Hypertension and Coronary Artery Disease
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Abstract
Hypertension is one of the major modifiable risk factors for atherosclerotic cardiovascular disease, with diastolic blood pressure being the strongest predictor of coronary artery disease. Hypertension is easily detectable and eminently treatable. Existence of J curve is a debatable issue. Effective treatment of blood pressure in hypertensive individuals reduces the risk of atherosclerotic coronary artery disease.

Key words: Hypertension, Coronary artery disease, Risk factor, J curve

Introduction
Hypertension is a major modifiable risk factor for all the various clinical manifestations of coronary artery disease (CAD). Diastolic blood pressure (DBP) is the strongest predictor of CAD in young and middle age population, whereas in age groups >60, pulse pressure (PP) shows the strongest correlation with CAD.

Pathophysiological mechanisms include BP as a physical factor on the formation of atherosclerotic plaque. Pulsatility and stiffness of the coronary arteries and the interplay of the two with respect to coronary perfusion play a role. Treatment of hypertension is proven to prevent coronary events in patients without clinical CAD. In patients with established CAD, the effect of BP lowering has shown a J-curve phenomenon, having an increase in coronary events at lower DBP, one explanation being that coronary perfusion is a predominantly diastolic phenomenon.

Epidemiology
The INTERHEART study demonstrated that about 50% population-attributable risk of myocardial infarction was accounted for by lipids, and hypertension accounting for 25%. The association of BP with various manifestations of CAD was studied in 1.25 million primary care patients in the UK aged 30 years and above. The findings of this study showed that hypertension had a lifetime risk of cardiovascular disease of 63.3% from 30 years of age compared to 46.1% for those with normal BP. The lowest risk for CAD was noted in the lowest BP group (systolic blood pressure [SBP]: 90–114 and DBP: 60–74) among the 30–79 years of age group. The association of SBP was strongest with intracerebral bleed, hazard ratio (HR) 1.44, subarachnoid bleed HR 1.43, and stable angina HR 1.41 and weakest for abdominal aortic aneurysm (AAA) HR 1.08. SBP had a greater effect on angina, MI, and PVD; DBP had a greater impact on AAA. PP association was inverse with AAA and strongest for PVD HR 1.23.

The FRAMINGHAM study showed that DBP was the strongest risk predictor among the <50 years of age group, and 50–59 years was a transition phase where SBP, DBP, and PP were comparable predictors. From 60 years and above, DBP had a negative correlation, with PP being the strongest predictor of CAD in this group. As recommended by the Austrian Society of Hypertension in 24 h BP monitoring, PP is a strong independent predictor of coronary events.

Pathophysiology
The myocardial oxygen demand during exercise is related to the increase in SBP, which is met almost exclusively by the decrease in coronary vascular resistance and increase in perfusion pressure. Oxygen extraction in the myocardium is maximal in basal state...
hence the dependence on coronary perfusion. Roughly 85% of the perfusion in the left ventricle occurs in diastole under resting condition, during heavy exercise, diastolic time shortens, and 40–50% of the total coronary flow occurs in systole, creating a substrate for subendocardial ischemia due to the throttling effect of cardiac contraction on the intramural vessels. The coronary vasculature can dilate five-fold, and thus, the flow reserve is five. This reserve is reduced by half with 80% stenosis of the epicardial coronary artery and near zero with 90% stenosis.

The compliance of the aorta plays a vital role in the interplay of BP and cardiac workload. Each systole creates a pressure wave which travels forward along the length of the aorta roughly at 5 m/s. As the aorta stiffens with age and degradation of elastin fibers in the media, this pulse wave velocity increases. The pressure wave front is reflected back from the branching points of the aorta. This reflected wave in young individuals reaches the ascending aorta in diastole, thus augmenting the DBP and coronary perfusion pressure. As age advances, the reflected wave front reaches earlier in the systole; this increases the wall tension and oxygen consumption and decreases the myocardial perfusion (DBP). The pulse wave velocity has a strong inverse relationship with coronary blood flow and flow reserve. Thus, measures of pulsatile hemodynamics are independent predictors of coronary events with or without established CAD.

Management

A recent meta-analysis of 68 randomized controlled trials (RCTs) studying the effect of antihypertensive medications on the occurrence of cardiovascular events was reported. Trials comparing antihypertensive medications to placebo showed a reduction in the occurrence of CAD by 16% (7 events per 5000 patient-years). In trials comparing less intense versus more intense, BP lowering CAD was reduced in the more intense group by 19%. This risk reduction was unrelated to the baseline BP. Benefit was seen also in Grade I hypertension and in patients with low-to-moderate cardiovascular risk. SBP <130 versus SBP >130 and DBP <80 versus DBP > 80 mm Hg were associated with a significant CAD risk reduction.

Among the drug classes, the risk reductions were achieved with diuretics (−16%), angiotensin-converting enzyme inhibitor (ACE-I) (−13%), BB (−12%), calcium channel blockers (CCBs) (−17%), angiotensin-receptor blocker (ARB) (−6%), and centrally acting drugs (−13%). These trials were not randomized head-to-head comparison, so they do not prove the superiority of each drug class over the other. When head-to-head comparisons were meta-analyzed, ACE-I was superior to all other drug classes. The other drug classes did not differ significantly from each other.

The recently reported SPRINT trial showed that, among non-diabetics with high cardiovascular risk, targeting a SBP <120 mm Hg compared to <140 mm Hg resulted in a significant reduction in cardiovascular events (25%), heart failure (38%), cardiovascular mortality (43%), and all-cause mortality (27%) and a non-significant reduction in myocardial infarction (17%). In this trial, the target BP was monitored by automated measuring system in a quiet room, and thus, the effect of white coat BP rise or office BP versus home-based BP measurements must be considered when applying the SPRINT trial findings into practice.

The concept of J-curve relationship between BP control and CV outcomes has been critically evaluated. In a recent analysis of 22,672 patients with stable CAD, after a median follow-up of 5 years, SBP ≥ 140 mm Hg and DBP ≥ 80 mm Hg were associated with increased CV risk. This increased risk was also noted with SBP < 120 and DBP < 70 mm Hg at higher CV risk. In a post hoc analysis of data from the International Verapamil-Trandolapril Study (INVEST), it was seen that the risk for all-cause death, and MI, but not stroke, progressively increased with low diastolic blood pressure. Caution should be exercised in reducing diastolic pressure in patients with CAD who are being treated for hypertension [Figure 1a and b]. Other analyses do not support the existence of a J-curve even in hypertensive patients at increased CV risk.

In patients with CAD who were free from congestive heart failure to begin with, in ONTARGET, BP reduction from baseline had no significant risk reduction in myocardial infarction.
but showed a lower risk of stroke.\textsuperscript{[18]} A meta-analysis was done by Law et al.\textsuperscript{[19]} The study group was divided into three groups, one without CAD, second group with history of CAD, and third with a history of stroke. When BBs were used in patients with CAD, the relative risk reduction was 13% comparable to the 15% risk reduction with all other drug classes, and 11% reduction in patients without CAD. The subgroup with a recent MI had more significant benefit with beta-blocker use.

Table 1 shows various trials where different drugs have been used to control hypertension in patients with CAD.

### Therapeutic Strategies Patients with CAD Receiving Antihypertensive Medications in (ESC 2018)

Hypertension is present in about 65–80% of patients presenting with acute coronary syndromes.\textsuperscript{[20]} Observational studies have suggested a poor prognosis with both a very high and very low BP. A high BP on presentation increases the risk of intracerebral bleed.\textsuperscript{[21]} Refractory hypertension (>180/110 mm Hg) is considered a relative contraindication to thrombolysis.\textsuperscript{[22]} Both high and low BPs are risk factors for bleeding in NSTEMI.\textsuperscript{[23]} Furthermore, BP fluctuation is known in early course of an ACS. There is a lack of dedicated RCTs for BP target in ACS. A reasonable BP goal in stable ACS patients is <140/90 mm Hg. A BP target <130/80 mm Hg at discharge may be considered in select patients.\textsuperscript{[24]} The addition of antihypertensive medications such as beta blockers and ACE I/ARBs is more with the intention of mortality benefit and cardiac remodeling post-acute coronary syndrome.

Antihypertensive treatment in patients of heart failure among patients treated for hypertension.\textsuperscript{[33-35]} This positive effect has been observed with beta blockers, ACE I, and ARBs. CCBs have been found to be less effective in comparative trials.\textsuperscript{[36]} Reducing BP also causes regression of LVH with a consequent decline in CV events, and mortality, ARBs, ACE I, and CCBs cause more effective regression in LVH than beta blockers or diuretics.\textsuperscript{[37]}

In patients with HFrEF, antihypertensive medications are initiated when BP >140/90 mm Hg (Tables 3 and 4). The target BP in this patient subset has not been clearly defined. As low BP has been shown to predict a poor outcome in heart failure, it is prudent to avoid actively lowering BP <120/70 mm Hg. However, some patients tolerate lower BPs seen while on guideline directed medications and are advisable to continue treatment for them.\textsuperscript{[38]} Sacubitril/valsartan lowers the BPs and reduces the risk of hospitalization, as it reduces the risk of incident heart failure among patients treated for hypertension.\textsuperscript{[33-35]} This positive effect has been observed with beta blockers, ACE I, and ARBs. CCBs have been found to be less effective in comparative trials.\textsuperscript{[36]} Reducing BP also causes regression of LVH with a consequent decline in CV events, and mortality, ARBs, ACE I, and CCBs cause more effective regression in LVH than beta blockers or diuretics.\textsuperscript{[37]}

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