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Review Article

Managing Hypertension in Coronary Artery Disease

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Abstract

Hypertension remains the strongest risk factor for development of coronary artery disease (CAD) and often both these conditions co-exist. Genetic and environmental factors interact to determine whether an individual may develop hypertension and related CAD. Blood pressure lowering itself reduces cardiovascular disease (CVD) risk in patients with hypertension ,however a residual cardiovascular risk persists and necessitates better evaluation and treatment of these individuals. For primary prevention of CAD, the key factor is lowering of blood pressure rather than the choice of the drug, whereas for secondary prevention there is merit in choosing the appropriate agent. From a practical standpoint, an office BP of <130/80 is the target for most patients, if well tolerated (except for people above age 65 years, for whom the 2018 ESC/ESH guidelines recommend a target of <140/80). Care needs to be taken to keep DBP above 70 mm in some patients. Certain drugs should be avoided in CAD with heart failure and in CAD without HF. While statins are recommended for secondary prevention of CVD in all hypertensives, they are recommended in those at moderate to high risk for primary prevention. Aspirin is indicated in all patients for secondary prevention, but has restricted recommendation for primary prevention.

Key words: Hypertension, Coronary artery disease, blood pressure targets, primary and secondary prevention

Introduction

Hypertension is one of the most important risk factors for coronary artery disease (CAD) which, in turn, is commonly its first presenting complication. The present review will address the following key questions:

1. What are the epidemiological relationships between hypertension and CAD?
2. What are the pathophysiologic mechanisms underlying the risk of CAD due to hypertension?
3. How effective is blood pressure (BP) treatment for reducing the risk of CAD?
4. Does the benefit of treatment accrue only from BP lowering effect or also from some additional uniquely protective actions of specific classes of drugs?
5. Why is there a residual risk of cardiovascular disease (CVD) and CAD despite optimal treatment of hypertension?
6. What are the systolic BP (SBP) and diastolic BP (DBP) targets that are appropriate in patients
   (i) With established CAD?
   (ii) Without established CAD?
7. How low should you go? Is there a J curve?
8. Which are the antihypertensive drugs that have shown particular efficacy (and should be used) in the secondary prevention of acute and chronic (stable) coronary syndromes and heart failure (HF) caused by CAD?
9. Which BP lowering drugs are inadvisable in patients with CAD?
10. Should all hypertensive people be on a statin? On aspirin?

Epidemiological Relationships with CAD

The INTERHEART study[1] showed that hypertension accounted for about ~25% of the population attributable risk of myocardial infarction. In another registry-based study[2] of over 1 million patients, angina and myocardial infarction were the cause of almost half (43%) the CVD free years of life lost over 5 years, from the age of 30 years, due to hypertension.

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A meta-analysis of 61 studies involving almost 1 million adults[3] showed that BP ranging from 115/75 to 185/115 for all ages was associated with fatal CAD such that the risk of a fatal coronary event doubled with each increase in SBP of 20 mmHg or in DBP of 10 mmHg. Although systolic hypertension (especially after age 50 years) and combined systolic diastolic hypertension (especially in the young) are associated with heightened CVD risk, there is a divergence of opinion with regard to the risk posed by isolated diastolic hypertension.[4,5]

Hypertension is associated with greater number of cardiovascular (CV) risk factors than normotension and these risk factors multiply the risk associated with hypertension. One or more coexistent risk factors are found in more than 80% of hypertensives and two or more in 55% of them.

Besides the concomitant presence of classical risk factors, some factors that have been found to be predictive of heightened chances of CAD and CVD in hypertensive people are as follows:

Coronary artery calcium (CAC) score,[6] biomarkers such as NT pro-BNP and troponins,[7] morning home BP,[8] serum uric acid,[9] inter-arm difference in BP,[10] exaggerated (>180) SBP rise on a treadmill test,[11] and early age of onset of hypertension.

Pathophysiologic Mechanisms Underlying the CAD Risk of Hypertension

There is an interplay of genetic and environmental factors through neurohormonal pathways (sympathetic nervous system, renin–angiotensin–aldosterone system activity, insulin resistance, vasodilators and vasoconstrictors, growth factors, and inflammatory cytokines), hemodynamic effects, structural and functional abnormalities in the arterial system, endothelial dysfunction, inflammation and oxidative stress to determine the risk of development of hypertension, and consequent CAD.

When the left ventricular hypertrophy (LVH) occurs in addition, it reduces coronary flow reserve, increases metabolic demands of the myocardium, and favors the development of ventricular arrhythmias. Diastolic dysfunction reduces the perfusion of the myocardium.

Antihypertensive Rx for Primary Prevention of CAD: How Effective?

Randomized trials[12] have shown reductions in CV risk that BP lowering brings about in hypertensive people.

In a meta-analysis of 123 studies with 613 815 participants, CAD was reduced by 17%,[13] stroke by 27%, HF by 28%, and all-cause mortality by 13% for every 10 mmHg reduction in SBP. Others[14] have shown a similar risk reduction with more intensive BP control.

The above-mentioned meta-analysis also showed that for prevention of major CVD events, stroke, and renal failure, β-blockers were inferior to other drugs. Calcium channel blockers were better for the prevention of stroke and diuretics for the prevention of HF, for which calcium channel blockers were inferior to other drug classes.

A beneficial effect of angiotensin-converting enzyme (ACE) inhibitors on CVD outcomes in individuals with established CVD or at high risk for its development has been shown in hypertensives and non-hypertensives in studies such as heart outcomes prevention evaluation, survival and ventricular enlargement, and European Trial on Reduction of Cardiac Events With Perindopril in Stable CAD.

ACCORD and SPRINT (see below) are recent trials that have shown the efficacy of hypertension treatment for primary prevention of CVD in patients with mean basal SBP of 139 mmHg.

Does the Benefit of Treatment Accrue Only from BP Lowering Effect or also From Some Additional Uniquely Protective Actions of Specific Classes of Drugs?

As per meta-analyses of most antihypertensive trials, BP lowering appears to be more important than a particular drug class for primary prevention of CAD.

On the other hand, for secondary prevention in individuals with underlying comorbid illnesses such as IHD, CKD, or recurrent stroke, different drug classes have shown differing levels of benefit [Table 1].

Why is There a Residual Risk in Treated Hypertensives?

Even after the office BP is controlled, a hypertensive patient under treatment has a substantial residual risk of any CV event. Indeed, there is up to 50% increased risk[15,16] in treated hypertensives as compared to untreated normotensives, which is why risk scores include "treatment for hypertension" as one of the risk factors in the equations. More specifically, the increase in risk was 46% for coronary disease, 75% for stroke, and 62% for CV death.

The reason for this increased risk could be multifold:

Higher underlying subclinical CVD burden in treated hypertensives

Indeed, as shown by Nadir *et al.*,[17] 34% of optimally treated hypertensives have silent, underlying cardiac abnormalities out of which LVH was the most prevalent (29%), followed by LV diastolic dysfunction (LVDD; 21%), left atrial enlargement (LAE; 15%), LV systolic dysfunction (LVSD; 6%), and silent myocardial ischemia (SMI; 6%) as assessed by resting and dobutamine 2 D echocardiography.

About 13% of all treated hypertensives have ≥3 silent cardiac abnormalities. Out of those with cardiac abnormalities, 1 abnormality was seen in 29%, 2 in another 31%, 3 in another 29%, and ≥4 in 10% of patients.

It has been suggested by them[17] that combined screening of treated hypertensives with BNP and hs TnT with cutoff values at 15 pg/mL and 5·9 ng/L, respectively, had a sensitivity and specificity of 87% and 65% for diagnosing underlying disease

Table 1: Antihypertensive drugs that have shown particular efficacy (and should be used) in the secondary prevention of CAD and its subsets

Hypertension with →	Stable CAD	ACS including unstable angina, NSTEMI, and STEMI	HFrEF with CAD	HFpEF with CAD
First-line therapy	GDMT BB*, ACE/ ARB, (Non DHP CCB if BB contraindicated in normal LV fn.)	BB**, NTG, ACEI/ARB, (Non DHP CCB if BB contraindicated in normal LV fn.)	GDMT BB***, ACE/ARB/ ARNI, AA, thiazide-type diuretics for HT, loop diuretics for volume control	Thiazide-type diuretics for HT, loop diuretics for careful volume control
Add-on therapy	LA DHP CCB for angina and HT Thiazides, AA, for HT	LA DHP CCB for residual angina and HT, thiazide-type diuretics for HT, loop diuretics for volume control, AA after STEMI in patients with LV dysfn. with LVF or diabetes	Hydralazine plus isosorbide dinitrate in Africans and those resistant or contraindicated to RAAS blockers	ACEI/ARB, BB, DHP CCB, (Non-DHP CCB if BB contraindicated, without concomitant DHB CCB)

ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, AA: Aldosterone antagonist, ARNI: Angiotensin receptor-neprilysin inhibitor, BB: Beta-blocker, LA: Long acting, NTG: Nitroglycerine (intravenous), DHP: Dihydropyridine, CCB: Calcium channel blocker, ACS: Acute coronary syndrome, HFrEF: Heart failure with reduced ejection fraction, HFpEF: Heart failure with preserved ejection fraction, HT: Hypertension. *GDMT BB guideline-directed management and therapy of stable IHD with beta-blockers (carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol), **A short-acting β1-selective beta-blocker without intrinsic sympathomimetic activity (metoprolol tartrate) or bisoprolol should be initiated orally within 24 h of presentation, provided that there is no contraindication. ***Guideline-directed management and therapy of HFrEF with beta-blockers (carvedilol, metoprolol succinate, or bisoprolol)

burden listed above. Thus, initial screening of hypertensives with these two biomarkers, followed by further testing of individuals with abnormal biomarker values to find specific cardiovascular abnormality and tailoring the treatment toward the same, may help to further reduce the risk.

This idea matches well with the findings of Pandey *et al.*[7] alluded to earlier that a biomarker-led based approach to CV risk assessment may help identify individuals with elevated BP or Stage 1 hypertension who may benefit from BP –lowering therapy but who are otherwise at low risk based on pooled cohort equation and would not have been recommended antihypertensive medication according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) BP guideline.

Indeed, in the study, approximately one-third of adults with elevated BP or Stage 1 hypertension had elevated high-sensitivity cardiac troponin T or NT-pro-BNP (N-terminal pro-B-type natriuretic peptide), putting them at more than 10% risk of atherosclerotic CVD (ASCVD) or HF over the 10-year follow-up period. Antihypertensive medication would not have been recommended to these patients according to the 2017 ACC/AHA BP guideline.

Another way to redefine risk for the sake of taking treatment decisions is by measuring CAC score. Although as per the new ACC/AHA guidelines, ASCVD risk score of 10% is the cutoff value to guide antihypertensive treatment, it has been shown in a recent analysis[6] that CAC can recategorize risk around this threshold; within the low-risk group defined by ASCVD risk score <10%, CAC >100 identified individuals with higher risk of CVD and CHD death compared with those in the higher risk group (ASCVD ≥10%) who had lower CAC scores.

Reliance on office BP alone for optimal BP control

Conditions such as masked hypertension, nocturnal hypertension, reduced or reversed nocturnal dip, morning surge, and BP variability are all significant predictors of risk which may be missed if only office BP is relied on for optimal BP control.[18-21] Indeed, non-dippers (night-time fall in BP <10%) have been reported to have a CV risk, which is significantly higher than normal dippers.[22]

Presence of other risk factors

Elevated BP seldom occurs without concomitant presence of other CVD risk factors. As said earlier, their combined risk is multiplicative rather than additive and may be one reason why even treated hypertensives remain at higher risk.

BP Targets

There is an apparent difference between the BP targets suggested by the two major guidelines across the Atlantic.[23,24]

For example, the 2017 ACC/AHA guidelines mention an office BP of <130/80 as the target for all patients, whereas according to 2018 ESC/ESH guidelines, the numbers are <140/90.

However, as said, the difference is more apparent than real. This is because (i) ESC/ESH recommends that the first step in management should be to reduce BP below 140/90 in all patients and, if the treatment is well tolerated, treated BP targets should be 130/80 mmHg or lower in most patients (except people above age 65 in whom the target is <140/80) and (ii) the strategy for managing people in the zone between 130/80 and 140/90 is the same in both guidelines, namely, non-pharmacological therapy for 3 and 6 months in low-risk people (at a 10-year ASCVD risk of <10%), and pharmacological therapy along with lifestyle changes with a goal of reaching 130/80 and below for people at higher risk or with CVD or target organ damage. Risk may be redefined as mentioned earlier by selective application of additional tests like biomarkers.

This BP goal of <130/80 has been arrived on the basis of two large recent trials, namely, SPRINT (A Randomized Trial of Intensive Versus Standard Blood-Pressure Control)[25] and

ACCORD (Action to Control CV Risk in Diabetes),[26] and a recent meta-analysis[27] of 42 trials and 44,220 patients which showed a linear relationship between mean achieved SBP and risk of CVD mortality, the lowest risk being at SBP of 120 and 124 mmHg.

Since the method of BP measurement in SPRINT and ACCORD studies was more stringent (Automated Office BP Measurement unattended in SPRINT and attended in ACCORD) than what is done in clinical practice, the SBP target recommended by guidelines (<130 mmHg) is set at somewhat higher level than that which was found to be beneficial in these studies (~ 120 mmHg in SPRINT for all end points and in ACCORD for stroke).

How Low Can You Go While Reducing BP? Is There a J Curve?

In hypertensive patients with CAD – the relationship between BP and CV events is J shaped, especially for DBP, with an increased risk of CV events (except stroke) among patients with DBP <70 mmHg as per *post hoc* analyses of randomized controlled trials[28,29] and observational studies.[30,31]

This could be especially relevant for secondary prevention of CAD, as coronary perfusion occurs in diastole which could be impaired with very low DBP worsening myocardial ischemia and causing events.

On the other hand, two recent randomized controlled trials showed no harm,[26] or a reduced harm[25] in the lowest BP groups up to a DBP of 60 mmHg, although the hazard ratios for CVD including IHD were 1.68 (1.16–2.43, $P = 0.006$) in patients without and 1.52 (0.99–2.34, $P = 0.06$) in patients with prior CVD,, respectively,[32] for diastolic pressure <55 mmHg versus 55–90 mmHg.

However, two factors can confound the relation between low DBP and CV outcomes.

1. The problem of reverse causality whereby low DBP would be a result of underlying poor health, rather than its cause, with the underlying physical condition itself leading to increased morbidity and mortality. Although dedicated randomized interventional trials will be required to disprove this, at least one study showed increased risk with lower (<70 mmHg) and higher (≥80 mmHg) DBP risk for the primary outcome, myocardial infarction, stroke, HF hospitalization, and all-cause mortality, which persisted after several sensitivity analyses ruled out the possibility of "reverse causality."[33]
2. Whether low DBP has an effect independent of the confounding impact of associated wide pulse pressure (PP) is not known. The CLARIFY registry (Prospective Observational Longitudinal Registry of Patients With Stable CAD)[34] followed up 22,672 hypertensive patients with CAD for a median of 5.0 years, and the relationship between PP and DBP, alone or combined, and the primary composite outcome (CV death or myocardial infarction) was analyzed using multivariable Cox proportional hazards models.

It was found that the J-shaped relationship between DBP (with increasing risk below and above 70 and 80 mmHg DBP, respectively) and CV events in hypertensive patients with CAD persisted in patients who were in the lowest risk PP range and is therefore unlikely to be solely the result of an increased PP associated with advanced vascular disease.

The Framingham Heart Study[35] found that DBP below 70 mmHg was linked with increased events, but the risk was greater among those with combined low DBP and wide PP.

What about the Impact of Low SBP on the J Curve of DBP?

In the INternational VErapamil-Trandolapril Study, Wokhlu *et al.*[36] categorized 17,131 hypertensive patients from the US cohort, aged at least 50 years with CAD, by tertiles of mean achieved SBP (<120, 120–<130, 130–<140, and ≥140 mmHg) and DBP (low, middle, and high per SBP category) during mean follow-up of 11.6 years.

DBP <70 mmHg was associated with excess mortality in older patients with CAD when SBP was <120 mmHg, but not when SBP ≥120–<140 mmHg. These findings point to an increased risk of lowering DBP when SBP is <120 mmHg.

Thus, BP targets should not be below 120 mmHg systolic or below 70 diastolic, especially in non-revascularized CAD patients (as some studies show lack of harm in revascularized CAD patients), the elderly, those with wide PP and those with SBP <120 mmHg.

1. Tailored treatment for secondary prevention of CAD and its subsets
   The antihypertensive drugs that are known to be effective (and should be used) in the secondary prevention of CAD and its subsets are shown in Table 1:[23,24,37]
2. Hypertensive drugs to be avoided in patients with CAD
   These are delineated in Table 2.
3. Should all hypertensives be advised a statin? An aspirin?

Primary prevention of hypertensives with statins

There is undisputable evidence showing benefit of statins in hypertensive patients who are at moderate to high CV risk.[38]

Primary prevention of hypertensives with aspirin

The authors of a Cochrane systematic review[39] which included four randomized trials with a combined total of 44,012 patients concluded that overall, for primary prevention of hypertensive people, aspirin did not reduce stroke or CV events compared with placebo.

Hence, aspirin is not recommended for primary prevention in hypertensive patients without CVD by the 2016 European Society of Cardiology guidelines.[40]

Three recent trials and a meta-analysis[41-44] have shown that aspirin for primary prevention reduces non-fatal ischemic events in some people (at high 10-year CVD risk and below 70 years age), but is counter balanced by significant increase in serious non-fatal bleeding events (gastrointestinal and intracranial), with no difference in mortality or cancer.

Table 2: Hypertensive drugs to be avoided in patients with CAD

CAD with HFrEF	CAD without HF (SCAD or ACS)
Non-DHP CCB (such as verapamil or diltiazem) Clonidine Moxonidine Hydralazine alone without a nitrate a-Adrenergic blockers such as doxazosin (to be used only if other drugs for the management of hypertension and HF are inadequate to achieve BP control at maximum tolerated doses)	Hydralazine (may provoke angina). Short acting nifedipine (except in prinzmetal or vasospastic angina)

HFrEF: Heart failure with reduced ejection fraction, HFpEF: Heart failure with preserved ejection fraction, SCAD: Stable coronary artery disease, DHP: Dihydropyridine, CCB: Calcium channel blocker

Hence, low-dose aspirin (75–100 mg orally daily) may be considered only among adults 40–70 years of age who are at higher risk of CVD but not at increased risk of bleeding by shared decision-making after a risk/benefit discussion as per the 2019 ACC/AHA guidelines[45] on the primary prevention of CVD. However, low-dose aspirin is not recommended on a routine basis for primary prevention of CVD among adults over 70 years of age or among adults of any age who are at increased risk of bleeding.

Thus, low-dose aspirin may be advisable for primary prevention in hypertensives below 70 years age for preventing non-fatal ischemic events only if their bleeding risk is low, BP is well controlled and ischemic risk is high.

Secondary prevention of hypertensives with statins

The presence of CVD places the patient at high or very high risk in which case statins show immense benefit and hence should be administered to target LDL-C levels below 70 mg/dL or 50 mg/dl or to below 50% of the baseline.

Secondary prevention of hypertensives with aspirin

For secondary prevention, the use of aspirin has shown greater benefit than harm in all clinical forms of IHD in hypertensives and is recommended. In patients who are unable to take aspirin and in those with a history of gastrointestinal bleeding, clopidogrel is a reasonable alternative.

A P2Y12 inhibitor is recommended to be added in patients with ACS or who undergo PCI.

With regard to CABG, as per the 2017 EACTS guidelines on perioperative medication in adult cardiac surgery, dual antiplatelet therapy (DAPT) after elective CABG may not benefit all patients but only the select group of patients of ACS or those that undergo coronary endarterectomy or off-pump surgery.

Conclusion

1. One of the strongest risk factors for developing CAD and hypertension frequently coexists with other risk factors and together they have a multiplicative effect on development of CAD.
2. The development of hypertension and related CAD is determined by an interplay of genetic and environmental factors working through neurohormonal activation, increased expression of growth factors and inflammatory cytokines, increased vascular stiffness, and endothelial dysfunction. LVH adds to the pathophysiology of ischemia.
3. BP lowering produces rapid reductions in CAD risk in hypertensive people.
4. BP lowering is more important than the particular drug class used for primary prevention of CAD.
5. An on-treatment hypertensive still has a substantial residual risk of any CV event due to various reasons listed which requires better evaluation and treatment of hypertension.
6. An office BP of <130/80 is the target for all patients, if well tolerated (except for people above age 65 years, for whom the 2018 ESC/ESH guidelines recommend a target of <140/80). The use of drugs in addition to lifestyle changes depends on (i) the level of BP (>140/90) and (ii) presence of CVD or 10-year risk above 10% by ASCVD risk calculator (for levels between 130/80 and 140/90). Low-risk patients with these latter levels to be observed for 3–6 months on lifestyle changes.
7. Care should be taken to keep DBP above 70 mm, especially in non-revascularized CAD patients, the elderly, those with wide PP and those with SBP <120 mmHg.
8. For secondary prevention in individuals with underlying comorbid illnesses such as CAD, CKD, or recurrent stroke, all drug classes have not shown optimal or even the same level of benefit.
9. Certain drugs are not advisable in CAD with HF and in CAD without HF.
10. While statins are recommended for secondary prevention of CVD in all hypertensives, they are recommended in those at moderate-to-high risk for primary prevention. Aspirin is indicated in all patients for secondary prevention, but has restricted recommendation for primary prevention.

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