Target Blood Pressure in Diabetes Mellitus: A Review

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Abstract

Hypertension and diabetes mellitus (DM) are major risk factors for atherosclerotic cardiovascular diseases (ASCVD). The prevalence of hypertension is more in people with DM compared to general population augmenting the risk of ASCVD. A systolic blood pressure (SBP) reduction below 140 mmHg in diabetes subjects is known to reduce cardiovascular events and mortality beyond doubt in several trials. A SBP $\leq 130$ mmHg should be targeted in individuals with high ASCVD risk scoring with careful monitoring for electrolyte imbalances and renal function. A target SBP of 130–139 should be targeted in elderly diabetes individuals with less strict control in patients with autonomic neuropathy and low diastolic BP (DBP). A DBP target of $\leq 80$ mmHg should be attained in diabetes subjects with hypertension.

Key words: Diabetes mellitus, Hypertension, Artherosclerotic cardiovascular diseases

Introduction

Individuals with diabetes mellitus (DM) are 2–4 times more prone to develop atherosclerotic cardiovascular diseases (ASCVD) than general population and often are affected at younger age. ASCVD accounts for 25% of all deaths in India, higher than the global average as per Global Burden of Disease study.\textsuperscript{(1,2)} Several clinical trials have established the relation of high blood pressure (BP) with ASCVD. A BP of $\geq 140/90$ mmHg was strongly associated with stable angina, myocardial infarction, and intracerebral hemorrhage even in non-diabetes subjects.

Hypertension is more common in people with type 2 diabetes than in the general population and per se is a major risk factor for ASCVD. The prevalence of hypertension in adult DM patients is estimated to be 73.6\% in the US population. Similar hypertension prevalence was found by Gupta et al. among Indian diabetes population with ASCVD risk.\textsuperscript{(3,4)} Patients with DM often have metabolic syndrome comprising hypertension, obesity, and dyslipidemia. The coexistence of DM and hypertension leads to major adverse cardiovascular events such as myocardial infarction, stroke, and microvascular complications such as retinopathy and nephropathy.

The United Kingdom Prospective Diabetes Study (UKPDS\textsuperscript{36}) group evaluated the effect of high BP on macrovascular and microvascular complications. A systolic BP (SBP) of $\geq 160$ mmHg had twice as high macrovascular complications as individuals with SBP $<120$ mmHg. There was an increase in both microvascular and macrovascular complications above SBP of 120 mmHg.\textsuperscript{(4)} This trial highlights the association between hypertension in diabetics and complications of diabetes potentially opening a window for further trials.

Effect of BP Control in Type 2 DM

UKPDS 38 evaluated the potential benefit of BP regulation in DM. Subjects in the intensive BP control arm with target BP $\leq 150/90$ mmHg had significantly reduced all-cause mortality compared to less tight control arm in whom BP target was $\leq 180/105$ mm of Hg. The median BP achieved in the intensive arm and less tight control arm were 144/82 mmHg and 154/82, respectively. The risk of stroke, myocardial infarction, and heart failure was significantly lesser in the intensive BP control arm. There was a linear relationship between SBP reduction up to 120 mmHg and adverse outcomes. This trial opened up the
potential benefits of BP regulation in DM individuals in the early 2000.[5]

The Action in Diabetes and Vascular Disease trial: ADVANCE trial compared intensive BP reduction versus placebo in diabetes individuals with pre-existing macrovascular or microvascular risk complications. The mean BP at entry to the trial was 145/81 mmHg and 41% patients had BP >140/80 mmHg. A SBP reduction of 5.6 mmHg and a diastolic BP (DBP) reduction of 2.2 mmHg were seen in the active arm compared to placebo. A relative risk of major and minor cardiovascular event reduction of 9% was seen in the active arm during follow-up for 4.5 years. There was no significant reductions in major and minor cardiovascular events when assessed individually.[6]

A BP target of 130/80 mmHg recommended by Joint National Committee (JNC) on prevention, detection, and evaluation of high BP in 2007 in the JNC7 report. This was widely prescribed by the scientific bodies such as American Diabetic Association (ADA), European Society of Cardiology (ESC), and European Society of Hypertension (ESH). However, the evidence for this target were based on small observational studies.[7,8] The Normotensive Appropriate BP Control in Diabetes failed to show reduction in cardiovascular events or nephropathy in patients with intensive BP target of ≤130/80 mmHg contrary to JNC7 recommendation. However, there was reduction in stroke, retinopathy progression, and albuminuria in these patients.[9]

The Action to Control Cardiovascular Risk in Diabetes-BP arm (ACCORD-BP) study of 2010 targeted a much lower target of BP, <120 mmHg. At 4.7 years follow-up, there was no difference in the cardiovascular diseases (CVD) outcomes in the intensive group (SBP target <120 mmHg) versus the standard group (SBP target <140 mmHg). Incidence of stroke was less in the intensive group. These beneficial effects were upset by increased incidence of side effects such as hyperkalemia, syncope, arrhythmias, and increased serum creatinine levels.[10] Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial showed no CVD benefit in SBP reduction below 130 mmHg. There was an increase in CVD mortality in the intensive study group (SBP <125 mmHg).[11]

In the SBP Intervention Trial (SPRINT), intensive SBP target of <120 mmHg versus standard SBP control of <140 mmHg was studied. Intensive SBP target group had 25% reduction in the risk of MI, stroke, heart failure, and death due to CVD. The main benefit of this study was in the age group of >75 years. There was increase in acute kidney injury, syncope, and electrolyte abnormalities in the intensive control group.[12] Diabetes individuals with hypertension were excluded from this trial. A meta-analysis of 13 randomized control trials on hypertension with DM by Bangalore et al showed 10% reduction in all-cause mortality with intensive SBP control <130 mmHg. However, there was no difference in micro- and macrovascular events. In another meta-analysis of 49 studies, SBP reduction from initial BP >150 mmHg showed reduction in all-cause mortality, stroke, and myocardial infarction. There was no benefit of BP reduction in individuals with baseline SBP <140 mmHg.[13,14]

Benefits of lowering the DBP in diabetics were shown in hypertension on target (HOT) trial. DBP lowering beyond 80 mmHg showed reduction in incidence of stroke, MI, and CVD-related deaths.[15]

Recommendations by Various Bodies on Target BP in Type 2 DM

The eighth JNC 8 report of 2014 recommends initiating treatment for hypertension in patients with diabetes with BP is >140/90 mmHg. A SBP target of <140 mmHg and DBP target of <90 mmHg is recommended.[16] International Diabetes Federation clinical practice recommendation for managing type 2 DM of 2017 suggests a SBP target between 130 and 140 mmHg and DBP target of <80 mmHg. IDF recommends to reduce SBP below 130 mmHg in patients with microvascular complications, especially albuminuria.[17]

The 2017 AHA/ACC guidelines recommend initiation of antihypertensive therapy at BP levels >130/80 mmHg or higher to target a BP <130/80 mmHg.[18] ESC and ESH guidelines of 2018 recommend treatment for people with DM with BP ≥140/90 mmHg. Following recommendations were given for people with DM and hypertension. A SBP target of <130 mmHg and >120 mmHg should be tried in DM patients with hypertension. A target DBP below 80 mmHg and not less than 70 mmHg should be attempted.[19] NICE guidelines recommend initiation of BP therapy at a threshold of 135/85 mmHg in diabetes patients. In diabetes patients with a BP >130/80 mmHg, NICE recommends initiation of treatment in the presence of albuminuria or two or more features of metabolic syndrome.[20]

ESC guidelines on diabetes, pre-diabetes, and CVD published in 2019 recommend following BP targets in DM subjects and emphasizes on individualization of target BP. The BP goal is to target SB to 130 mmHg in patients with DM and <130 mmHg if tolerated, but not <120 mmHg considering the expected adverse events with further reduction. A target SBP of <130 mmHg should be achieved in diabetes patients with chronic kidney disease and high risk of cerebrovascular disease. In older people (aged >65 years), the SBP goal is to a range of 130–139 mmHg. The DBP target is <80 mmHg, but not <70 mmHg in view of anticipated increase in orthostatic hypotension.[21] The ADA in the standards of care 2020 has made following suggestions. In diabetics with hypertension at higher cardiovascular risk (existing ASCVD or 10-year ASCVD risk ≥15%), a BP target of 130/80 mmHg can be targeted safely. In those with 10-year ASCVD risk, <15% target BP for treatment should be <140/90 mmHg, Table 1.[13,14,22,20,22]

BP Target in Type 1 DM

ADA recommends to start therapy for BP >140/90 mmHg in type 1 DM.

Hypertension target in elderly

The elderly are more sensitive than younger population for low BP and as perfusion to vital organs such as brain and heart is
BP dependent. Further, orthostatic hypotension, postprandial hypotension, CKD, and isolated systolic hypertension with low DBP complicate BP control threshold. The Hypertension in the Very Elderly Trial demonstrated reduction in stroke, heart failure, and CVD in subjects above 80 years of age.\(^\text{[23]}\) The Japanese Trial to Assess Optimal SBP in Elderly Hypertensive Patients included subjects of 65–85 years age group (11.8% of these subjects were diabetics) at 2 years follow-up there was no significant difference in the rates of CVD, renal events, and mortality in the group with SBP <140 mmHg and SBP of 140–160 mmHg.\(^\text{[24]}\)

Systolic Hypertension in the Elderly Program in elderly patients >60 years with isolated systolic hypertension, treatment with chlorthalidone showed significant benefits in diabetics and non-diabetics and no additional benefit was seen in reducing SBP <140 mmHg.\(^\text{[25]}\) SPRINT study has shown that lowering SBP <120 mmHg has reduced all-cause mortality predominantly in the age group of >75 years. However, the same was not implied by ACCORD trial. However, SPRINT trial had no diabetes subjects.

Isolated systolic hypertension defined as SBP>140 mmHg with DBP<90 mmHg is common in elderly patients, presents in 30% of the elderly in a study done in the USA.\(^\text{[26]}\) DBP in these individuals is lower and treatment of SBP can precipitate a low DBP. This is the potential mechanism of J-shaped curve association between DBP and CV events at DBP lower than 60–70 mmHg.\(^\text{[27]}\) Hence, in elderly patients with diabetes with isolated systolic hypertension, SBP target lowering should be attempted in individuals with DBP >60 mmHg. A higher SBP cutoff of 160 mmHg should be targeted in diabetics with DBP <60 mmHg. In elderly diabetics with CAD, a BP target of <140–150/90 mmHg should be tried. Evidence to this is reduction in the vascular events with BP reduction below 143/82 mmHg in the Second Manifestations of ARTerial disease trial. Target BP should be carefully chosen to avoid positional hypotension which could lead to falls and syncope.\(^\text{[22,28]}\)

Majority of the bodies on hypertension in 2014 recommended a BP target of ≤150/90 mmHg in elderly diabetics aged more than 80 years.\(^\text{[26,27]}\) ESC and ESH guidelines recommend a SBP target of 130–139 mmHg in people with diabetes and age ≥65 years.\(^\text{[19,21,24]}\)

### Conclusion

From the several RCT and guidance from various professional bodies, it’s evident that lowering the SBP below 130 mmHg results in reduction of cardiovascular events and microvascular complications. Further, lowering SBP below 120 mmHg has shown only reduction in the occurrence of strokes with several adverse events such as syncope, orthostatic hypotension, and electrolyte imbalances such as hyperkalemia and worsening of renal functions. Hence, individualization of BP target should be considered based on cardiovascular risk factors and diabetes-related complications.

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**Table 1:** Summary of BP target recommendations by various professional bodies and the basis for recommendations

| Recommending organization | Target BP                                                                 | Year of publication | Basis for recommendation                                                                 |
|----------------------------|---------------------------------------------------------------------------|---------------------|------------------------------------------------------------------------------------------|
| ADA                        | ≤130/80 mmHg for individuals with 10-year ASCVD risk score ≥15%            | 2020                | • ACCORD                                                                                 |
|                            | ≤140/80 mmHg for individuals with 10-year ASCVD risk score <15%            |                     | • ADVANCE                                                                               |
|                            | SBP <130 mmHg for age <65                                                | 2019                | • HOT                                                                                   |
|                            | SBP 130–139 mmHg for age ≥65                                              |                     | • SPRINT                                                                             |
|                            | DBP <80 mmHg, not <70 mmHg                                                |                     |                                                                                         |
| ESH/ESC                    | ≤130 mmHg, but not <120 mmHg                                             | 2018                | • Meta-analysis\(^\text{[13,29]}\)                                                   |
|                            | DBP <80 mmHg, but not <70 mmHg                                            |                     |                                                                                         |
| AHA/ACC                    | <130/80 mmHg                                                              | 2017                | • ACCORD                                                                               |
|                            |                                                                           |                     | • Meta-analysis\(^\text{[26-31]}\)                                                   |
| NICE                       | 135/85 mmHg                                                               | 2019                | • ACCORD                                                                               |
|                            | <130/80 in case of albuminuria/two or more features of metabolic syndrome |                     | • SPRINT                                                                               |
| IDF                        | SBP <140 mmHg                                                             | 2017                |                                                                                         |
|                            | SBP <130 mmHg in case of albuminuria                                      |                     |                                                                                         |
|                            | DBP <80 mmHg                                                              |                     |                                                                                         |
| JNC8                       | <140/80 mmHg                                                              | 2014                | • ACCORD                                                                               |
|                            |                                                                           |                     | • ADVANCE                                                                               |
|                            |                                                                           |                     | • UKPDS38                                                                           |

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ASCVD: Atherosclerotic cardiovascular disease, BP: Blood pressure
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