

THE ROLE OF AMLODIPIN FOR THE ARTERIAL HYPERTENSION THERAPY IN PATIENTS WITH CORONARY ARTERY DISEASE

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Arterial hypertension (AH) and coronary artery disease (CAD) are commonly comorbid conditions. The analysis of 9 prospective trials [13] showed a relative CAD growth depending on the increase of diastolic blood pressure (DBP). According to the REACH Registry [3] the high blood pressure (BP) in patients with CAD is more frequent than disorders of lipid metabolism. The necessity to reduce the high BP is based on the sufficient proof base and doesn't give rise to a doubt. Meta-analysis [11] of 61 prospective, observational studies (one million adults, 12.7 million person-years) showed that even a small decrease in BP can produce a significant reduction in cardiovascular mortality – a 2 mmHg reduction in SBP has been shown to be associated with a 7 % reduction in death from CAD and a 10 % reduction in death from stroke; the risk of cardiovascular mortality doubles with each elevation of BP by 20/10 mmHg. However, despite the benefit of optimal BP control in patients with hypertension [14], BP is still badly monitored in the society [27]. This may explain the fact of CAD being the leading cause of mortality and disability in developed countries and according to the prognosis by 2020 it will generally contribute to mortality indicators in the developing countries [19]. The aim of treatment patients with AH and CAD is to reduce high BP, ischemia and prevent CV events. The article considers the drug treatment of the patients with AH and CAD.

In the Guidelines of the European Society of Cardiology (ESC) (2013) the SBP target for CAD patients is recommended to be below 140 mm Hg was indi-

rectly approved in the unscheduled evaluation of the data from the INternational VERapamil SR-Trandolapril STudy (INVEST) [verapamil SR plus trandolapril] (all patients had CAD) [15]. It has been proved that the proportion of visits with BP control was associated with mean follow-up systolic BP, both being independently related to primary outcome [16]. As for the drugs to prescribe to the patients with AH there is evidence on more benefits of β -adrenergic blocking agents (β -blockers) after recent myocardial infarction (MI) [10]. In this case, angiotensin-converting enzyme (ACE) inhibitors were successfully used [21]. In the future any antihypertensive drugs (from the main classes of antihypertensive medicines) can be used [10]. But β -blockers and calcium channel blockers (CCBs), also called calcium antagonists, should be preferred, at least at available signs of angina pectoris [15].

Arterial hypertension. At present CCBs are one of the main classes of medicine for AH treatment. In European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) Guidelines for the management of arterial hypertension, CCBs are recommended for AH patients with specific conditions, such as asymptomatic atherosclerosis presence, left ventricle hypertrophy, angina pectoris, peripheral arterial disease, isolated systolic hypertension, metabolic syndrome, pregnancy, belonging to the black race [15].

Desirable antihypertensive effect of amlodipine was proved during the first years of its clinical use. Its notable hypotensive effect in relation to SBP and DBP is demonstrated. Long half-life of amlodipine provides more continuous BP control over 24 hours with a single daily dose [2]. Treatment with amlodipine lowers BP in a dose-dependent manner. In prospective randomized controlled studies – ALLHAT and VALUE, amlodipine did seem to be equally effective in reducing BP as the ACE inhibitors, antagonists AT1-angiotensive receptors, diuretics and β -blockers

Besides, there are a number of advantages of CCBs at AH, foremost it is their ability to slow down of target organs lesion. It is proved that CCBs have a more efficacious in retarding progression of atherosclerosis and left ventricle hy-

pertrophy (LVH) than β -blockers [5, 28]. In the multicenter, randomized, placebo-controlled study TOMHS (Treatment of Mild Hypertension Study) [12], involving 902 patients with stage I hypertension, the comparison of antihypertensive effectiveness and tolerance of monotherapy of amlodipine, chlortalidone, acebutolol, enalapril and doxazosine was carried out. Diuretic chlortalidone as add on therapy was used if there was no adequate BP control. In patients who already had taken diuretic was given inhibitor ACE enalapril. The therapeutic effectiveness was estimated not only by BP lowering, but also by the dynamics of left ventricular mass and the metabolic profile. Once daily amlodipine 5–10 mg provided the BP-lowering effect in 82.5 % patients and led to a reduction in LVH by 11.5 %, ceding only to ACE inhibitor. Moreover, amlodipine therapy was associated with favorable metabolic effects (reducing the concentration of uric acid, total cholesterol, low-density lipoprotein cholesterol, triglycerides, serum creatinine concentration). LVH regression by CCBs, apparently is a result of its direct modulating effect on the calcium-dependent processes in myocardium fiber. In three large studies the similar regression of LVH during treatment with ACE inhibitors (lisinopril, enalapril and fosinopril) and CCBs (amlodipine, nifedipine) was recorded

Coronary heart disease. Dihydropyridine CCBs are effective antianginal agents. This medicine group, through their direct vasodilatation and beneficial effects on coronary blood flow and coronary vascular resistance, increases oxygen supply. By virtue of CCBs ability to decrease afterload and peripheral resistance, cardiac workload is decreased and therefore myocardial oxygen demand is decreased. Controlled clinical studies have confirmed antianginal effects of amlodipine. Thus, treatment with amlodipine decreased the weekly number of anginal attacks and the weekly number of nitroglycerin tablets consumed, the frequency and duration of myocardial ischemia on Holter monitoring and increased the tolerance of physical activity.

In the Circadian Anti-Ischemia Program in Europe (CAPE) trial [4] the angina frequency, nitroglycerin use, and the circadian pattern of myocardial ischemia in 48-h ambulatory ECG monitoring in patients with chronic stable angina (n=250)

were assessed. Compared with placebo, amlodipine significantly reduced both the frequency of ST segment depression episodes (60% for amlodipine versus [vs.] 44% for placebo, $p = 0.025$) and total integrated ST ischemic area (62% mm-min vs. 50% mm-min, $p = 0.042$). Amlodipine reduced ischemia over the 24 h with the intrinsic circadian pattern maintained. In addition, diary data showed a significant reduction in angina (70% for amlodipine vs. 44% for placebo, $p = 0.0001$) and in nitroglycerin consumption (67% vs. 22%, respectively, $p = 0.0006$). Amlodipine and placebo demonstrated similar safety profiles (adverse events 17.3% for amlodipine and 13.3% for placebo; discontinuation rates due to adverse events were 2% vs. 4.4%, respectively).

First, in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) [20] 825 patients with angiographically documented CAD (30% or less diameter stenosis) were randomized to amlodipine (5-10 mg daily) or placebo for 36 months. The primary outcome was the change in diameter of coronary segments with stenosis, and a secondary measure was the effect on carotid atherosclerosis measured by ultrasonography. Other study parameters include the total mortality and cardiovascular morbidity. Significant influence of amlodipine on regression of carotid atherosclerosis, by measuring the effect of intima-media thickness with ultrasound was shown.

Without differences in the change in coronary diameter, patients treated with amlodipine reduced the progression of carotid atherosclerosis, as measured by the change in the intima-media thickness, compared with those treated with placebo. In contrast, amlodipine had a significant effect on the progression of carotid atherosclerosis: the placebo participants had a 0.033-mm increase in IMT during 3-years of follow-up, and the amlodipine participants had a 0.013-mm decrease ($p = 0.007$). When stratified according to carotid segment, the estimated 3-year changes in the common carotid were -0.046 -mm regression for amlodipine vs. $+0.011$ -mm progression for placebo (95% confidence interval [CI] on difference -0.090 to -0.024 mm). The mechanism of amlodipine in slowing the progression of intima

media thickness may be related to its antiatherogenic effect, as well as to its effect on cellular growth and hyperplasia of the arterial wall.

There was no treatment difference in the rates of all-cause mortality or major cardiovascular events, although amlodipine use was associated with fewer cases of unstable angina (60 vs. 85, hazard ratio [HR] 0.67 [0.48 to 0.93]) and coronary revascularization (53 vs. 86, HR 0.57 [0.41 to 0.81]) regardless of the use of β -blocker, nitrates, or lipid-lowering therapy. An improvement in coronary vasomotor tone could be due to a direct effect on vascular smooth muscle or endothelial function [20]. Thus, the reduction in hospitalization for angina pectoris and the need for coronary revascularization may have important implications for current practice.

The similar results were obtained in the Coronary AngioPlasty Amlodipine REStenosis Study (CAPARES) [6] investigated the effect of amlodipine vs. placebo on minimal luminal diameter detected by quantitative coronary angiography in patients with stable angina pectoris undergoing percutaneous coronary angioplasty (PTCA). In a prospective, double-blind design, 635 patients were randomized to 10 mg of amlodipine or placebo two weeks before PTCA and were followed for four months after PTCA. The trial showed that treatment with amlodipine did not affect minimal lumen diameter assessed by quantitative coronary angiography (-0.30 ± 0.45 mm vs. -0.29 ± 0.49 mm; $p = 0.84$) after a four-month period. However, the study showed that the incidence of repeat PTCA was significantly lower in patients treated with amlodipine vs. the placebo group (3.1 % vs. 7.3 %, $p = 0.02$, relative risk ratio [RR]: 0.45, 95% CI: 0.22 to 0.91). The incidence of angina was significantly lower in the amlodipine group compared with the placebo group both early (2 weeks) and late (20 weeks) after PTCA ($p = 0.04$ and 0.03). Exercise-induced ischemia was reduced by 40% ($p = 0.009$) early and 34% ($p = 0.02$) late after PTCA in the amlodipine group, and ischemia on ambulatory electrocardiography was reduced by 18% early and 28% late after PTCA compared with placebo ($p = 0.06$ and $p = 0.009$) [7].

The greatest interest in terms of antiatherogenic properties is the Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial [18], compared treatment with either amlodipine or enalapril to placebo in patients with known angiographic coronary disease >20% and DBP <100 mmHg. Mean baseline BP was 129/78 mmHg. The primary end point was a composite of cardiovascular death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina or congestive heart failure (HF), fatal or nonfatal stroke, transient ischemic attack, and new diagnosis of peripheral arterial disease. A total of 1991 patients with CAD with or without treatment, were randomized to receive either amlodipine 10 mg daily (n = 663), enalapril 20 mg daily (n = 673), or placebo (n = 655) for 24 months. A substudy of 274 patients measured atherosclerosis progression by intravascular ultrasound (IVUS). The IVUS end point was change in percent atheroma volume. The incidence of the composite end point was 23.1 % in the placebo group compared to 16.6 % in the amlodipine-treated group and 20.2 % in the enalapril-treated group. Only the amlodipine-treated group had a statistically significant reduction in risk (HR 0.69, 95% CI: 0.54 to 0.88, p = 0.003). The enalapril-treated arm had a HR 0.85 (95% CI: 0.67 to 1.07, p = 0.16). Primary end point comparison for enalapril vs amlodipine was not significant (HR 0.81, 95% CI: 0.63 to 1.04, p = 0.10). While the BP reduction was similar with both treatment arms (4.8/2.5 mmHg with amlodipine and 4.9/2.4 mmHg with enalapril), the once daily dosing of both drugs raises the possibility that BP lowering may not have been as stable with enalapril (half-life of ~11 h) compared to amlodipine (half-life of ~50 h) [1].

The IVUS substudy showed a trend toward less progression of atherosclerosis in the amlodipine group vs placebo (p = 0.12), with significantly less progression in the subgroup with SBP greater than the mean (p = 0.02). Paired analyses comparing change from baseline in each of the treatment groups showed progression for placebo (p = 0.001), a trend toward progression for enalapril (p = 0.08), and absence of progression for amlodipine (p = 0.31). Using linear regression analysis, adjusting for baseline blood pressures, the correlation between blood

pressure reduction and progression rate was $r = 0.19$, $p = 0.07$ in the amlodipine group. In the enalapril and placebo groups, there was no statistically significant correlation between BP reduction and progression rate.

Thus, administration of amlodipine to patients with CAD and normal BP resulted in reduced adverse cardiovascular events. Directionally similar, but smaller and nonsignificant, treatment effects were observed with enalapril. Moreover, in the IVUS substudy the authors found evidence of slowing of atherosclerosis progression in amlodipine-treated patients [18, 23].

The comparative assessment of valsartan therapy to amlodipine therapy was carried out in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial [24] included 15,245 hypertensive patients at high coronary risk, who were randomised to antihypertensive treatment based on either valsartan or amlodipine, with the addition of hydrochlorothiazide and open antihypertensive therapy when required. The primary outcome was cardiac morbidity and mortality.

Blood pressure was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period (BP 4.0/2.1 mmHg lower in amlodipine than valsartan group after 1 month; 1.5/1.3 mmHg after 1 year; $p < 0.001$). After a mean follow-up of 4.2 years, the trial failed to show the main outcome of cardiac disease did not differ between the treatment groups (HR 1.04, 95% CI: 0.94 to 1.15, $p = 0.49$). But amlodipine was superior to valsartan in the prevention of MI (19 %; $p = 0.02$) and stroke (15 %; $p = 0.08$) [21]. On the other hand, valsartan had more benefits in preventing HF. Heart failure in the valsartan group was lower both in the period on monotherapy (during 3.2 years) and subsequent therapy (HR 0.63, $p = 0.004$ and 0.78, $p = 0.045$, respectively). Longer duration of monotherapy amplified between-group differences in HF [8]. Thus, the findings emphasise the importance of prompt blood-pressure control for the prevention of cardiovascular disease (CVD), at least in hypertensive patients at high cardiovascular risk, and this was achieved earlier and more effectively by amlodipine treatment. Another important aspect of the VALUE results was the effectiveness of the combination of amlodipine and thiazide diuretic.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [22], included 33,357 patients aged 55 years or older with hypertension and at least 1 other CAD risk factor, who were randomised to receive antihypertensive treatment based on chlorthalidone, amlodipine, lisinopril or doxazosin, although the latter group was halted prematurely. The primary outcome was combined fatal CAD or nonfatal myocardial infarction. Secondary outcomes were all-cause mortality, stroke, combined CAD (primary outcome, coronary revascularization, or angina with hospitalization), and combined CVD (combined CAD, stroke, treated angina without hospitalization, HF, and peripheral arterial disease). After six years of follow-up, the primary outcome occurred in 11.3 % of amlodipine group, 11.4 % of lisinopril group and 11.5 % of chlorthalidone group (RR of amlodipine vs chlorthalidone 0.98, 95% CI: 0.90 to 1.07). SBP was significantly higher in the amlodipine (0.8 mmHg, $p = 0.03$) and lisinopril (2 mmHg, $p = 0.001$) groups compared to the chlorthalidone-treated patients and DBP was significantly lower with amlodipine (0.8 mmHg, $p < 0.001$). For amlodipine vs chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2 % vs 7.7 %; RR 1.38; 95% CI: 1.25 to 1.52). Treatment with lisinopril was associated with an increased rate of stroke (6.3 % vs 5.6 %; RR 1.15; 95% CI: 1.02 to 1.30). The rate of combined CVD and HF was also higher with lisinopril [25]. Thus, the results of ALLHAT indicate that for patients who cannot take a diuretic (which should be an unusual circumstance), first-step therapy with CCBs and ACE inhibitors could be considered with due regard for their higher risk of 1 or more major manifestations of CVD [25].

Data clinical studies suggest that the reflex increase in sympathetic nervous activity accompanying a reduction in BP may contribute to the untoward effects of dihydropyridine CCBs [2]. Plasma norepinephrine concentrations, as the most widely reported marker of sympathetic nervous system activity, showed greater increases in patients treated with amlodipine than with nifedipine GITS. The evidence indicates that both these once-daily dihydropyridine CCBs lower BP effectively with minimal effects on heart rate. There are small differences between the

drugs in the extent to which each activates the sympathetic nervous system with an overall non-significant trend in favour of nifedipine GITS [26].

The ESC guidelines on the management of stable CAD [17] recommend β -blockers or heart-rate lowering CCBs, including dihydropyridine CCBs as the first line antianginal therapy in stable CAD patients without contraindications. Long-acting CCBs can be used to control anginal symptoms in patients with stable coronary artery disease (class I, level A). In the ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation the dihydropyridine CCBs are recommended for patients with signs of angina pectoris in addition to nitrates (class I, level A), patients with vasospastic angina pectoris (class I, level C), as well as angina pectoris when β -blockers are not effective or contraindicated for some reasons (class I, level B) [9].

Thus, clinical data confirm that amlodipine holds the position of the main medicine for long-term treatment of patients with AH and CAD. The results of the clinical trials prove that long durations of hypotensive action. The findings of the clinical studies confirm that long-term hypotensive effect of amlodipine provides an effective BP monitoring. Amlodipine is associated with benefits for all major cardiovascular endpoints as well as total mortality, indicating its benefit in high-risk cardiac patients. Antianginal and protective properties of amlodipine on myocardium determine its favorable effects on prognosis, the frequent hospitalizations and survival of patients with CAD. The beneficial effects of amlodipine on arterial thickening of the carotid artery, progression of atherosclerosis, left ventricular myocardial mass and on the prevention of ischemic events suggest that amlodipine may be recommended for the management of all patients with CAD. Pharmacological therapy with amlodipine is safe and well tolerated in patients with stable CAD and AH.

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Место амлодипина в лечении артериальной гипертензии у пациентов с ишемической болезнью сердца

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Резюме

В статье рассматриваются актуальные вопросы лечения артериальной гипертензии (АГ) у больных с ишемической болезнью сердца (ИБС). Артериальная гипертензия является одним из основных модифицируемых факторов риска развития инсульта, сердечной недостаточности, ИБС. Артериальная гипертензия и ИБС часто являются коморбидными состояниями, имеющими общие патогенетические механизмы. Огромное социальное значение этих заболеваний и их осложнений является основой для поиска путей повышения эффективности лечения больных с данной сочетанной патологией.

На основании данных многочисленных клинических исследований показана целесообразность применения дигидропиридиновых блокаторов

кальциевых каналов (БКК) в качестве эффективной терапии АГ в сочетании с ИБС. На примере применения БКК, в частности амлодипина, показана эффективность данной группы препаратов для лечения пациентов с АГ и высоким риском сердечно-сосудистых осложнений. Амлодипин обладает выраженным антигипертензивным и антиангинальным действием, проявляет антиатеросклеротические свойства, обладает протективными свойствами в отношении миокарда, кроме того, амлодипин имеет благоприятный профиль безопасности, что обуславливает его активное использование в клинической практике, в частности, для лечения АГ в сочетании с ИБС.

Ключевые слова: артериальная гипертензия, ишемическая болезнь сердца, лечение, амлодипин

Місце амлодипіну в лікуванні артеріальної гіпертензії у хворих на ішемічну хворобу серця

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Резюме

У статті розглядаються актуальні питання лікування артеріальної гіпертензії (АГ) у хворих на ішемічну хворобу серця (ІХС). Артеріальна гіпертензія є найважливішим чинником розвитку інсульту, серцевої недостатності, ІХС, що модифікується. Артеріальна гіпертензія і ІБС часто є коморбідними станами, що мають загальні патогенетичні механізми. Величезне соціальне значення цих захворювань і їх ускладнень є основою для пошуку шляхів підвищення ефективності лікування хворих з цією поєднаною патологією.

На підставі даних численних клінічних досліджень показана доцільність застосування блокаторів кальцієвих каналів (БКК) похідних дигідропіридину в якості ефективної терапії АГ у поєднанні з ІХС. На прикладі застосування БКК, зокрема амлодипіну, показана ефективність цієї групи препаратів для лікування пацієнтів з АГ і високим ризиком серцево-судинних ускладнень. Амлодипін має антиангінальний та антигіпертензивний ефекти, проявляє антиатеросклеротичні та кардіопротективні властивості, крім того, амлодипин має сприятливий профіль безпеки, що обумовлює його активне використання в клінічній практиці, зокрема, для лікування АГ у поєднанні з ІБС

Ключові слова: артеріальна гіпертензія, ішемічна хвороба серця, лікування, амлодипін

THE ROLE OF AMLODIPIN FOR THE ARTERIAL HYPERTENSION THERAPY IN PATIENTS WITH CORONARY ARTERY DISEASE

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Summary

The article considers the drug treatment of the patients with arterial hypertension (AH) and coronary artery disease (CAD). Arterial hypertension is one of the main modifying risk factors of stroke, cardiovascular failure and CAD. Arterial hypertension and CAD are generally co-morbid conditions having common pathogenic mechanisms. The great social impact of these diseases and their complications predetermine the search for new ways of improving treatment of patients with above mentioned combined pathology.

Numerous clinical studies confirmed the advisability of dihydropyridine calcium channel blockers (CCB) as an effective therapy of hypertension associated with CAD. For example of CCB, in particular amlodipine, the efficiency CCB in hypertensive patients at high cardiovascular risk is demonstrated. Amlodipine is effective as both antihypertensive and antianginal agent with antiatherosclerotic and cardioprotective properties. Besides amlodipine has a high level of safety which explains its active use in clinical practice, in particular, for treating patients with hypertension associated with CAD.

Key words: arterial hypertension, coronary artery disease, therapy, amlodipine