

HYPERTENSION AND CORONARY HEART DISEASE

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Hypertension (HTN) is a major independent risk factor for the development of coronary heart disease (CHD). On the other hand, the presence of CHD, an established form of cardiovascular disease (CVD), carries very high risk for subsequent events, and modifies the therapeutic approach of an individual with hypertension (HTN). Nevertheless, the choice of an appropriate blood pressure (BP) lowering treatment remains challenging and the data about the optimal BP targets in this population are contradictory.

Epidemiological data, pathophysiology and diagnostic approach

There is a continuous relationship between BP levels and the development of CHD in all ages, genders and ethnic groups. Overall, at ages 40 – 69 each 20 mm Hg increase in systolic BP (SBP) [or each 10-mm Hg increase in diastolic BP – (DBP)] doubles the risk of a fatal coronary event ¹. In all hypertensive patients, assessment and stratification of total CV risk is imperative in order to individualize treatment (drug regimen and intensity of treatment). However, the presence of established CHD (myocardial infarction, angina pectoris, and/or myocardial revascularization) automatically stratifies a given patient in the highest risk category, and eliminating the need for further estimation of CV risk ². There are many mechanisms responsible for the strong relationship of HTN to CHD. Genetic factors may predispose to both conditions (eg polymorphisms of genes of the RAAS). Other factors as hemodynamics, related to increased afterload and pulse wave velocity, hence greater pulse pressure, result in increased myocardial oxygen demand. The same mechanisms responsible for hypertension genesis also damage target organs, including the coronary arteries and the myocardium: Increased oxidative stress and endothelial dysfunction, sympathetic and RAAS overactivity adversely modulate the atherogenetic potential of elevated BP ³.

Left ventricular hypertrophy (LVH) itself markedly alters coronary reserve. While coronary flow is normal as an absolute number in patients with LVH, if calculated per unit of mass of the hypertrophic LV, it is reduced. Coronary autoregulation (ie the ability of coronary circulation to maintain constant flow in a broad range of perfusion pressures) is markedly impaired in these patients, particularly in conditions of low coronary perfusion pressures (low DBP values – arterial stiffness with early reflection - high augmentation index) and increased intra-cardiac diastolic pressures (diastolic dysfunction, and/or ischaemia) thus leading to poor flow in the subendocardium.

Flow reserve is the increase in coronary flow caused by maximal coronary vasodilation and is noticeably reduced in hypertensive patients with LVH. Clinical angina pectoris in the absence epicardial coronary lesions is not so uncommon, and it appears that the impaired coronary flow reserve is responsible for this particular syndrome.

The diagnostic approach of CHD in the presence of HTN can be cumbersome. Pre-existing ST segment depression (strain pattern) is the most evident culprit when present. Its etiology, LVH and microvascular dysfunction with the resulting diminished flow reserve, even not evident in rest ECG recordings, can render a treadmill stress test positive, in the absence of coronary epicardial stenoses, thus limiting its specificity ^{4,5}. Stress imaging modalities suffer from lack of specificity even those who rely on motion abnormalities (stress echo, stress MRI) especially in specific patterns of hypertrophy ⁶.

An anatomical approach of ischemia has yet a long way to go: In the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) 10,003 patients (65% hypertensive) randomized either to usual care using a functional testing strategy, or to an initial anatomic testing strategy with CT angiography. The latter approach did not result in improved clinical outcomes ⁷. Novel strategies using CT angiography derived fractional flow reserve seem promising with cost reducing potential ⁸, although there are no specific performance comparisons published for patients with HTN. Until definitive data are available,

an algorithmic approach taking into account the overall patient risk for CHD and target organ damage, namely LVH, might dictate guideline proposed, non-invasive test selection ^{9,10}.

Antihypertensive drugs in patients with CHD

Aggressive management of risk factors is the most crucial part of the management of a patient with CHD. It should be noted that revascularization (PCI or CABG), except in acute coronary syndromes and in certain anatomic subsets in patients with stable angina, cannot provide survival benefit ¹⁰. On the other hand, optimal medical treatment offers hard end point benefit ¹¹, but only if optimal medical targets are achieved. Among the 15,828 patients with stable CHD participating of Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) study, the 97, 96, 79 and 77% of the participants were receiving statin, antiplatelets, beta blockers and ACEi/ARB respectively at baseline. Nevertheless 29% of them had an LDL > 100 mg/dL, 46% had BP > 140/90 mmHg, and 18% of them were currently smokers ¹². One should not disregard that uncontrolled HTN is a major predictor of risk for haemorrhagic events in CHD patients treated with antithrombotics.

In the presence of LV systolic dysfunction hypertensive patients should be treated as per current CHF guidelines with the preferential use of ACEi's (or ARBs in case of contraindications – untoward effects) and beta blockers and for some of them mineralocorticoid receptor antagonists (MRAs) and angiotensin receptor – neprilysin inhibitor (ARNI) ¹³.

The use of beta blockers early after a myocardial infarction or in cases of systolic dysfunction is guideline advocated and beneficial. Nevertheless, no hard end point evidence exists for their preferential use in CHD: They can be used in the context of BP reduction per se, or for prevention of anginal attacks but they offer no survival benefit compared to other antihypertensive or antianginal drugs.

In the REduction of Atherothrombosis for Continued Health (REACH) registry 14,043 patients with known prior MI, 12,012 with known CHD, but no MI and 18.653 with only CHD risk factors and a mean follow-up of 44 months, the use of β-blockers was not associated with a lower risk of composite cardiovascular events ¹⁴.

In another study with data from the Myocardial Ischaemia National Audit Project, a total of 179,810 survivors of hospitalization with acute myocardial infarction without HF or LV Systolic dysfunction, between were assessed. Unadjusted 1-year mortality was lower for patients who received beta blockers compared with those who did not (4.9% vs. 11.2%; p < 0.001). However, after weighting and adjustment, there was no significant difference in mortality between those with and without β-blocker use ¹⁵.

Should a β-blocker be used for treatment of HTN in a patient with CAD, adverse metabolic actions have to be taken into account. Then, β1 selective and especially vasodilating beta blockers have to be preferred ¹⁶.

The approach of ESH/ESC guidelines ¹⁷ is that all drug classes can be used in order to treat HTN as far as the BP lowering goal is achieved, while compelling indications, comorbidities and contraindications are taken into account. ACEis remain the main step of treatment due to their neutral metabolic profile and on the other hand due to their favourable results "beyond blood pressure control" as shown in big trials recruiting patients with CHD without overt HF ¹⁸. Studies as Heart Outcomes Prevention Evaluation Study (HOPE) with ramipril and EUROPE trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) have verified this concept especially for higher risk patients. In lower risk populations as those studied in the Patients in the Prevention of Events With Angiotensin Converting Enzyme Inhibition (PEACE) study, trandolapril failed to demonstrate a beyond blood pressure reduction effect. As for ARBs, the benefits over other antihypertensive

drug classes in preventing CHD are not so consistent and their use can be advocated when ACEis are not tolerated³.

Treatment Thresholds and Targets – The J curve and antianginal treatment

There is much confusion on the proper BP thresholds and targets lately. The Systolic Blood Pressure Intervention Trial (SPRINT) assigned 9361 persons with a systolic blood pressure of ≥ 130 mm Hg and increased CV risk, but without diabetes, comparing SBP targets of < 120 mm Hg vs < 140 mm Hg (standard treatment) measured with an unattended method. After one year the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. There was a 25% lower rate of the primary composite outcome and 27% lower all-cause mortality in the intensive-treatment group than in the standard-treatment group but at the price of higher frequency of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure¹⁹. Much ink has been spilled since its publication, over the method of BP measurement and how it compares to the traditional method used in HTN mega-trials and everyday life, on the lack of benefit on stroke incidence (the most easily achieved goal in every BP reduction strategy) and on the fact that the lower rate of the primary endpoint was mainly driven by heart failure incidence reduction.

Recently published ACC/AHA HTN guidelines²⁰ based largely on the SPRINT results adopt the definition of 130-139/80-89 mmHg as stage 1 hypertension and advocate the initiation of antihypertensive treatment on patients with CHD with these BP values, aiming to a target BP of below 130/80 mmHg (a class I recommendation but with a level of evidence C – expert opinion – for DPB targets). They advocate the use of beta blockers (except atenolol and sympathomimetic ones) along CCBs for control of hypertension in patients with angina but with a lower class of recommendation (IIb C) beyond three years after a myocardial infarction. To criticize the newly defined stage 1 HTN and BP targets, remains beyond the scope of this newsletter, but one should await the publication of the 2018 ESH/ESC HTN guidelines for the European perspective on the matter. Nevertheless, it is only three years ago, that American guidelines published by the JNC 8, adopted a BP threshold of 150/90 mmHg for everyone older than 60 years, based on the then available evidence. Should only a study change our practice, even though the unattended BPs achieved are recorded by a totally different to our everyday practice method which yields much lower BP values than the guideline advocated office BP values²¹? Could the new definitions cause confusion in the medical community and the general public labelling overnight the 46% of the whole adult population as hypertensives²⁰? And furthermore, should we forget the pathophysiology and recently published evidence on the existence of a J curve at least for patients with CHD? Coronary perfusion pressure in patients with CHD is related to the coronary artery diastolic pressure distal to a significant coronary obstruction, which, however, is lower than the aortic diastolic pressure and thus, even if aortic diastolic pressure is satisfactory, the diastolic pressure distal to a coronary artery stenosis may not be adequate. Thus, aortic diastolic pressure is a poor indicator of coronary perfusion pressure in patients with obstructive CAD. A large body of evidence

indicative for the existence of a J curve, came from many HTN mega-trials, as the International Verapamil SR Trandolapril Study (INVEST), the Randomized Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and the International Verapamil SR Trandolapril Study (INVEST), to name only a few, although one can argue that they were not designed to assess this fact²².

Results from 22,672 patients enrolled in the prospective observational Longitudinal Registry of patients with stable coronary artery disease (CLARIFY) and treated for hypertension have shed more light. In this study, increased SBP ≥ 140 mm Hg and DBP ≥ 80 mm Hg were each associated with increased risk of cardiovascular events. On the other hand, SBP of < 120 mm Hg and DBP of < 70 mmHg were both associated with an increase in the primary composite outcome of cardiovascular death, myocardial infarction, or stroke (adjusted HR 1.56 for SBP < 120 mmHg, 1.41 for DBP 60–69 mm Hg and 2.01 for DBP < 60 mmHg)²³.

Vasoactive drugs (β -blockers, CCBs, nitrates) are prescribed to patients with CHD for a reason other than hypertension management, that is anginal symptoms control, so awareness of the deleterious effects of iatrogenic hypotension is warranted. Current ESC guidelines on stable CHD categorize the medications for symptomatic relief of angina as first and second line antianginal drugs, and then provide little guidance. The fact, on one hand, that in the absence of heart failure, or early after an acute coronary syndrome, no antianginal drug provides survival benefit, along with the fact that newer antianginal drugs as ranolazine and ivabradine have been the only ones studied on the top of all the disease modifying regimens (aspirin, statins, ACEis/ARBs) on the other, calls for a more personalized approach respecting each patient's compelling indications, comorbidities and SBP and heart rate (HR) thresholds rather, than respecting strict first and second line categories. Moreover, respecting a SBP threshold of 120 mmHg and a heart rate threshold of 60bpm (or 70 in case ivabradine is used) beyond of which no antianginal drugs that lower SBP and/or HR may be prescribed/up-titrated safely, seems more than wise. Practical algorithms taking into account this tailored approach are available^{24,25}.

Concluding Remarks

- Hypertension is a major risk factor for CHD. The presence of HTN modifies the physiology of coronary circulation and can render the diagnosis of CHD cumbersome
- Aggressive risk factor management is crucial for patients with HTN and CHD. Optimal medical targets should be sought
- The choice of drugs for HTN management should focus on BP reduction as well on proven hard end point outcomes and patients' comorbidities
- Lower BP thresholds and targets than those endorsed in the ESH/ESC HTN guidelines is currently not adequately justified
- The evidence for a J – curve phenomenon calls for caution especially in patients with angina treated with vasoactive drugs leading to low SBP and HR values. Specialized algorithms can guide efficient and safe anti anginal therapy decisions.

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