Review Article

CORRELATION OF ANTIHYPERTENSIVE DRUGS AND NEW ONSET DIABETES: A REVIEW

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ABSTRACT

Hypertension is the leading cause of mortality worldwide and is a leading risk factor for the development of coronary heart disease and stroke. Diabetes and high blood pressure tend to occur together because they share certain physiological traits. Antihypertensive drugs are prescribed mainly to reduce the morbidity and mortality caused by hypertension and its complications. Clinical practice guidelines suggest antihypertensive classes are acceptable first-line agents for the management of uncomplicated hypertension. These classes include angiotensin receptor blockers, thiazide diuretics, angiotensin-converting enzyme inhibitors (ACE-I), calcium channel blockers, beta-blockers. It has been observed that type-2 diabetes has been promoted by not only hypertension but also by antihypertensive therapies. Several studies indicate and beta blockers and diuretics impair the glucose metabolism, hence not only the disease itself but also antihypertensive therapies may promote the development of new-onset diabetes. The β -blockers and diuretics have also the role in decreasing the morbidity and mortality by cardiovascular reasons, identified in clinical trials. It is also pertinent to add that the risk of new onset diabetes has been found increasing by thiazide diuretics and β -blockers. If these both classes are used in combination the effect is noticed stronger. The incidence of new onset diabetes in hypertensive patients might have reduced by ingestion of angiotensin receptor blockers (ARBs), or ACE inhibitors (ACEIs). This is reflected in the suggestions issued in the reviews of several clinical trials. It is also found that the co-existence of hypertension and diabetes mellitus is destructive to cardiovascular system, which may consequently lead the risk of stroke or even cardiovascular mortality, hence caution should be taken while prescribing antihypertensive medications.

Key words: New onset diabetes (NOD), Hypertension, Angiotensin receptor blockers (ARBs), ACE inhibitors (ACEIs).

INTRODUCTION

Hypertension if not diagnosed early and treated correctly may lead to myocardial infarction, renal failure, stroke, leading cause of mortality worldwide and even ultimate death as it is a hemodynamic disorder associated with increase in peripheral vascular resistance.¹ Hypertension affects more than a third of adults aged 25 and above scoring about a billion people worldwide, this has been revealed in some of recent estimates of World Health Organization (WHO).² Therapeutic options include diet and lifestyle changes (comprising weight loss, smoking cessation, and increased physical activity), antihypertensive medications, and in special situations surgery is required. Thiazide diuretics are commonly recommended as prime therapy for the cure of hypertension.^{3,4} Drug therapy should be applied with 2 antihypertensive drugs in hypertensive

patients mostly, if the blood pressure is more than 20/10 mm Hg above the goal blood pressure.⁵ Fasting plasma glucose level ≥ 126 mg/dl, symptoms of hyperglycaemia, and a casual plasma glucose level ≥ 200 mg/dl, are prevalent criteria for diagnosis of diabetes or a 2-h postchallenge plasma glucose level ≥ 200 mg/dl during an oral glucose tolerance test and fasting plasma glucose < 100 mg/dl and 2-h plasma glucose < 140 mg/dl are considered 'normal'. Maintenance of glycaemic control has been shown to reduce the risk of microvascular complications, including retinopathy, nephropathy and neuropathy.⁶ Recently, some multiple prospective trials in hypertension opened a debate about the clinical value of new-onset diabetes NOD in treated hypertensive patients and suggested that ingestion of angiotensin receptor blockers (ARBs) or ACE inhibitors (ACEIs) might reduce the incidence of new-onset diabetes in hypertensive patients.^{7,8}

Table 1: Hypertension Thresholds and Goals in Diabetics⁹

Guideline	Year Published	Threshold for Treatment	Goal Blood Pressure
JNC 7	2004	$\geq 130/80$	$\leq 130/80$
JNC 8	2014	$\geq 140/90$	$\leq 140/90$
ASH/ISH	2014	$\geq 140/90$	$\leq 140/90$
ESH/ESC	2013	$\geq 140/85$	$\leq 140/85$
CHEP	2014	$\geq 130/80$	$\leq 130/80$
ADA	2013	$\geq 140/80$	$\leq 140/80$
WHO/ISH	2003	$\geq 130/80$	$\leq 130/80$

Abbreviations: ADA- American Diabetes Association; ASH, American Society of Hypertension; CHEP- Canadian Hypertension Education Program; ESH/ESC- European Society of Hypertension/European Society of Cardiology; ISH- International Society of Hypertension; JNC 7- Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; JNC 8- Eighth Report of the Joint National Committee; WHO- World Health Organization.

Hypertension Pharmacotherapy and Guidelines

Clinical practice guidelines suggest that antihypertensive classes are acceptable first-line agents for the management of uncomplicated hypertension. These classes include angiotensin receptor blockers thiazide diuretics, angiotensin-converting

enzyme inhibitors, calcium channel blockers and beta-blockers.^{10,11} It is very difficult to achieve BP targets with monotherapy and most patients require a combination of two or three drugs to get to target.¹² Guidelines regarding hypertensive drug therapy vary between countries, patient characteristics, and organizations.¹³

Table 2: Preferred treatment options for general population by guideline¹⁴

Guidelines	Initial treatment	Two-drug combinations	Three-drug combinations
JNC 8	Thiazide diuretic, CCB, ACEI or ARB (Alone or in combination)	Add a drug from another class: thiazide diuretic, CCB, ACEI or ARB	CCB + thiazide + ACEI or ARB
ASH/ISH	Stage 1: ACEI or ARB Stage 2: 2 drugs	CCB or thiazide + ACEI or ARB	CCB + thiazide + ACEI or ARB
AHA/ACC / CDC	Stage 1: Thiazide for most patients or ACEI, ARB, CCB Stage 2: Thiazide + ACEI, ARB or CCB OR ACEI + CCB	Add a drug from another class, either, thiazide diuretic, CCB, ACEI or ARB	Not specified
CHEP	Thiazide, β -blocker, ACEI, ARB, CCB (Consider combination if SBP ≥ 20 mmHg or DBP ≥ 10 mmHg above target)	Add a drug from another class, either, thiazide, β -blocker, CCB, ACEI or ARB	Not specified
ESH/ESC	Stage 1: Diuretics, ACEI, ARB, CCB or β -blocker Stage 2: 2 drugs	Preferred combinations: Thiazide + ARB or ACEI Thiazide + CCB, CCB + ARB or ACEI	Add a drug from another class: thiazide diuretic, CCB, ACEI, ARB or β -blocker
France	Initiating treatment with ARB or ACEI (better persistence versus diuretic or β blocker), CCB (for adherence) is preferred versus diuretic or β -blocker		
NICE	<55 years, ACEI or ARB >55 years CCB	CCB + ACEI or ARB	CCB + thiazide + ACEI or ARB
Taiwan	Stage 1: Thiazide diuretic, CCB, ARB or ACEI Stage 2: 2 drugs	ACEI or ARB + CCB or thiazide	CCB + thiazide + ACEI or ARB
China	Stage 1: Thiazide diuretic, CCB, ARB, ACEI or β -blocker Stage 2: SPCs of 2 drugs	CCB + ACEI or ARB OR ACEI or ARB + thiazide OR CCB + thiazide. OR CCB + β -blocker	CCB + ACEI or ARB + thiazide OR CCB + ACEI or ARB + β -blocker OR ACEI or ARB + thiazide + α -blocker

Abbreviations: AHA/ACC/CDC- American Hypertension Association/American College of Cardiology/Centers for Disease Control and Prevention, ASH/ISH- American Society of Hypertension/International Society of Hypertension, CHEP- Canadian hypertension education program, ESH/ESC- European Society of Hypertension/European Society of Cardiology, JNC8 - Eighth Joint National Committee, NICE- National Institute for Clinical Excellence (UK), ACEI - angiotensin converting enzyme inhibitor, ARB- angiotensin receptor blocker, CCB - calcium channel blocker, SPC- single pill combination

Relation between Diabetes and Hypertension

Diabetes and high blood pressure are likely to occur together as they share certain physiological characteristics. High blood pressure is a dangerous condition that becomes even more troublesome with diabetes.¹⁵ Hypertensive people are 2.5 times more likely to develop diabetes mellitus within five years. This may be due to the presence of an underlying metabolic syndrome and made worse by the type of antihypertensive drug used.¹⁶ Accompaniment of insulin resistance generally causes hypertension. Increased hepatic glucose release and decreased insulin sensitivity occur by consequent elevations of angiotensin II and aldosterone and activation of the renin-angiotensin-aldosterone system (RAAS).⁸ The coexistence of DM and hypertension is devastating to the cardiovascular system, and the results may increase the risk of stroke or even cardiovascular mortality.¹⁷ Various analyses have indicated that some of the antihypertensive drugs promote the development of type-2-diabetes mellitus. Several studies indicate that, glucose metabolism is impaired by beta blockers and diuretics; hence not only the disease itself, but also antihypertensive therapies may promote the development of new-onset diabetes.¹⁸ Furthermore,

drugs for the treatment of hypertension exhibit a long record of potentially affecting also gluco-metabolic parameters, such as blood glucose, insulin sensitivity, and HbA1c. In particular, beta-blockers (also the so-called cardio-selective ones) and thiazide / thiazide-like diuretics have been known to increase blood glucose for many years, including the precipitation of hyperosmolar hyperglycemic coma at high dose by the latter. So, it seems to be an important issue whether antihypertensive drugs which increase blood glucose should be avoided, i.e. drugs which may worsen glycemic control in patients with diabetes or induce new onset diabetes in patients with hypertension.¹⁹

Clinical Studies Demonstrating the Correlation Between Antihypertensive Drugs & NOD -

Numerous analyses have demonstrated that not only hypertension, but also antihypertensive therapies promote the development of type-2 diabetes mellitus.¹⁸ The effects of different antihypertensive regimens on new-onset diabetes as demonstrated by some major hypertension trials are shown in the Table 3.^{20,21}

Table 3: Randomized trials that examined incidence of new-onset diabetes

Trial	Primary treatment	Increase in new-onset diabetes by primary treatment	Comparator
SHEP	Placebo	↓ 5%	Thiazide diuretic ± BB
STOP-2	BB/thiazide diuretic	No difference from comparator	ACEI/CCB
CAPP	Thiazide diuretic/BB	↑ 13%	ACEI
HOPE	Placebo ± BB/thiazide diuretic	↑ 52%	ACEI
INSIGHT	Thiazide diuretic/BB	↑ 43%	DHP-CCB
LIFE	BB/thiazide diuretic	↑ 32%	ARB ± thiazide diuretic
ALLHAT	Thiazide diuretic	↑ 16%/30%	DHP-CCB/ACEI
INVEST	BB ± thiazide diuretic	↑ 17%	Non-DHP-CCB based
VALUE	DHP-CCB	↑ 25%	ARB based
ASCOT	BB ± thiazide diuretic	↑ 32%	DHP-CCB based

Abbreviations: ACEI- ACE inhibitor, ARB- angiotensin II receptor blocker, BB- blocker, DHP-dihydropyridine, SHEP- Systolic Hypertension in Elderly Program, STOP-2- Second Swedish Trial in Old Patients with Hypertension, CAPP- Captopril Prevention Project, HOPE- Heart Outcomes Prevention Evaluation, INSIGHT- Intervention as a Goal in Hypertension Treatment, LIFE- Losartan Intervention For Endpoint reduction in hypertension, ALLHAT- Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, INVEST- International Verapamil Trandolapril Study, VALUE- Valsartan Antihypertensive Long-Term Use Evaluation, ASCOT- Anglo-Scandinavian

Evidences from Clinical Trials

After a follow up of 14.3 years in the Systolic Hypertension in the Elderly Program SHEP trial it was evaluated that, patients with isolated systolic hypertension treated with CTD (Chlorthalidone) ²² have an increased incidence of diabetes as compared to placebo and diabetes that developed during the trial among subjects on placebo was associated with increased CV adverse outcome and total mortality rate, whereas diabetes that developed among subjects during diuretic therapy did not have significant association with CV mortality rate or total mortality rate. ²³ In the VALUE Trial, the greater incidence of NOD in the amlodipine arm can be explained tentatively by the greater occurrence of hypokalemia induced by the association of hydrochlorothiazide. ²⁴ HOPE study reported benefits of ACEI beyond blood pressure lowering, that is greater prevention in stroke and it is important to note that ACEI leads to greater blood pressure lowering. ²⁵ The incidence of NOD was reported with diuretics and beta blockers on comparing with ACEI and CCBs in Captopril Prevention Project (CAPP) and the Intervention as a Goal in Hypertension Treatment Study (INSIGHT). Moreover, in the recent trials, the incidence of new onset diabetes was highest in the diuretic or β -blocker groups compared with other antihypertensive drugs: Atenolol versus Losartan and CCBs in LIFE and STOP-2 trials, verapamil versus conventional therapy (i.e., β -blockers) in INVEST, chlorthalidone versus amlodipine or lisinopril in ALLHAT. ²⁰ In the large ASCOT trial it was also concluded that new onset diabetes was more frequent with conventional therapy than amlodipine base regimen. ²¹ Examination of data from clinical trials on comparing impact of 'new' (calcium antagonists, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists) versus 'old' (diuretics and beta-blockers) drugs on new-onset diabetes it is indicated that compared with diuretics and beta-blockers, new-onset diabetes is less common with 'new' drugs, and that conventional antihypertensive compounds, particularly when combined together. ²⁷ Risk for new-onset diabetes was increased with β -blockers compared with ACE inhibitors, ARBs, and calcium-channel blockers; risk did not differ from placebo or diuretics. ²⁸ Although hyperglycaemic effects are mostly seen with high doses of thiazides (25–50 mg), combination with a β -blocker, especially high-dose atenolol (100 mg), increases the risk for new onset diabetes in these patients. ²⁹

New-Onset Diabetes: Impact of Blood Pressure-Lowering Drugs

Nowadays New onset diabetes (NOD) is common among hypertensive patients and it has become an issue of major

interest in clinical trials of antihypertensive therapy and a major practical concern for both patients and their physicians. ²⁶

Diuretics- Diuretics specially thiazides are widely used in the treatment of hypertension. ² Diuretic-induced hyperglycaemia may be due to decreased insulin secretion as a result of hypokalaemia. ¹¹

Thiazides- have a common side effect of lowering serum potassium which can be associated with increased risk of new-onset diabetes. ³⁰ Hydrochlorothiazide have negative impact on metabolism which include alterations in lipids, depletion of potassium (hypokalemia) ³¹ in a dose dependent fashion ³², impairment of glucose metabolism, impaired insulin release ³³ and, therefore, the occurrence of type 2 diabetes by increasing hepatic insulin resistance. ^{34, 35} The exact pathway has not been elucidated for thiazide-induced glucose intolerance. The inverse relationship between potassium and glucose was confirmed and potassium supplementation was correlated with a smaller increase in serum glucose ³⁶ and hyperuricemia induced by them may be responsible for some adverse metabolic effects and may be associated with increased cardiovascular risk and renal injury. ³³

β -Blockers- mechanism involving diabetes induced by beta blockers may include weight gain, alterations in insulin clearance and reduced first-phase pancreatic insulin secretion, peripheral glucose utilization ³⁴ and probably most importantly, reduced peripheral blood flow as a result of increased peripheral vascular resistance. ²¹ In particular, β -blockers may decrease the first phase of insulin secretion, possibly through an impairment of β_2 -mediated insulin release. In general, attenuation of the first phase of insulin secretion represents a crucial step in the natural history of type 2 DM, and has been suggested as an important predictor of this disease. Thus, this action of β -blockers could be another important contributor towards the development of type 2 DM. ³⁷

ACE-I/ARB- The Renin-Angiotensin System (RAS) is an important component for the homeostasis of blood flow. ³⁸ So the use of ACE-I and ARB have utility in prevention of diabetes and also had known benefits on the prevention of diabetes induced nephropathy. ^{39,40} On comparing to other antihypertensive drugs as diuretics and beta-blockers, patients receiving ARB or ACE-I had a 25%-30% lower risk of developing new-onset diabetes despite similar reduction in blood pressure. ^{40,41} Through inhibition of kinase II mediated degradation, ACE inhibitors increases bradykinin levels. It has been identified that an increased production of prostaglandins (prostaglandin E1 & E2) and nitric oxide, that improve exercise

induced glucose metabolism and muscle sensitivity to insulin are caused by the higher kinin levels, which consequently causes enhanced insulin mediated glucose uptake and peripheral vasodilatory action of ACE inhibitors and ARBs, which lead to an improvement in skeletal muscle blood flow and finally to enhancement of glucose uptake.⁴²

Calcium channel blockers (CCBs) - Vasodilatation and improved peripheral blood flow may explain the improvement

in insulin sensitivity seen with calcium channel blockade.⁴⁰ On comparison to beta-blockers and thiazide diuretics, CCBs have not been associated with glycemic adverse effects. These agents generally thought to exhibit negligible effects on glucose metabolism.¹⁰ These agents may improve insulin sensitivity by exerting vasodilatory action in insulin-sensitive tissues without stimulating sympathetic nervous activity, by preventing the inhibition of glucose transporters and glycogen synthase by calcium, or through antioxidant effects.³⁴

Table 4: Mechanisms associated with metabolic effects of antihypertensive drugs⁴³

RAS Blocking Agents (ACEIs and ARBs)	Improved Insulin Sensitivity: Increased skeletal muscle perfusion Decreased hepatic glucose production (↓ Ang II) Enhanced adipocyte differentiation (↓ Ang II) Alterations of insulin signaling Change in proportions of oxidative muscle fibers
	Improved Pancreatic β Cell Function: Increased pancreatic perfusion Increased serum potassium (improving K ⁺ -ATPase function) Restoration of first phase insulin secretion (↓ Ang II)
Thiazide Diuretics	Diminished Insulin Sensitivity: Decreased skeletal muscle perfusion Increased hepatic glucose production (↑ Ang II) Inhibition of adipocyte differentiation (↑ Ang II) Increased endothelial inflammation Visceral and hepatic fat deposition
	Diminished Pancreatic β Cell Function: Decreased pancreatic perfusion Decreased serum potassium (hindering K ⁺ -ATPase function) Inhibition of first phase insulin secretion (↑ Ang II)
β Blockers	Reduced insulin secretion Reduced skeletal muscle perfusion Reduced pancreatic perfusion Weight gain Alteration of lipoprotein lipase activity

DISCUSSION

Control of hypertension and maintenance of ideal blood pressure is the main point that leads to beneficial effects in most of the diabetic patients but there is evidence that antihypertensive treatment has a significant influence on the incidence of diabetes mellitus. Numerous studies have consistently demonstrated that certain classes of antihypertensive medications have differential effects on carbohydrate and lipid metabolism in humans. Whereas the incidence is higher for patients treated with diuretics or beta blockers than for patients treated with calcium-channel blockers, ACE inhibitors and ARB and this effect is much stronger when both substance classes are used in combination. It was reflected that hypokalemia induced by diuretics and possibly impairment of β₂-mediated insulin release by beta blockers causes hyperglycemia, and the other drug classes ARB, CCB do not have major effects on glucose homeostasis hence their use was not associated with NOD. On comparison with diuretics and β-blockers, ACE-I & ARBs have been shown to reduce insulin resistance. This justifies the recommendation of guidelines to avoid isolated or combined administration of diuretics or β-blockers in patients predisposed to diabetes such as those with metabolic syndrome. In general, higher doses of thiazide diuretics (i.e., ≥25 mg/day hydrochlorothiazide) and β-blockers, at any antihypertensive dose, worsen glycemic control, with β-blockers worsening insulin sensitivity. Several studies demonstrate that diuretics and beta-blockers were independently associated with an increased risk of NOD by exhibiting adverse glycemic effects in the elderly. Further research is required to confirm the role of ACE inhibitors and ARB in the prevention of type-2 diabetes and to assess the risk for cardiovascular events and mortality due to drug-induced diabetes.

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