WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 1, 1173-1185. Review Article ISSN 2277– 7105

MANAGEMENT OF BLOOD PRESSURE IN PATIENTS WITH CONCURRENT HYPERTENSION AND DIABETES: A REVIEW

A. R. Shabaraya and Sabtha Hakmal*

Department of Pharmacy Practice, Srinivas College of Pharmacy, Mangalore, Karnataka-574143.

Article Received on
15 Nov. 2022,

Revised on 05 Dec. 2022,
Accepted on 26 Dec. 2022

DOI: 10.20959/wjpr20231-26829

***Corresponding Author**
Sabtha Hakmal
Department of Pharmacy Practice, Srinivas College of Pharmacy, Mangalore, Karnataka-574143.

ABSTRACT

The co-existence of hypertension and diabetes, both being major risk factors for cardiovascular events, increase the occurrence of possible microvascular and macro-vascular complications. Treatment of hypertension in patients with diabetes is challenging due to their higher risk of developing resistant hypertension and their lower tolerance to aggressive antihypertensive treatment. The optimal blood pressure range for hypertensive diabetic patients is slightly different in different standard guidelines, which over years of research produced a range that may result in the best possible health outcome, yet the recent studies have different suggestions on debate. The management of hypertension in diabetes requires a strategic approach in accordance with the standard guidelines, and on the basis of cardiovascular status and complex metabolic derangements seen in the population subgroup. Although the aggressive management of blood pressure remains to be the initial approach in all patients with hypertension regardless of the comorbid conditions, there are certain clinical trials that prove in contrast with the recommended strategies. All the major antihypertensive classes of drugs are used in patients with diabetes, but certain classes of drugs such as beta-blockers have been reported to have a negative impact on diabetes, which must be reconsidered for their risks over benefits before administration. The objective of this review is to discuss target blood pressure goals, strategic approach and choice of agents for the treatment of hypertension in patients with concurrent diabetes. In this study, we also assess the impact of hypertension therapy on diabetes and their associated complications.

KEYWORDS: Antihypertensive treatment, concurrent diabetes, blood pressure management, aggressive BP control, cardiovascular risks.

INTRODUCTION

Hypertension is one of the major comorbidities of type 2 diabetes mellitus (T2DM), both constituting the major cardiovascular risk factors, increases the chances of related microvascular and macro-vascular events in coexistance.[1] Almost 70% of adult (type 2) diabetes patients have clinical hypertension and it is debatable whether the association of hypertension with diabetes is an independent syndrome or an epidemiologic coincidence. Both conditions are age-dependent and frequently coexist in the same individuals, making it difficult to draw firm conclusions about their association.[2] Moreover, patients with hypertension often exhibit insulin resistance and have a higher risk of developing diabetes compared to normotensive individuals.[3] High blood pressure is reported in over two-thirds of patients with type 2 diabetes, and its development coincides with the development of hyperglycaemia, and both microvascular and macro-vascular problems in diabetes are accelerated by raised systemic blood pressure.[4,5] The aggressive management of blood pressure to achieve the target remains the main the priority in treatment of hypertension in diabetes, even though the precise blood pressure targets for patients with diabetes remain unresolved.[6,7] Controlling blood pressure can help diabetes patients avoid cardiovascular complications by the reduction in the risk of developing any diabetes-related complication and mortalities, myocardial infarction, and the risk of cardiovascular events.[8] The management of hypertension in adults with diabetes is not well established though it is crucial in these patients.[9] It is unclear whether there are any variations in management of blood pressure in hypertensive patients with diabetes, despite the recommendations by standard guidelines for more aggressive hypertension management.[10] Furthermore, different guidelines place subtly different emphases on optimal therapy for hypertensive diabetics, and recent research on antihypertensive drugs has shown that they can also effect insulin sensitivity, thereby confusing the association.[11]

The purpose of this paper is to provide evidence-based recommendations to determine blood pressure goals, treatment regiments, appropriate antihypertensive drug classes, and treatment priorities for hypertension in patients with diabetes. The study will also examine the available literature and assess the impact of hypertension therapy on diabetes and associated cardiovascular complications.

1. Target Blood Pressure in Patients with Diabetes

It is crucial to maintain optimal blood pressure in order to minimize diabetes-related morbidity. The benefits of achieving the target blood pressure in patients with diabetes are emphasized in the reports from the United Kingdom Prospective Diabetes Study (UKPDS).[1,12,13] The study showed that tight blood pressure control reduces the incidence of diabetes-related fatalities and complications in people with hypertension and type 2 diabetes, which is clinically significant.[13] Each 10 mmHg drop in mean systolic blood pressure was associated with 12% lower risks for all complications connected to diabetes, 15% lower rates of mortality related to diabetes, 11% lower rates of myocardial infarction, and 13% lower rates of microvascular complications.[8] The WHO and the seventh report of the Joint National Committee (JNC) advised the systolic blood pressure target of ≤130 mmHg and that pharmacologic therapy be initiated in diabetic patients when SBP ≥130 mmHg.[14,15] The intensive therapy group in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial did show a significant reduction in the progression of retinopathy, albuminuria, and absolute risk of stroke, with an achieved mean blood pressure of 128/75 mm Hg (systolic target ≤130 mm Hg).[19,20] However, the systolic blood pressure target of <130 mm Hg previously recommended by major guidelines for diabetic patients was not based on evidence from any large-scale randomized trials, as most of these trials had the absolute in-treatment SBP values >130 mm Hg, except in the above mentioned ABCD trial.[19,32]

The 8th report of JNC guidelines that was published later in the year 2014 recommended initiating treatment when SBP is ≥140 mm Hg, with a target SBP goal of ≤140 mmHg.[16] It is noticeable that the guidelines published in recent years have shifted the target blood pressure from ≤130/80mmHg to ≤140/90mmHg, leading to considerable gap.[14] The European Society of Hypertension (ESH) and American Society of Hypertension (ASH) that were published in the year 2013 and 2014 respectively, support the target blood pressure of ≤140/90mmHg.[20,26,32] The American Diabetes Association (ADA) applied the same target in patients in the age group between 18-50 years.[24] This target range was also supported by the previously conducted ACCORD trial and furthermore, studies such as the Action in Diabetes and Vascular Disease (ADVANCE) trials and UKPDS showed the result supporting the latest recommendations.[12,17] Furthermore, according to the current body of evidence obtained from the meta-Analyses of 13 randomized trials by *Bangalore S et al.*, target systolic blood pressure of 130-135 mmHg is concluded acceptable for individuals with type 2 diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance.[28] But the ideal blood

pressure target in the subgroup still remains unclear as the evidence from several other clinical trials suggest that the blood pressure readings greater than 130/80 mmHg being associated with a higher risk of renal and cardiovascular illness.[28,29] Even though no convincing number of evidences supported the idea that lowering systolic blood pressure below 130 mmHg was beneficial for patients with diabetes, there are numerous evidence suggesting that the diastolic blood pressure of ~80 mmHg in diabetic patients is associated with the greatest reduction in cardiovascular mortality.[36,37]

Guideline	Target blood pressure	Recommended First-Line Agents
WHO	≤130/80 mmHg	ACE inhibitors or ARBs
JNC-7	≤130/80 mmHg	ACE inhibitors, ARBS, BB or CCBs
ESH/ESC	≤130/85 mmHg	ACE inhibitors or ARBs
ADA	≤140/80 mmHg	ACE inhibitors or ARBs
ASH	≤140/80 mmHg	ACE inhibitors or ARBs
JNC-8	≤140/90 mmHg	Thiazide type diuretics, ACE inhibitors, ARBs or CCBs
CHEP	≤130/80 mmHg	ACE inhibitors or ARBs

Target blood pressure and first-line agents that are recommended by various standard guidelines. Abbreviation: WHO- World Health Organization; JNC- Joint National Committee; ESH- European Society of Hypertension; ESC- European Society of Cardiology; ADA- American Diabetes Association; ASH- American Society of Hypertension; CHEP- Canadian Hypertension Education Programme.

2. Hypertension Therapy in Diabetes

Treatment of hypertension in patients with diabetes is challenging due to their higher risk of developing resistant hypertension and other cardiovascular complications that can lower the tolerance to aggressive antihypertensive treatment.[1,13] The management of hypertension in adults with diabetes is not well established though it is crucial in these patients.[9] Hence, an effective treatment regimen must be instituted considering the cardiovascular status and complex metabolic derangements seen in the population subgroup.[1,21] An integral component of the management of hypertension in patients with diabetes is the institution of lifestyle changes.[20] These include reducing one's weight, getting more exercise, drinking less alcohol, nicotine cessation, and reduction in sodium consumption (less than 2.4 g/d).[22,23,37] Apart from behavioural therapy and recommended lifestyle modifications, pharmacological therapy is implemented based on the patient's condition.[11] And the antihypertensive treatment regimen recommended by standard guidelines varies based on

different facets.[11] The American Diabetes Association (ADA) recommends the first-line therapy consisting of a medication class with proven cardiovascular advantages, such as a renin-angiotensin system (RAS) inhibitor: angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARBs); or thiazide-like diuretic, or calcium channel blocker (CCB).[24] If the baseline blood pressure is greater than 150/90 mmHg or if the target BP is not met with RAS blockers, it is advisable to add a second medication, ideally a thiazide diuretic (chlorthalidone or hydrochlorothiazide) or a CCB, since they can provide cardiovascular protection.[25] Titration of the thiazide-type diuretic to 25 mg/d or CCB to the highest acceptable dose is advised if, after 2 to 4 weeks of adding a diuretic or CCB, the blood pressure is still not at the desired level.[20] A thiazide-type diuretic (Chlorthalidone) outperformed an adrenergic blocker (doxazosin) in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trials (ALLHAT), and it also found to have decreased CV events in diabetes more than CCBs (amlodipine) or ACEIs (Lisinopril) did.[26,40,46] Since blood pressure control is more challenging to accomplish in diabetic patients than in those without diabetes, it is necessary to use combination therapy. According to the *Journal of the American College of Cardiology,* ACE inhibitors and ARBs having the highest efficacy on urine albumin excretion of all drug classes can be used in the combination with other antihypertensive drugs.[26] Alternately, combining a dihydropyridine CCB in moderate doses with a non-dihydropyridine CCB (such as verapamil or diltiazem) has synergistic effects on reducing the blood pressure and will aid in achieving target blood pressure in diabetic patients.[3,41] In the remaining circumstances where target blood pressure is still not achieved, a fourth and possibly a fifth agent will be needed, in which case an adrenergic blocker or an aldosterone antagonist can be used.[24]

3. Preferred Antihypertensive Drug Class in Patients with Concurrent Diabetes

The management of hypertension in diabetes can benefit from the use of all main antihypertensive medication classes, including ACE inhibitors, ARBs, CCBs, and diuretics.[26] It is evident that various classes of antihypertensive medications have different effects on blood pressure, and different clinical consequences such as microvascular complications and cardiovascular events further alter the efficacy of drug classes.[14] Regardless of race, JNC 7 addressed the choice of suitable antihypertensive classes for the management of hypertension in people with diabetes mellitus: Diuretics, ACE inhibitors, beta-blockers, ARBs, and CCBs were the classes advised.[15] The 8th report of JNC noted that there is insufficient information to show that certain classes of agents have different results,

however, the recommendation included either thiazide-type diuretics, ACE inhibitors, ARBs, or CCBs as initial therapy for non-black patients with diabetes mellitus.[16] According to other guidelines including ESH, WHO, and ASH, the treatment strategy in people with diabetes should include an ACE inhibitor or an ARB as their preferred antihypertensive class.[20,32] These drugs are considered to be highly efficient as they significantly slowed the course of moderately to substantially elevated albuminuria in a meta-analysis of RCTs with hypertensive diabetic patients.[26] According to Canadian Diabetes Association (CAD), the control of blood pressure is thought to be equally successful with ACEIs/ARBs, CCBs (dihydropyridines), or thiazide/thiazide-like diuretics in those with diabetes and hypertension.[27] Even though ESH/ESC recommendations emphasize that all classes of antihypertensive drugs are approved for individuals with diabetes, there are studies that suggest the potential adverse of using beta blockers.[7,32] However, they can be taken into account for blood pressure control if the pulse rate increases even after using at least two distinct antihypertensive medications.[20,29]

4. Aggressive Blood Pressure Control

The aggressive blood pressure control remains one of the most prioritised treatment approach for the management of hypertension, but in the presence of additional comorbidities such as diabetes, it is unclear whether this method is benefitted or possess a relative threat.[6,7] However, the results from ADVANCE trial showed that an aggressive systolic and diastolic blood pressure reduction (mean achieved blood pressure of 134/74 mm Hg versus 140/76 mm Hg) significantly reduced microvascular events, cardiovascular fatalities, and all-cause mortality.[17,18] Furthermore, the ACC/AHA researchers emphasize that reducing blood pressure is the primary method for lowering cardiovascular risk in hypertensive individuals without making a preference for which antihypertensive medication should be started initially.[26] Contrary to this, a large hospital-based cohort study conducted by *Berlowitz DR et al.*, found that aggressive blood pressure control (i.e., SBP <120 mmHg or DBP <70 mmHg) was associated with an increased risk of cardiovascular diseases among patients with type 2 diabetes.[30] Although the blood pressure goals of ≤140/90 mmHg are generally recommended for the management of hypertension, a more aggressive aim of 130/80 mmHg for individuals with diabetes mellitus was not found to be helpful according to the ACCORD trial.[28] Recent studies suggest that aggressive blood pressure management, though highly recommended, may not be in the patient's best interests. Aggressively achieved low levels of diastolic blood pressure (DBP) have been associated with increased cardiovascular events, a

situation known as the J-curve effect.[31] Results from multiple meta-analyses of randomized outcome studies on populations with or including a sizable subgroup of people with diabetes support a conservative rather than an aggressive blood pressure target.[28,32] Multiple epidemiological population studies and a meta-analysis of randomized controlled trials reveal an inverse association between mortality risk and blood pressure in older participants from the general population, making the aggressive treatment even more debatable as people age.[34,35] The findings from post hoc analysis in the cohort of diabetes patients conducted by *Cooper-DeHoff RM et al.,* showed that tight systolic blood pressure management was not linked to better cardiovascular outcomes when compared to conventional control. The study concluded that it was advisable to maintain the systolic blood pressure between 130 and 139 mm Hg all the while concentrating on weight loss and maintaining a healthy diet to reduce long-term cardiovascular risk.[36]

5. Impact of Hypertension Therapy on Diabetes

Although the antihypertensive treatment can help reduce the risk of cardiovascular events, there are several studies uplifting the few positive and several negative impacts these drugs possess over the presence of concurrent diabetes. Clinical evidence suggests that while treating hypertension, α-adrenergic blocking drugs, central nerve sympatholytic drugs, and ACE inhibitors enhance insulin sensitivity, whereas β-blockers and diuretics may impair insulin resistance.[2] One would anticipate that some of these medications may, over time, either lower or increase the rates of new-onset diabetes because insulin resistance is a precursor to diabetes. Recent research has produced some intriguing findings that raise the possibility of this being the case considering the negative effects of some antihypertensive drugs on glycaemic control and their worsening metabolic risk factors.[38] These investigations have shown that the majority of antihypertensive drugs decreases insulin sensitivity concurrently with changes in the atherogenic lipid profile.[39] Some retrospective studies have found evidence of an increase in cardiovascular mortality in diabetes patients taking diuretics.[37] Also in the study conducted by *Harper R et al.,* a significantly low in-vivo insulin sensitivity was shown by diuretics (bendrofluazide) at a daily dose of 5 mg.[40] Combining atenolol (beta blockers) with low-dose chlorthalidone (thiazide diuretics) was linked to elevated triglyceride levels and decreased insulin sensitivity.[41] Additionally, previous observational studies have generally reported an elevated risk of diabetes among people taking thiazide diuretics,[44] and that high doses of thiazide diuretics have the potential to exacerbate critical metabolic factors like glucose and cholesterol levels.[45]

On the other hand, treatment with beta-blockers has been linked to weight gain and a diminished release of insulin by pancreatic beta cells, both of which may be risk factors for diabetes.[38,39] In the study conducted by *Gress TW et al.*, the use of beta-blockers was found to have been associated with a 28% rise in the risk of diabetes.[42] The risk has also been warned in earlier observational studies, with the estimates of the relative risk being often larger. For example, in a study conducted by *Samuelsson O et al.*, participants who took beta-blockers (propranolol) had a risk of diabetes that was up to 6.1 times higher than those who did not.[43] The ALLHAT study comparing an adrenergic blocker against calcium channel blockers and ACE inhibitors showed a rise in cardiovascular events in patients taking the adrenergic blockers.[37,46] However, ALLHAT has highlighted the decreased cardiovascular events in patients treated with a thiazide-type diuretic (Chlorthalidone), which had even outperformed a CCB and ACE inhibitor, concluding that thiazide diuretics were relatively safe in diabetic patients.[26,40,46] On this basic, even though beta blockers could show negative effect in the subgroup, it was advised to be used in the patients after careful consideration of efficacy against the possible adverse effects on patients with diabetes.[42,43]

CONCLUSION

One of the major challenges confronting current healthcare is the treatment of hypertension in diabetic individuals, as the subgroup is far more likely to experience cardiovascular problems. Therefore, it is necessary to first achieve the target blood pressure and following the initiation of the treatment, conduct screening to evaluate for any negative effects or adjustments. There is an agreement that interventions should be initiated earlier in hypertensive diabetics than in their nondiabetics, but once the blood pressure is achieved, a stratified consideration of the therapeutic approaches designed in order to reduce complications in this subgroup must be followed. All the main classes of antihypertensive medication, including ACE inhibitors, ARBs, CCBs, and diuretics are used in the management of hypertension in diabetes, and their different effects on blood pressure and different clinical consequences cardiovascular events further alter the efficacy of drug classes. Various clinical trials suggest focusing on aggressive blood pressure control over the class of antihypertensive used, yet it is necessary to maintain optimal blood pressure and the selection of appropriate drug class.

Although there are worries about negative metabolic consequences and a lack of hypoglycaemic consciousness among adrenergic blockers and diuretics, they play an

important role in the care of diabetic patients. Thus it is advisable that the careful consideration of risk and benefits must be calculated before administrating these classes of drugs. This study helps to understand that the utilization of appropriate antihypertensive drug regimens based on patient condition can effectively decrease the incidence of cardiovascular events in hypertensive diabetic patients.

REFERENCES

1. Sowjanya Naha MD, Gardner MJ, Darshan Khangura MD, Kurukulasuriya LR, Sowers JR. Hypertension in Diabetes. Interventions, Aug 2, 2021; 2: 5.
2. Julius S, Majahalme S, Palatini P. Antihypertensive treatment of patients with diabetes and hypertension. American journal of hypertension, Nov 1, 2001; 14(S7): 310S-6S.
3. Przezak A, Bielka W, Pawlik A. Hypertension and Type 2 Diabetes—The Novel Treatment Possibilities. International Journal of Molecular Sciences. Jun 10, 2022; 23(12): 6500.
4. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. The Lancet, Aug 11, 2012; 380(9841): 601-10.
5. Jandeleit-Dahm K, Cooper ME. Hypertension and diabetes. Current Opinion in Nephrology and Hypertension, Mar 1, 2002; 11(2): 221-8.
6. Garcia-Touza M, Sowers JR. Evidence-Based Hypertension Treatment in Patients With Diabetes. The Journal of Clinical Hypertension, Feb, 2012; 14(2): 97-102.
7. Grossman E, Messerli FH. Hypertension and diabetes. Cardiovascular diabetology: Clinical, metabolic and inflammatory facets, 2008; 45: 82-106.
8. Lago RM, Singh PP, Nesto RW. Diabetes and hypertension. Nature clinical practice Endocrinology & metabolism, Oct, 2007; 3(10): 667.
9. Passarella P, Kiseleva TA, Valeeva FV, Gosmanov AR. Hypertension management in diabetes: 2018 update. Diabetes Spectrum, Aug 1, 2018; 31(3): 218-24.
10. Berlowitz DR, Ash AS, Hickey EC, Glickman M, Friedman R, Kader B. Hypertension management in patients with diabetes: the need for more aggressive therapy. Diabetes care, Feb 1, 2003; 26(2): 355-9.
11. Grossman A, Grossman E. Blood pressure control in type 2 diabetic patients. Cardiovascular diabetology, Dec, 2017; 16(1): 1-5.
12. Laakso M. Benefits of strict glucose and blood pressure control in type 2 diabetes: lessons from the UK Prospective Diabetes Study. Circulation, Feb 2, 1999; 99(4): 461-2.

13. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. Bmj, Sep 12, 1998; 317(7160): 703-13.
14. Cryer MJ, Horani T, DiPette DJ. Diabetes and hypertension: a comparative review of current guidelines. The Journal of Clinical Hypertension. Feb, 2016; 18(2): 95-100.
15. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. Jama, May 21, 2003; 289(19): 2560-71.
16. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama, Feb 5, 2014; 311(5): 507-20.
17. Patel A, ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. The Lancet, Sep 8, 2007; 370(9590): 829-40.
18. Zoungas S, De Galan BE, Ninomiya T, Grobbee D, Hamet P, Heller S, MacMahon S, Marre M, Neal B, Patel A, Woodward M. Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: new results from the ADVANCE trial. Diabetes care, Nov 1, 2009; 32(11): 2068-74.
19. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney international, Mar 1, 2002; 61(3): 1086-97.
20. Bakris GL, Sowers JR, American Society of Hypertension Writing Group. ASH position paper: treatment of hypertension in patients with diabetes—an update. The journal of clinical hypertension, Sep, 2008; 10(9): 707-13.
21. Gæde P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. New England Journal of Medicine, Jan 30, 2003; 348(5): 383-93.
22. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V. Prevention

of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New England Journal of Medicine, May 3, 2001; 344(18): 1343-50.

23. Stewart KJ. Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension: plausible mechanisms for improving cardiovascular health. Jama, Oct 2, 2002; 288(13): 1622-31.
24. De Boer IH, Bangalore S, Benetos A, Davis AM, Michos ED, Muntner P, Rossing P, Zoungas S, Bakris G. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes care, Sep 1, 2017; 40(9): 1273-84.
25. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ, Camelot Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. Jama, Nov 10, 2004; 292(18): 2217-25.
26. Whelton, P.K., Carey, R.M., Aronow, W.S., Casey, D.E., Collins, K.J., Dennison Himmelfarb, C., DePalma, S.M., Gidding, S., Jamerson, K.A., Jones, D.W. and MacLaughlin, E.J., 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 2018; *71*(19): e127-e248.
27. Cheng AY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. Canadian journal of diabetes, Mar 26, 2013; 37: S1-3.
28. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. Circulation, Jun 21, 2011; 123(24): 2799-810.
29. Bakris G, Sowers J, Epstein M, Williams M. Hypertension in patients with diabetes: Why is aggressive treatment essential?. Postgraduate Medicine, Jan 1, 2000; 107(2): 53-64.
30. Zhao W, Katzmarzyk PT, Horswell R, Wang Y, Li W, Johnson J, Heymsfield SB, Cefalu WT, Ryan DH, Hu G. Aggressive blood pressure control increases coronary heart disease risk among diabetic patients. Diabetes care, Oct 1, 2013; 36(10): 3287-96.
31. Chrysant SG. Current status of aggressive blood pressure control. World Journal of Cardiology, Mar 3, 2011; 3(3): 65.

32. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Boehm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). European heart journal, 2013; 34(28): 2159-219.
33. Berlowitz DR, Ash AS, Hickey EC, Glickman M, Friedman R, Kader B. Hypertension management in patients with diabetes: the need for more aggressive therapy. Diabetes care, Feb 1, 2003; 26(2): 355-9.
34. Van Hateren KJ, Landman GW, Kleefstra N, Groenier KH, Kamper AM, Houweling ST, Bilo HJ. Lower blood pressure associated with higher mortality in elderly diabetic patients (ZODIAC-12). Age and ageing, Sep 1, 2010; 39(5): 603-9.
35. Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard R, Casiglia E, Kerlikowske K, Coope J, INDANA Group. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. The Lancet, Mar 6, 1999; 353(9155): 793-6.
36. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, Pepine CJ. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. Jama, Jul 7, 2010; 304(1): 61-8.
37. Arauz-Pacheco C, Parrott MA, Raskin P. The treatment of hypertension in adult patients with diabetes. Diabetes care, Jan 1, 2002; 25(1): 134-47.
38. Struthers AD, Murphy MB, Dollery CT. Glucose tolerance during antihypertensive therapy in patients with diabetes mellitus. Hypertension, Nov, 1985; 7(6_pt_2): II95.
39. Jacob S, Rett K, Henriksen EJ. Antihypertensive therapy and insulin sensitivity: do we have to redefine the role of β-blocking agents?. American journal of hypertension, Oct 1, 1998; 11(10): 1258-65.
40. Harper R, Ennis CN, Heaney AP, Sheridan B, Gormley M, Atkinson AB, Johnston GD, Bell PM. A comparison of the effects of low-and conventional-dose thiazide diuretic on insulin action in hypertensive patients with NIDDM. Diabetologia, Jul, 1995; 38(7): 853-9.
41. Schneider M, Lerch M, Papiri M, Buechel P, Boehlen L, Shaw S, Risen W, Weidmann P. Metabolic neutrality of combined verapamil-trandolapril treatment in contrast to beta-blocker-low-dose chlortalidone treatment in hypertensive type 2 diabetes. Journal of hypertension, May 1, 1996; 14(5): 669-77.

42. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. New England Journal of Medicine, Mar 30, 2000; 342(13): 905-12.
43. Samuelsson O, Hedner T, Berglund G, Persson B, Andersson OK, Wilhelmsen L. Diabetes mellitus in treated hypertension: incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial Göteborg, Sweden. Journal of human hypertension, Apr 1, 1994; 8(4): 257-63.
44. Stolk RP, Van Splunder IP, Schouten JS, Witteman JC, Hofman A, Grobbee DE. High blood pressure and the incidence of non-insulin dependent diabetes mellitus: findings in a 11.5 year follow-up study in The Netherlands. European journal of epidemiology, Mar, 1993; 9(2): 134-9.
45. Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: blood pressure goals, choice of agents, and setting priorities in diabetes care. Annals of internal medicine, Apr 1, 2003; 138(7): 593-602.
46. Messerli FH. Implications of discontinuation of doxazosin arm of ALLHAT. The Lancet., 2000; 355(9207): 863-4.