Blood Pressure Variability in Patients with Diabetes Mellitus with Hypertension: Treatment Recommendations and Role of Amlodipine

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Abstract

Recently, blood pressure variability (BPV) has gained focus owing to its role in predicting cardiovascular (CV) outcomes. Additionally, alterations in BPV contribute to the progression of end organ damage and trigger vascular events in hypertensive patients. Therefore, amelioration of BPV is considered a potentially important target and different classes of drugs are used to achieve the desired blood pressure (BP) goal. Based on several studies and clinical trials, treatments with CCB such as amlodipine have been found to be most effective in the management of BPV in hypertensive patients with diabetes. Growing evidence substantiates the role of amlodipine in significant reduction of BPV, thus, lowering the risk of diabetes related complications. This review sheds light on the importance of BPV reduction and the effectiveness of amlodipine in preventing cardiovascular morbidity and mortality in hypertensive patients with diabetes.

Introduction

Clinical evidence suggests a correlation between blood pressure (BP) and cardiovascular (CV) complications in patients with diabetes mellitus (DM).¹ Patients with DM are already at an increased risk of developing cardiovascular diseases (CVDs) as compared to subjects without DM. As high as 80% mortality in patients with DM have been associated with CV complications.² Hypertension (HT) is considered a major comorbidity of diabetes and coexistence of these conditions further increases the risk of heart failure, nephropathy, and other micro- and macro-vascular events.³ Blood pressure variability (BPV) has been an important focus in recent times, especially since its role got established in predicting cardiovascular (CV) outcomes, especially stroke. There is enough evidence to implicate BPV as an independent risk factor, which needs to be identified, followed up, and got rid of. This review tries to throw some light on clinical trial based evidence focussing on BPV and therapeutic armamentarium addressing this largely modifiable risk factor with particular reference to patients with co-existing HT and DM.

Impact of HT - Indian Scenario

Recently published meta-analysis documents that approximately one-third and one-fourth of the adults in urban and rural India, respectively, are hypertensives.⁴ Prevalence of HT have been projected to reach 22.9% and 23.6% for Indian men and women respectively by 2025.⁵ Such a concerning rise in HT portrays a frightening scenario for the 17.8% of the world’s population residing in India. The World Health Report 2002 has predicted CVDs as the major cause of mortality and disability among the Indian population by 2020 ⁶ and HT is considered as a crucial risk factor for increased incidence of CVDs in India.⁷ In sync with such predictions, an alarming role of HT has already been reported as the primary cause of 57% and 24% of all deaths due to stroke and coronary heart disease (CHD), respectively, in India.⁸

Blood Pressure Variability – The Next Big Target in HT

Blood Pressure (BP) control is highly important for CV protection as it is considered as a leading risk factor for CVDs.⁹ Blood pressure variability (BPV) has been defined as an average BP variation throughout the day, which is measured as the standard deviation of ambulatory BP readings. BPV is characterized based on two forms ¹⁰

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of fluctuations—short-term BPV, occurring over minutes or hours, as detected by 24-hour ambulatory blood pressure measurement (ABPM), and long-term BPV, in which fluctuations occur over prolonged periods of time, as detected by repeated recordings over days, weeks, months, and years, often referred to as visit-to-visit BPV.

BPV is of particular importance in patients with HT. The amplitude of BPV in patients increases progressively with increasing levels of HT. A study on intra-arterial BP monitoring of patients stratified into three major categories (mild, moderate, and severe HT) based on the mean 24-h BP revealed that the degree of BPV increased progressively with worsening HT. The relationship between BPV and the complications of HT has been explored in a study by Kikuya et al., and there is a body of evidence of an association between the degree of BPV and HT-induced end-organ damage, CV morbidity and CV mortality.

Although most studies have focused on mean BP measured in clinic or “out of office” settings as the CVD risk indicator, there is a strong body of evidence on noticeable oscillations in BP over both short and long term. Such variability poses a hindrance to the accurate measurement of mean BP and has been recognized as a potential risk factor. Further, analysis of cohort studies and randomized trials revealed long term BPV as a predictor of stroke and coronary events in high risk patients. Increased stress on the walls of the blood vessels and heart are considered as contributing factors to such variability. Both cross-sectional and longitudinal studies have confirmed the correlation between BPV and target-organ damage, and also demonstrated that such an effect is independent of the mean BP.

**Impact of BPV in Patients with Diabetes and HT—A Double-Edged Sword**

In India, amongst patients with diabetes, about 50% are affected with HT. Hypertensives with diabetes are at a significantly high risk for premature microvascular and macrovascular complications. The presence of HT is responsible for about 7.2-fold increase in mortality in patients with diabetes.

Analysis of data from a factorial randomized controlled trial (ADVANCE trial) of lowering blood pressure and control of blood glucose in 8811 T2DM patients without major macrovascular and microvascular events revealed that visit-to-visit systolic BPV and maximum SBP were independent risk factors for macrovascular and microvascular complications in such patients and were positively associated with myocardial infarction (MI) and CV death. Additionally, the findings of a study on the effect of short-term BPV, assessed in 36 T2DM patients with overt nephropathy who were subjected to ambulatory BP monitoring, revealed that elevated nighttime BPV was associated with more than 3 folds increased risk of CAD and proportional sympathetic activation in diabetes related nephropathy. These findings corroborate that BPV is an important predictor of microvascular complications and development of nephropathy among patients with diabetes.

There are several possible mechanisms that can explain the link between BPV and macrovascular and microvascular events in patients with diabetes. High BPV in T2DM patients suggests possible deleterious effect of hyperglycaemia on the blood vessels, that is responsible for large BP fluctuations. The population-based Hoorn Study reported an association between T2DM with increased arterial stiffness in both elastic (carotid) and muscular (femoral and brachial) arteries. Additionally, structural changes such as increased carotid intima-media thickness have also been reported. As a consequence, patients with diabetes undergo large systolic and diastolic BP fluctuations (Figure 1) which in turn can accelerate end-organ damage.

![Fig. 1: Systolic and diastolic blood pressure variations in patients with type 2 diabetes mellitus and normal individuals (controls). Based on Mokhtar et al. Asian Cardiovasc Thorac Ann. 2010;18:344-8. T2DM: type 2 diabetes mellitus; SBPV: systolic blood pressure variation; DBPV: diastolic blood pressure variation](image-url)
such high-risk population. There are reports that even moderate BP reductions can substantially reduce CV morbidity and mortality. A meta-analysis of data from 61 prospective observational studies on vascular disease-related deaths in individuals without known vascular disease at baseline demonstrated that even 2 mmHg SBP reduction could decrease stroke mortality by 10% and ischemic heart disease or other vascular events by 7%. In line with such findings, another observational study with diabetes patients found that 10 mmHg reduction in SBP to be positively associated with reduced risk of diabetes-related complications and deaths. Therefore, early detection followed by effective treatment of BPV in hypertensive patients with diabetes mellitus is paramount for reducing risks of CVD.

Therapeutic Interventions for the Management of BPV: Role of CCBs

Therapeutic intervention should be targeted not only towards reducing mean BP levels but also to stabilize BPV with the aim of achieving consistent BP control over time. Several classes of antihypertensive drugs are used for the control of BPV in diabetes patients with hypertension, namely angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide diuretics. Study by Webb et al., on the effect of antihypertensive treatment on inter-individual BP variance demonstrated that BPV was effectively reduced by CCBs and non-loop diuretic drugs, while it was increased by ACEIs, ARBs and beta blockers (Figure 2). Authors also found that CCB was responsible for maximum BPV reduction when compared with placebo. Similar findings were also reported by Levi-Marpillat et al., in a study on the efficacy of mono and combination therapy on short-term BPV as assessed in 2780 hypertensive patients, in which CCBs and diuretics were associated with lower BPV when compared to ACEIs, ARBs or β blockers. A meta-analysis by Ettehad et al., of 123 studies and 613,815 participants, further confirmed the superiority of CCBs over other classes of drugs in stroke prevention. Ushigome et al. conducted a study with 954 T2DM patients to investigate the effectiveness of antihypertensive drug class in managing BP. Their results confirmed the distinct advantage of selecting CCBs in hypertensive patients with diabetes mellitus for the reduction of home BPV.

Amlodipine - Gold Standard in Reducing BPV

Amlodipine is considered a well-established and long-acting CCB for the treatment of HT, including patients with diabetes. The well-known Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) study on 5137 patients with T2DM, reported lower risk of stroke when treated with amlodipine as compared to the treatment with atenolol (hazard ratio 0.78, 95% CI 0.67-0.90), and was attributed to the effectiveness of amlodipine in lowering of BPV. A post-hoc analysis of 710 patients, with known status of diabetes, was conducted by Jeffers et al. Data was pooled to determine the incremental effect of amlodipine titration to a daily dose of 10 mg daily on BP-lowering efficacy in hypertensive patients with diabetes, unresponsive to a daily dose of 5 mg amlodipine. The findings revealed that increasing amlodipine from 5 mg to 10 mg accounted for observed incremental reduction in BP (−12.5 mmHg/8.3% reduction in SBP, −6.0 mmHg/6.8% reduction in DBP) in hypertensive patients with diabetes, thus decreasing the risk of diabetes related complications. Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was conducted to determine the pharmacological effect of amlodipine, chlorthalidone and lisinopril on visit-to-visit BPV, recorded over a period of 6-28 months. Findings of these studies confirmed the marked lowering of visit-to-visit BPV by amlodipine and chlorthalidone in comparison to lisinopril.
Although there is limited evidence of the association of BPV with the microvascular complications in diabetes, a cross-sectional study of 422 Japanese T2DM patients demonstrated close association between Systolic BPV and the prevalence of albuminuria. The Diabetes Control and Complications Trial also reported that in patients with type 1 diabetes, the standard deviation in SBP and diastolic blood pressure (DBP) were predictive of future development of nephropathy. These studies indicate an association between BPV and impaired renal function in patients with diabetes. Previous studies on patients with diabetes have confirmed the renoprotective role of amlodipine. In the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial with 11,506 HT patients, amlodipine based regimen was successful in 48% reduction in the progression of nephropathy. Study for Assessment for Kidney Function by Urinary Microalbumin in Randomized (SAKURA) trial was a prospective, multicentre, open-labelled, randomized trial, in which the antialbuminuric effects of cilnidipine and amlodipine were examined. The findings suggest similar effects of cilnidipine and amlodipine on changes in urinary albumin to creatinine [Cr] ratio (UACR) after 12 months of therapy and successful renoprotection in RAS inhibitor-treated hypertensive patients with T2DM and microalbuminuria. Another study compared the effects of amlodipine versus fosinopril on urinary albumin excretion (UAE) in 147 elderly (60 to 75 years) elderly HT patients T2DM. The findings suggested that long-term treatment with both amlodipine and fosinopril effectively reduced UAE in elderly hypertensive patients with diabetes and suffering from microalbuminuria.

Conclusion

Given the alarming rise in the prevalence of HT in patients with DM, combined with the observed and increased macro and microvascular risk attributable to HT, effective BP management strategies are paramount for reducing risks of future CVDs. BPV has now emerged as an independent risk factor the development of chronic diabetes related complications. Several antihypertensive drugs are suggested for BPV control, out of which, treatment with CCB has been found to be more beneficial than treatment with ARBs or ACEIs. Based on several studies and clinical trials, the CCB amlodipine has been reported to reduce both mean BP levels and BPV, and therefore is most effective in the management of HT in patients with diabetes. There is growing evidence on the ability of amlodipine in significantly reducing SBP and DBP variability in T2DM patients, which can translate to meaningful reductions in diabetes related complications and improved renoprotection in the high-risk patients. Thus, amlodipine as a therapeutic option can safely be advocated for patients for the effective management of BPV in patients with DM and HT.

References


