How Tight Should Hypertension Control in CAD Be? – A Review
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Abstract
Guidelines for the management of hypertension have been constantly updated and with them targets for hypertension control have been evolving. There has been special concern for targets to achieve in hypertensive with coronary artery disease (CAD). Concern has been raised whether too low a value is harmful especially with concept of J curve being emphasized. This review attempts to analyze data for and against existence of a J curve and dissects various trials for and against this concept and attempts to come to a conclusion on ideal target for hypertension control in CAD patients. The data have been a little different in diabetics with CAD and trials in this field are also analyzed. Special concerns of tight hypertension control in the elderly are looked into. Mechanisms proposed for explaining J curve postulate are also discussed in the review. Approach of striking an ideal balance in therapy between good controls of systolic blood pressure with not so low diastolic blood pressure is proposed. Finally, an attempt has been made to zero in on ideal target blood pressure in various clinical spectra of vascular disease.

Key words: Coronary artery disease, hypertension, treatment targets

Background
It is well proved that hypertension (HTN) is a risk factor for coronary artery disease (CAD), heart failure, and stroke. It is a more powerful risk factor for acute myocardial infarction (MI) than diabetes mellitus (DM) as per data from INTERHEART study. High BP accelerates atherosclerosis and destabilizes vascular lesions and precipitates acute coronary syndromes (ACS).[^1] Risk of having a fatal coronary event doubles for every 20/10 mm rise in blood pressure (BP). Hypertensive heart disease with the left ventricular hypertrophy (LVH) has impaired coronary autoregulation and reduced coronary flow reserve causing ischemia with normal coronary arteries (INOCAs).

In this context, it is logical to assume that control of BP should reduce coronary risk. However, there are differing opinions on how much to reduce BP and what target to keep. Is lower the better? Are there any concerns if BP is lowered beyond a limit? This review tries to address these concerns and zero in on a target value to achieve for systolic BP (SBP) and diastolic BP (DBP) in hypertensive with CAD.

Current ACC/AHA guidelines[^2] recommend a blood pressure target of <130/80 mm of Hg in hypertensive with relaxation up to <140/80 mm of Hg in the elderly. The core practical concern is that attempts to lower SBP below 130 mm of Hg often lower DBP to levels as low as <60–70 mm of Hg, which may be harmful in CAD. Framingham study showed that low DBP and wide pulse pressure increase cardiovascular events.

Why is Low Blood Pressure Harmful?
Lower DBP has been linked to worsening angina in CAD. Coronary perfusion pressure the difference between aortic diastolic pressure and left ventricular end-diastolic pressure (LVEDP). If diastolic BP falls, coronary perfusion pressure should fall outside limits of autoregulation. Normal response to low DBP is autoregulation due to dilation of coronary resistance vessels. If DBP is very low, resistance vessels are already maximally dilated and if DBP falls further, coronary perfusion will suffer.[^3] Coronary autoregulation gets exhausted in low DBP in setting of atherosclerotic narrowing of epicardial coronaries. Hypertensive...
with LVH is more vulnerable to have subendocardial ischemia when coronary perfusion falls. In patients with chronic total occlusions and collateral donor artery stenosis, a U-shaped pattern is seen between blood pressure and development of coronary collaterals. As DBP falls below 80 mm Hg, it is shown that difference in pressure between central aortic pressure and intracoronary pressure distal to occluded segment falls. This reduces collateral flow. This fall is approximately 20% if DBP is 70–79 mm Hg, 28% if DBP is 60–69 mm Hg, and 38% if DBP is <60 mm Hg.4

**Does That Mean That A J Curve Exists?**

JM Cruickshank first reported J curve phenomenon in the treatment of hypertension in which J-shaped relationship was noted between DBP during therapy and occurrence of myocardial infarction (MI) with lowest point of the J at DBP 85–90 mm of Hg. This suspicion was mirrored by data from many trials.

HOT TRIAL5 evaluated the J curve phenomenon prospectively and had three DBP targets – 90, 85, and 80 mm of Hg. The decline in major cardiovascular event rate in a patient with CAD at baseline was not different between three groups. However, the group with <80 DBP had 43% lesser strokes. The drawbacks were that the trial did not assess the effects of lowering DBP < 80 as only 8% in the study group reached that level.

In Syst-Eur trial,6 cardiovascular event rates were found to be higher when DBP fell <70 in patients 60 years and above, and it was statistically significant when DBP fell <60 mm of Hg.

The landmark diabetic study ACCORD7 done in 40–79 years old diabetics showed no difference in composite outcome of cardiovascular death, non-fatal MI, and non-fatal stroke between intensive (<120 mm of Hg) and standard BP control (<140 mm of Hg). Intensive BP control group had 2% increase in absolute risk for adverse events (3.3% vs. 1.3%). However, the study was confounded by low event rate even in standard therapy group.

In ACCOMPLISH trial,8 major CVS events were lower in those with SBP < 130–140 mm of Hg, but composite endpoint of MI, hospitalized angina, or sudden death (not stroke) increased when SBP fell below 120 mm of Hg. Similar findings supporting J curve were found in INVEST trial9 with death and MI at nadir at BP of 119/84, TNT trial[10] where SBP < 110–120 or DBP < 60–70 increased non-stroke cardiovascular events and PROVE-IT TIMI 22 trial[11] where BP < 110/70 caused harm.

Registry data too like CLARIFY registry[12] showed that SBP > 140 and DBP > 80 increased cardiovascular events, but SBP < 120 and DBP < 70 too increased composite endpoint of death, MI, and stroke.

A Taiwanese study[13] of 2045 stable CAD patients of Chinese ethnicity who underwent PCI showed that SBP < 120 and > −160 or DBP < 70 is associated with major cardiovascular events at 12 months and 24 months.

However, one should remember that J curve may be different in hypertensive and normotensive. Hypertension shifts autoregulation rightwards to a higher range and LV mass also is higher. Both may explain higher risk of adverse events at lower BP values. Hence, inflection of J curve may occur at lower BP values in normotensive than hypertensive.12

**Data against J Curve – Sprint and the Rest**

One of the initial data against existence of J curve came from an interesting intravascular ultrasound study called CAMELOT trial[14] done in patients who underwent PCI or had angiographic diameter stenosis >50%. Study found that most favorable rate of atheroma progression occurred in those with SBP < 120/80.

However, the strongest data against J curve came from the landmark NIH funded RCT – SPRINT trial.15 This study randomized 9361 non-diabetic patients >50 years age to SBP target < 120 (achieved 121.4) versus SBP target < 140 (achieved 136.2) with 3.26 years follow-up. It showed that intensive treatment reduced primary composite outcome (MI/ cardiovascular death/stroke/acute decompensated heart failure) by 25% and all-cause mortality 27%. However, this trial had only 16.7% of patients with clinical cardiovascular disease and cannot be extrapolated fully to CAD group. However a meta-analysis of SPRINT showed that intensive BP control resulted in similar risk reduction in both CAD and non-CAD group. Intensive treatment increased side effects such as hypotension, syncope, reversible acute renal failure, and electrolyte defects. Number needed to treat NNT for preventing one primary outcome was 61, death 90, and cardiovascular death 172. Largest data against J curve have recently been presented in BPLTTc meta-analysis data[16] at ESC congress 2020. It analyzed 48 trials including 348,854 patients and analyzed seven groups with achieved BP < 120, 120–129, 130–139, 140–149, 150–159, 160–169, and >170. Study showed that antihypertensive drug therapy reduced MI and stroke in all seven groups. Neither the presence of cardiovascular disease or blood pressure at study entry modified effect of therapy.

One should, however, remember that J curve may be more important in DBP targets rather than SBP targets and these trials do not refute the possibility that a DBP < 70 may be more harmful than a SBP < 130. It is possible that lower DBP may be a marker of frailty or medical illness and need not be the cause for higher events. Even non-cardiac mortality may be higher in this population.3

**Are Targets Different in Diabetics?**

Diabetes is considered a marker of baseline risk of CAD, which, in turn, could affect relative treatment effect of intrinsic BP lowering. Furthermore, since diabetics have more diffuse disease, multivessel disease, and chronic total occlusions, the risk of lowering diastolic BP may be more in diabetics than non-diabetics.

Current recommendation of target BP in diabetics is <130/80; <140/80 in the elderly.2 INVEST study[9] showed that
cardiovascular risk is reduced in type 2 diabetics with diastolic BP < 90, but increased when DBP is <70. All-cause mortality increased in diabetic hypertensive above 50 years treated to SBP < 115. This RCT had 22,576 patients with hypertension and CAD, and the subgroup with SBP < 130 had higher all-cause mortality than the groups with SBP130–139 and >139. Similar increase in adverse events except stroke was seen with SBP <120 which was seen in ONTARGET\cite{17} and TRANSCEND\cite{18} trials too. The data of the large ACCORD study arguing against strict hypertension control in diabetics have already been discussed before.

In diabetics with ACS, data from EXAMINE trial\cite{19} showed a U relationship between BP and cardiovascular outcomes in diabetic. BP of < 130/80 worsened cardiovascular outcomes and degree of risk was more if BP < 120/70 was achieved.

Hence, caution is needed before accepting the concept that lower is the better in hypertensive patients with DM and CAD. One should also be aware of the fact that risk of stroke behaves differently and risk falls when BP is < 120/70. PROGRESS trial showed that stroke risk falls even with SBP < 115, probably due to excellent cerebral autoregulation with hardly any evidence of J curve in cerebral circulation. Similarly, “SPRINT eligible diabetics” (with additional risk factor) may benefit from stricter BP targets as seen in ACCORD-BP trial.

The discordance between the major trials SPRINT and ACCORD may be because latter was based on BP recordings made in the presence of an observer (white coat effect) and not on home BP as in SPRINT, and hence, ACCORD patients would have actually had lower BP at start of study than SPRINT and hence benefits were diminished. Furthermore, an interesting analysis of SPRINT eligible patients of ACCORD-BP trial (those diabetics who had an additional cardiovascular risk factor) showed that intensive BP control reduced composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, revascularization, and heart failure.

Are There Special Issues in the Elderly?
The elderly often have high SBP with low DBP reflecting increased aortic stiffness. In this scenario, lowering SBP < 140 has shown benefit even though DBP falls further. If patient has CAD, it may be prudent to keep DBP >60–70 while using anti-angina drugs such as beta-blockers and calcium channel blockers. The special concern of J curve in very elderly >80 years was addressed in systolic hypertension in elderly trial (SHEP)\cite{20} where benefit of BP lowering was reduced once DBP fell below 60.

Which is More Important in Cad – Systolic Goal or Diastolic Goal?
CLARIFY registry\cite{21} of 5956 stable CAD patients with average BP < 140/90 showed that in patients with stable CAD, a DBP 80–90 was associated with higher cardiovascular risk compared to DBP 70–79. However, SBP 130–139 did not increase risk compared to SBP 120–129. This suggested that lower diastolic BP achievement is more important than systolic BP goal achievement in stable CAD. This registry suggested that it is more important to achieve DBP< 80 than achieving SBP < 130. Similar inference was made from post hoc analysis of ONTARGET and TRANSCEND trials where in patients who achieved a SBP 120–139, a DBP of 80–89 had higher risk of stroke and heart failure hospitalization compared to 70–79.

Can We Arrive at a Reasonable Conclusion with Plethora of Data?
In hypertensive with CAD, it may be prudent to aim BP <130/80, but not <120/70. Target can be relaxed up to 140/90 in those with acute coronary syndromes or chronic total occlusions. While achieving SBP target <130, it may be prudent to ensure that DBP remains in 70–79 range. DBP < 60 is likely to be harmful in CAD. If angina relief is a concern at these DBP levels, it may be prudent to use ranolazine/trimetazidine/ivabradine like drugs without hemodynamic effect.\cite{21}

Dilemma occurs in patients with SBP >140 on therapy, where DBP has already fallen below 70. Framingham study has identified that this group with low DBP and wide pulse pressure has high cardiovascular risk.

Based on the current data\cite{22-26} target BP goals in hypertensives with CAD can be summarized as follows.

<table>
<thead>
<tr>
<th>Group</th>
<th>SBP goal (mm of Hg)</th>
<th>DBP goal (mm of Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unspecified hypertensive</td>
<td>120–130</td>
<td>70–80</td>
</tr>
<tr>
<td>General CAD population</td>
<td>120–130</td>
<td>70–80</td>
</tr>
<tr>
<td>ACS</td>
<td>130</td>
<td>80</td>
</tr>
<tr>
<td>Diabetic CAD</td>
<td>120–130</td>
<td>70–80</td>
</tr>
<tr>
<td>Post-stroke/TIA</td>
<td>120–130</td>
<td>70–80</td>
</tr>
<tr>
<td>Carotid disease/peripheral vascular disease/aortic aneurysm</td>
<td>130</td>
<td>70–80</td>
</tr>
<tr>
<td>Very elderly &gt;80</td>
<td>130–140</td>
<td>80</td>
</tr>
</tbody>
</table>

However, outcomes of trials do not always translate into real world practice, and often, clinical judgment of risk and patient choice too would get reflected in prescription patterns, especially regarding achieving target BP goals.

References


How to cite this article: Ramachandran P. How Tight Should Hypertension Control in CAD Be? – A Review. Hypertens 2020;6(4): 8-11.

Source of support: Nil, Conflicts of interest: None