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Hypertension and ischemic heart disease

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ABSTRACT

Hypertension is one of the major risk factors for ischemic heart disease and appropriate control of blood pressure is the cornerstone of both primary and secondary ischemic heart disease prevention. Effective blood pressure (BP) control is recommended in primary prevention, i.e., maintaining blood pressure <140/90 mmHg, while in secondary prevention values <130/85 mmHg used to be recommended. Treatment of hypertension in patients with ischemic heart disease is based on ACE inhibitors and/or AII antagonists (trials HOPE, EUROPA, and PEACE) in combination with beta blockers or with verapamil if beta blockers are not tolerated.

According to epidemiologic data, cardiovascular mortality increases with blood pressure, starting as low as from the 110/70 mmHg level. Czech, European, and American guidelines from the early 21st century recommend that blood pressure in patients with ischemic heart disease (IHD) be maintained below 130/80 mmHg. Data from the INVEST a ACCORD trials led, however, to reappraisal of these strict recommendations and the blood pressure values currently recommended in secondary prevention correspond to high-normal blood pressure, i.e., 130–139 mmHg/80–89 mmHg.

INVEST is the largest clinical trial that focused on hypertonic patients with IHD. Its results showed that verapamil is an appropriate alternative to beta blockers and that while lowering of blood pressure below 140/90 mmHg is necessary, its further decrease below 130/80 mmHg is not associated with any additional benefit.

Trials with beta blockers demonstrated that lowering of heart rate (HR) improves the patients' prognosis. This hypothesis was definitely verified by trials BEAUTIFUL a SHIFT. The recommended heart rate for patients in secondary prevention is 50–70 bpm.

Contents

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1. Hypertension and ischemic heart disease

When treating patients with high blood pressure, we always have to look for target organ damage (left ventricular hypertrophy, microalbuminuria, retinal angiosclerosis/retinopathy) and for ensuing complications (ventricular dysfunction and manifestation of ischemic disease). Cardiovascular mortality is still high despite continuous decrease of total and cardiovascular mortality in most developed countries. Timely prevention and treatment of hypertension and ischemic heart disease can thus result in further improvement of the current situation.

In general, hypertension doubles the risk of cardiovascular disease and accelerates significantly the development of atherosclerosis [1]. Blood pressure plays a crucial role in the atherosclerotic process. Atherosclerosis manifests only rarely in parts of circulation with low blood pressure, e.g., in pulmonary arteries or veins. The risk of cardiovascular complications increases continually along with the blood pressure, starting as low as from the 110/70 mmHg level. Systolic blood pressure is more predictive of mortality, especially in the elderly who most often suffer from isolated systolic hypertension. The situation when hypertension is not accompanied by other risk factors for atherosclerosis is rare. On the contrary, combination of hypertension with dyslipidemia, impaired glucose tolerance or diabetes, abdominal obesity, hyperinsulinemia, and hyperuricemia is very common, lately being referred to as so-called metabolic syndrome.

Basic workup in a hypertonic patient should include the assessment for possible ischemic heart disease using ECG or echocardiography (coronarography when pain or dyspnea are present), all components of metabolic syndrome, and possible nefropathy—excluding microalbuminuria using the dipstick method. Detection of albumin in urine is associated with 2–4fold increase in risk of heart damage so it should lead not only to intensification of therapy but also to possible further diagnostic workup. Diabetes mellitus has been linked to similar 2–4fold risk increase.

Treatment of hypertension in patients with ischemic heart disease is based on angiotensin-converting enzyme inhibitors (ACE-I), which is consistent with the results of trials HOPE, EUROPA, and PEACE [2–4] completed at the end of 20th or beginning of the 21st century. When ACE-I are not tolerated, it is possible to use the blockers of receptor 1 for angiotensin II (ARB). These can be combined with beta blockers, preferably selective, without ISA activity. Verapamil can be used in cases of beta blocker intolerance. Patients suffering from angina can use dihydropyridine-type calcium channel blockers; diuretics are indicated in cases of heart failure.

2. Blood pressure control in chronic IHD

The treatment of hypertension and ischemic heart disease is being discussed continuously, especially in the context of association between high but also low values of diastolic blood pressure and the number of IHD deaths (so-called J-curve). HOT (Hypertension Optimal Treatment) was the first large trial whose authors attempted to solve this question in the 90ties [5]. It was a randomized study of hypertension with 19,193 participants from 26 countries aged 50–80 (mean: 61.5) years, whose diastolic blood pressure was 100–115 mmHg (mean: 105 mmHg). The patients were randomized to three groups with different target values of diastolic blood pressure (below 90, below 85 or below 80 mmHg). The differences among groups concerning the rates of predefined events and deaths according to target blood pressure values were minimal and only the trend towards decrease of myocardial infarction rate in the group with lower target blood pressure reached statistical significance (28% decrease in the rate of events with the “below 80 mmHg” vs “below 90 mmHg” target). The rate of major cardiovascular events was the lowest with blood pressure 138.5/82.6 mmHg.

The 2007 European guidelines for evaluating and treating hypertension state that patients with ischemic heart disease should have their blood pressure lowered below 130/80 mmHg [6]. Since these guidelines were re-evaluated in 2009, it is prudent to take into account the following [7,8]:

- Treatment target: Systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg are appropriate for every patient, independently of his/her age. When considering the clinical trials it is clear, however, that no single large clinical trial evaluated the benefit of systolic BP lowering below 140 mmHg in the elderly. The recommendations are thus based on general agreement about the benefit but they are not a product of evidence-based medicine (EBM).
- Completed large clinical trials (HOT, VALUE, INVEST, ONTARGET) [5,9–11] demonstrate the benefit of treatment leading to blood pressure decrease below 140/90 mmHg. On the other hand, lowering of systolic blood pressure below 130 mmHg is not supported by any study. A trend towards decrease of cerebrovascular event rate was reported in the ONTARGET trial. This study clearly demonstrated the equality of an ACE inhibitor and a blocker of receptor 1 for angiotensin II.
- Similarly, the recommendation to lower the blood pressure below 130/80 mmHg in diabetics and/or patients with ischemic heart disease is not supported by major clinical trials and is purely speculative.
- The existence of “J” curve was never confirmed directly. According to some post hoc analyses performed in large clinical trials, there probably is a certain blood pressure threshold below which the lowering of blood pressure would be already dangerous. One subanalysis of the trial INVEST [12] data further divided the patients with systolic BP below 130 mmHg into subgroups characterized by progressive systolic BP drops of 5 mmHg and it was shown that systolic BP <115 mmHg was associated with higher total mortality. Epidemiologic studies also demonstrate

increase in cardiovascular event rate starting from 110/70 mmHg. Intervention studies show that appropriate target blood pressure should be 120–140/70–90 mmHg.
- Since clinical trials can only last a limited number of years (for economic, medical, and social reasons), the extrapolation of long-term prognosis of patients based on data from clinical trials always remains speculative and has many drawbacks.

3. Hypertension, diabetes mellitus and ischemic heart disease

Type 2 diabetes mellitus is about 20 times more common than type 1 diabetes mellitus and the prevalence of hypertension in type 2 diabetes mellitus is as high as 70–80%. The coexistence of hypertension and diabetes increases the risk of both cardiovascular and renal complications, a very sensitive marker of the initial insults thus being microalbuminuria. It is also beyond any doubt that lowering of blood pressure in hypertonic–diabetic patients has led to decrease in the rate of cardiovascular complications in virtually all studies including all types of antihypertensive medications, i.e., diuretics, beta blockers, calcium channel blockers, ACE inhibitors, and sartans, which means that it is the lowering of blood pressure per se that matters. Some meta-analyses then showed that diabetic patients profit from the treatment of hypertension even more than non-diabetic patients do. The 2007 ESC/EHS guidelines could be interpreted such that therapy should be started even in cases of high-normal pressure and that the target pressure is below 130/80 mmHg. The medications of choice should be ACE inhibitors or sartans (ARB) in patients suffering from cough [6].

When treating hypertension in diabetics, one should bear in mind the following:

- Pharmacologic antihypertensive therapy is appropriate in patients with high-normal pressure and microalbuminuria.
- All antihypertensives can be viewed as plausible options but beta blockers and diuretics are not the first-choice medications since they increase the insulin resistance.
- Non-pharmacologic measures are suitable especially in cases of type 2 diabetes mellitus—weight loss and decrease of sodium intake to be attempted in the first place.
- Target blood pressure values are $\leq$130/80 mmHg.
- RAAS system blockade (using ACEI or ARB) is preferred. Combination therapy is often necessary. Microalbuminuria represents an indication for therapy with RAAS blockers (especially those with dual excretion—trandolapril, spirapril, fosinopril) independently of the blood pressure values. In diabetics, we try to intervene against all risk factors because of the high cardiovascular risk, including therapy with statins.

4. Trials in diabetics with ischemic heart disease and hypertension

As shown by data from the UKPDS study, patients with hypertension, diabetes mellitus, and tight blood pressure control have lower rate of microvascular complications. The evaluated antihypertensives were atenolol and captopril, tight control of hypertension being defined as blood pressure $<$150/85 mmHg and less tight control as blood pressure $<$180/105 mmHg. Tight blood pressure control was associated with decrease of cerebrovascular event rate (RR 0.56; 95% CI 0.35–0.89; $p=0.013$), heart failure rate (RR 0.44; 95% CI 0.20–0.94; $p=0.0043$) and the risk of microvascular complications (RR 0.63; 95% CI 0.44–0.89; $p=0.0092$). The more intensive therapy of hypertension, however, did not have any significant influence on the myocardial infarction rate or on the overall mortality [13].

The ACCORD trial—blood pressure arm evaluated whether lowering of systolic blood pressure below 120 mmHg would

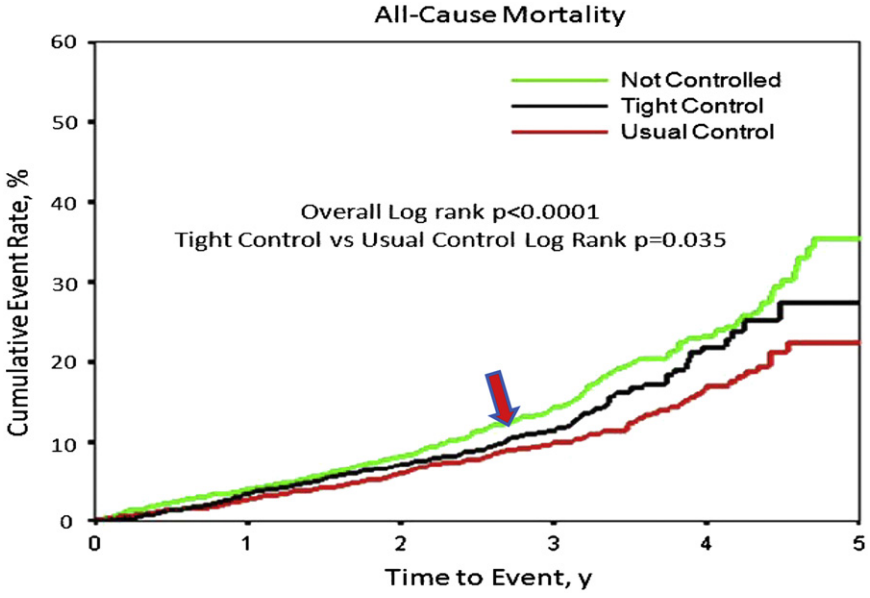

Fig. 1 – Blood pressure control in diabetic participants of the INVEST trial.

result in decrease of cardiovascular risk in diabetics. Lowering of blood pressure below 120 mmHg vs below 140 mmHg was not associated with any significant improvement of cardiovascular event rate. On the contrary, the rate of side effects was higher with more intensive hypertension treatment. It has to be admitted, though, that more intensive antihypertensive treatment was associated with decrease in the risk of cerebrovascular events [14].

In the INVEST trial, 6400 diabetics with ischemic heart disease and hypertension were randomized to receive atenolol or verapamil combined with a diuretic or trandolapril, the target blood pressure being <130/85 mmHg [7]. The patients were divided according to the achieved systolic blood pressure to three groups—tight blood pressure control (<130 mmHg), usual blood pressure control (≥130–140 mmHg), and uncontrolled blood pressure (≥140 mmHg). The highest rate of cardiovascular events was observed in the group of patients with uncontrolled systolic blood pressure. Surprisingly, the patients with usual blood pressure control (≥130–140 mmHg) had better prognosis than patients with tight hypertension control and with systolic blood pressure <130 mmHg, starting approximately from the third year of the trial duration [12] (see Fig. 1).

5. Ischemic heart disease and heart rate (HR)

Heart rate is a predictor of mortality in healthy people, in patients with a history of hypertension, myocardial infarction, heart failure, metabolic syndrome, and in the elderly. Resting tachycardia is associated with decreased life expectancy. It is not quite clear whether this is solely the result of sympathetic nervous system activation or whether different pathophysiological mechanisms are involved. It thus seems prudent to decrease the heart rate and, at the same time, myocardial demand of oxygen. However, increased resting heart rate has not been considered a significant risk factor for cardiovascular disease development so far. The reason is that no prospective trial has proved the association between heart rate lowering and decrease of cardiovascular and overall mortality. Similarly, it is not quite clear which heart rate is optimal or physiological in a man. In nonhuman animals, there is a linear association between the heart rate and lifespan. Man is exceptional in the sense that he lives much longer than would correspond to his heart rate. Women also have higher heart rate than men and yet they live longer.

As early as in 1945, Levy has shown that heart rate is a risk factor for hypertension and in 1957, Widimský added that patients with mild hypertension almost always have increased heart frequency. In the GISSI 3 trial, heart rate over 100 bpm in patients with a history of myocardial infarction was associated with almost 10fold increase of mortality compared with heart rate below 60 bpm [15]. Based on data from clinical trials, the risk factor is now defined as heart frequency ≥70 bpm.

By lowering the heart rate we attempt to control both mortality and complications, including heart failure. It cannot be excluded so far that the positive influence of bradycardia-inducing medications is related rather to their other pharmacological qualities while the heart rate lowering represents just a side effect. Cardiologic medications used with the specific aim to control the heart rate include verapamil-type calcium channel blockers (phenylalkylamines), beta blockers (without ISA activity), digitalis, and I_f channel blockers.

In the Danish DAVIT II trial, 878 patients with a history of myocardial infarction received verapamil 360 mg daily and 897 patients with the same history were given placebo. Treatment was initiated between 7 and 14 days after the myocardial infarction and lasted for 18 months while all patients taking beta blockers were excluded. After 1.5 years of treatment, a trend in favor of verapamil was observed, the risk of major cardiovascular events being 20% lower ($p=0.03$) [16]. In the international INVEST trial comprising 22,576 patients with a history of myocardial infarction, verapamil-based treatment was associated with the same risk of death, re-infarction or cerebrovascular event as atenolol-based treatment, atenolol being considered the gold standard until then. Significantly less newly diagnosed diabetics were identified, however, in the group with verapamil-based treatment and these diabetics had significantly less cardiovascular events [10]. Good blood pressure control <140/90 mmHg during the entire trial was associated with the lowest cardiovascular event rate. Patients with blood pressure below 140/90 mmHg during more than ¾ visits suffered from cardiovascular events half less often than patients with good blood pressure control during every 4th visit only. Systolic blood pressure <115 mmHg was associated with highly significant increase in mortality [12].

Lowering of heart rate in cases of heart failure should result in left ventricular function improvement, slowing of the progression of heart failure and eventually in decrease of the cardiovascular event rate including cardiovascular mortality—i.e., in improving the prognosis. Large clinical trials with beta blockers showed that significant improvement of prognosis does indeed occur in patients with chronic heart failure. In the CIBIS trial, for example, treatment with bisoprolol lead to decrease of resting heart rate by about 15 bpm compared to placebo [17]. Heart rate lowering represented the most robust predictor of survival in a multivariate analysis of data acquired in this trial. The ensuing and larger CIBIS II trial demonstrated that resting heart rate and the change in heart rate during treatment were significant predictors of mortality [18]. The best prognosis was associated with the lowest basal resting heart rate and with the highest drop in heart rate during therapy.

The role of digoxin in patients with IHD was studied in most detail by the DIG trial. The total number of 6,800 patients was randomized to digoxin or placebo with the possibility to add-on either ACE inhibitor or diuretic. The overall mortality remained unchanged. The only two outcomes influenced positively and significantly by digoxin were the total number of hospitalizations and the number of hospitalizations for heart failure [19].

BEAUTIFUL was a clinical trial focusing on the question whether a decrease in the heart rate caused by a specific inhibitor of I_f channels in the sinoatrial node – ivabradine – would result in lowering of the cardiovascular mortality and morbidity in patients with stabilized ischemic heart disease and systolic dysfunction of the left ventricle [20,21]. In the

placebo arm, a hypothesis was tested that increased resting heart rate represents a marker of future cardiovascular mortality and morbidity. Total number of 10,917 patients with documented IHD and left ventricular ejection fraction <0.40 was enrolled and these patients were randomized to ivabradine or placebo. In the entire study population, ivabradine did not show any benefit with respect to both primary and secondary endpoint compared to placebo. Subanalyses within the placebo group compared patients with resting heart rate ≥ 70 bpm vs <70 bpm and revealed that patients with heart rate ≥ 70 bpm had a higher risk of cardiovascular mortality (by 34%; $p=0.0041$), hospitalizations for heart failure (by 53%; $p<0.001$), hospitalizations for myocardial infarction (by 46%; $p=0.0066$), and coronary revascularization (by 38%; $p=0.037$). Treatment with ivabradine was safe and well tolerated.

SHIFT was a following trial aimed at testing the hypothesis that lowering of heart rate per se by ivabradine in patients with chronic heart failure would decrease cardiovascular event rate [22]. Total number of 6,558 patients with systolic heart failure of ischemic or non-ischemic etiology, NYHA class II–IV, ejection fraction ≤ 0.35, and sinus rhythm of ≥ 70 bpm at the baseline was enrolled. Enrolled patients were treated according to current recommendations for the treatment of heart failure including beta blockers. After mean follow-up period of 23 months, ivabradine treatment resulted in a mean heart rate drop of 8 bpm compared to placebo. This heart rate lowering resulted in decrease of the composite primary clinical endpoint (cardiovascular mortality and hospitalizations for progression of heart failure) by 18% ($p<0.0001$). This decrease could be primarily explained by drop in hospitalizations for heart failure by 26% ($p<0.0001$) and deaths caused by heart failure by 26% ($p=0.014$). Lowering of cardiovascular mortality per se with ivabradine by 9% failed to reach statistical significance ($p=0.128$).

Bradycardia-inducing medications have a clear role in the treatment of patients with a history of myocardial infarction and they have other pharmacological properties besides lowering of heart rate – they increase the myocardial contractility, decrease the sympathetic activity and cause vasodilatation. Thus, their use has clear indications but also contraindications. Digitalis is indicated in cases of atrial fibrillation; beta blockers should be given to most patients with dominant heart failure; verapamil SR is beneficial in patients without heart failure and with a heart rate >70 bpm, atrial fibrillation, diabetes or metabolic syndrome, and in all cases where beta blockers are contraindicated. Ivabradine treatment is most appropriate in patients with heart failure and heart rate >70 bpm together with a maximal tolerated beta blocker dosage.

6. Conclusion

The treatment of hypertension in patients with a history of myocardial infarction is based on the following:

- Blockade of the renin – angiotensin – aldosterone system. Angiotensin-converting enzyme inhibitors (ACE-I), blockers of receptor 1 for angiotensin II (ARB) and aldosterone blockers (in patients with heart failure) are used.
- Beta blockers—selective beta blockers without ISA should be preferred. If not tolerated, verapamil can be used in patients without heart failure.
- In patients with atrial fibrillation, beta blockers are recommended; verapamil and digitalis offer the control of both rhythm and frequency; ACE inhibitors or ARB represent a so called upstream therapy.
- Target blood pressure is $<140/90$ mmHg.
- Target heart rate is ≤ 70 bpm (EBM for patients with heart failure).
- Ivabradine is recommended in patients with heart rate >70 bmp together with a maximal tolerated beta blocker dosage.
- Hypolipidemics should also be given—mostly statins, with a target total cholesterol level below 200 mg/dl (4.5 mmol/l). If triglycerides are high, HDL cholesterol is low, and the patient is on antiplatelet therapy, fibrates can be added. The cornerstone of antiplatelet therapy is an acetylsalicylic acid in doses 75–360 mg, combined with clopidogrel for several months. Alternative use of prasugrel a ticagrelor is already suggested by the new recommendations.

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