levels the authors found that the high-normal BP group showed intermediate values of PWV and higher values of IMT. This corresponds to intermediate prevalence of arterial stiffness, while there were no differences for increased IMT or carotid plaque. No subjects showed left ventricular hypertrophy. At multivariable analysis, the odds of having arterial stiffness or carotid HMOD in the high-normal group resulted not different to the normal group.

Based on these results, it could seem that subjects with high-normal BP values present a significantly higher prevalence of arterial stiffness when compared to normal BP subjects (<130/85 mmHg) and a lower prevalence of the same HMOD when compared to subjects with hypertensive values. Despite adjusted linear regression analysis confirms this trend, the significance was lost when outcome was categorized. No significant differences were seen for carotid HMOD while prevalence of LVH was too low to allow further analyses.



In conclusion, in this otherwise healthy population, high-normal BP values were not associated to aortic, carotid or cardiac HMOD. Since all the evaluated HMODs are strongly related to future CV events, those subjects are probably at low risk for such outcomes. In fact, for subjects in the high-normal BP values current guidelines indicate antihypertensive treatment only when a previous event or a very high-risk is found.

Seasonal Variation in Blood Pressure: Current Evidence and Recommendations for Hypertension Management[12]

Narita, K., Hoshide, S. & Kario, K. Seasonal variation in blood pressure: current evidence and recommendations for hypertension management. Hypertens Res (2021). https://doi-org.rsm.idm.oclc.org/10.1038/s41440-021-00732-z

Blood pressure (BP) exhibits seasonal variation, with an elevation of daytime BP in winter and an elevation of nighttime BP in summer. The wintertime elevation of daytime BP is largely attributable to cold temperatures. The summertime elevation of nighttime BP is not due mainly to temperature; rather, it is considered to be related to physical discomfort and poor sleep quality due to the summer weather. The winter elevation of daytime BP is likely to be associated with the increased incidence of cardiovascular disease (CVD) events in winter compared to other seasons. The suppression of excess seasonal BP changes, especially the wintertime elevation of daytime BP and the summertime elevation of nighttime BP, would contribute to the prevention of CVD events.

Herein, Narita et al review the literature on seasonal variations in BP, and they recommend the following measures for suppressing excess seasonal BP changes as part of a regimen to manage hypertension:

(1) out-of-office BP monitoring, especially home BP measurements, throughout the year to evaluate seasonal variations in BP;
(2) the early titration and tapering of antihypertensive medications before winter and summer;
(3) the optimization of environmental factors such as room temperature and housing conditions; and
(4) the use of information and communication technology–based medicine to evaluate seasonal variations in BP and provide early therapeutic intervention.

For the suppression of seasonal changes in BP values, the authors recommend the following measures in the management of hypertension:

(1) home BP measurements throughout the year to evaluate seasonal changes in BP;
(2) early adjustment (titration or tapering) of antihypertensive medications;
(3) the optimization of environmental factors such as room temperature and housing conditions; and
(4) the use of information and communication technology (ICT)-based medicine to evaluate seasonal BP variations and provide early therapeutic intervention.

In conclusion, in the management of hypertension, seasonal variation in BP may be an important treatment target for the prevention of CVD events. In order to assess seasonal variations in BP precisely, out-of-office BP measures such as home BP are recommended. Optimal adjustments of room temperature and the doses of antihypertensive medications should be considered to prevent excess seasonal changes in BP. In addition, ICT-based medicine will be a useful method for managing hypertension while considering seasonal variations in BP. Based on the many reported findings regarding seasonal variations in BP, the pathological significance of seasonal changes in BP is becoming increasingly clear. However, further accumulation of scientific evidence regarding the seasonal variation in BP is needed.

Olmesartan Combined With Amlodipine on Oxidative Stress Parameters in Type 2 Diabetics, Compared With Single Therapies: A Randomized, Controlled, Clinical Trial[13]

Derosa G, Mugellini A, Pesce RM, DǧAngelo A, Maffioli P. Olmesartan Combined With Amlodipine on Oxidative Stress Parameters in Type 2 Diabetics, Compared With Single Therapies: A Randomized, Controlled, Clinical Trial. Medicine (Baltimore). 2016 Mar;95(13):e3084. doi: 10.1097/MD.0000000000003084. PMID: 27043671; PMCID: PMC4998532.

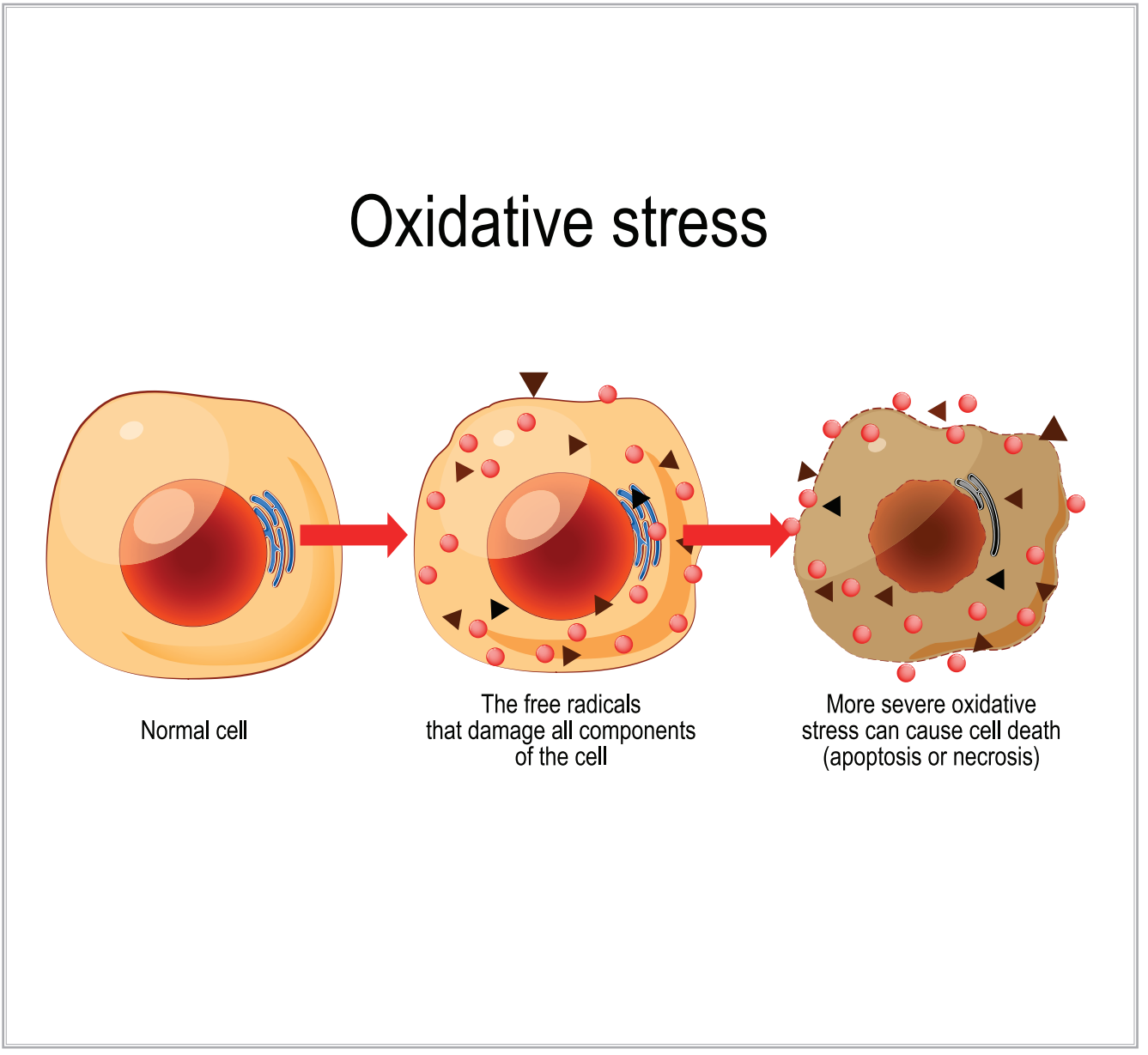
The aim of this study was to evaluate the effects of a fixed olmesartan/amlodipine combination 20/5mg compared with olmesartan 20mg or amlodipine 10mg alone on some parameters indicative of endothelial damage and oxidative stress in patients with hypertension and type 2 diabetes mellitus. In particular, Derosa et al were interested to evaluate if a fixed combination was better than single monotherapies in reducing blood pressure (BP), even at low dosage.

The authors enrolled 221 patients; 74 were randomized to olmesartan 20 mg, 72 to amlodipine 10 mg, and 75 to olmesartan/amlodipine fixed combination 20/5 mg for 12 months. They assessed blood pressure monthly; in addition, they also assessed at baseline, and after 6 and 12 months, the following parameters: lipoprotein (a), myeloperoxidase (MPO), isoprostanes, and paraoxonase-1 (PON-1). Blood pressure values obtained with fixed olmesartan/amlodipine combination were significantly lower than those reached with single monotherapies. There was a reduction of lipoprotein (a), and isoprostanes levels with olmesartan/amlodipine fixed combination, both compared with baseline, and with single monotherapies.

On the other hand, there was an increase of PON-1 with fixed olmesartan/amlodipine combination, both compared with baseline, and with single drugs. All treatments reduced MPO compared with baseline; however, in group-to-group comparison, MPO reduction was greater with olmesartan/amlodipine fixed combination.

In this study, the authors observed that a fixed olmesartan/amlodipine combination better improved oxidative stress, increasing PON-1 levels and reducing isoprostanes levels. These results are in line with what was already reported in the OLAS (OLmesartan/Amlodipine vs olmesartan/hydrochlorothiazide in metabolic Syndrome), trial, which suggested that combination therapy comprising an angiotensin type 1 receptor blocker plus a calcium channel blocker may offer advantages in patients at high cardiovascular risk and with underlying metabolic issues. The authors also recorded a better effect of the fixed combination in reducing LP(a) and MPO levels that have been recognized as new emerging markers of cardiovascular risk.

In conclusion, fixed combination of olmesartan/amlodipine was more effective than single monotherapies in reducing oxidative stress, especially in increasing PON-1 and reducing Lp(a) and isoprostanes levels in diabetic and hypertensive patients.



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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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