Pharmacotherapy of Hypertension and Diabetes Co-morbidity in the Elderly: A Narrative Review

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Abstract

Introduction: Ageing is a normal physiological process, and with improving healthcare and standard of living, the elderly population is projected to increase substantially over time. Hypertension occurs in up to 80% of type 2 diabetes cases, and co-morbidity between the two conditions is common among the elderly, posing significant challenges in clinical management. If not adequately addressed, this co-morbidity can lead to increased mortality and complications such as retinopathy, neuropathy and nephropathy.

Materials and Methods: This narrative review searched Google Scholar, ResearchGate, PubMed and Scopus for literature on the pharmacotherapy of hypertension and diabetes co-morbidity published up to May 2025. A total of 117 articles meeting the inclusion criteria were selected and analysed.

Results: The review describes the pathophysiology of and interactions between hypertension and diabetes, the complications arising from their co-morbidity, and the clinical guidelines and pharmacological strategies used in their management. Treating elderly patients with both conditions requires a nuanced, multidisciplinary approach, as age-associated alterations in drug metabolism, polypharmacy, frailty and comorbid conditions must all be considered to avoid adverse outcomes and promote adherence while ensuring optimal efficacy.

Conclusion: Effective management of hypertension and diabetes co-morbidity in the elderly requires individualised, multidisciplinary care guided by current clinical guidelines, with emerging approaches such as personalised medicine and telemedicine offering promise for improving outcomes in this population.

Keywords: ageing**,** co-morbidity, diabetes, hypertension, pharmacotherapy

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INTRODUCTION

All people will experience and cope with the ageing process at some point in their life; it is a natural and unavoidable phenomenon. Being thirty years old indicates that a person has experienced all of the stages of life, including newborn, toddler, preschool, adolescent, adult and elderly. These different stages of life begins both biologically and psychologically.[1] In the world, people who aged more than 60 years old was amounted to 13.4% of the whole human population in 2013, and this percentage was estimated to be doubled up to 25.3% in 2050, in which 8% of these elderly people live in Asia.[2] Two alterations in the natural/physiological functioning of the body's systems and various organs will occur gradually in the aged. As a result of biological changes, older people will experience a variety of physical issues, including the occurrence of chronic illnesses, sometimes

known as non-communicable diseases (NCDs). NCD is a long-lasting condition that typically progresses slowly and cannot be spread from person to person. The four main types of NCD are cardiovascular disease (e.g. hypertension), cancer, chronic respiratory disease, and diabetes mellitus (DM). Almost three quarters of NCD deaths (28 million) occur in low- and middle-income countries; 16 million NCD deaths occur before the age of 70; 82% of these "premature" deaths occurred in low- and middle-income countries.[3]

There are several physiological similarities between diabetes and hypertension, including increased body fluid, increased arterial stiffness, and impaired insulin regulation. Similar symptoms, including as increased body mass, excessive fat and processed sugar intake, and decreased physical activity, may be seen in patients. It's likely that either can result in the other.

Hypertension occurs in up to 80% of type 2 diabetics.[4-6] Among the elderly, the probability of exhibiting co-morbidities is common, although rates vary significantly by countries (Netherlands, Sweden, Spain, Australia, US, Canada), where prevalence ranges from 55% to 98%[7]: the highest rates always occur among older people, women and individuals in lower socio-economic classes. Co-morbidity significantly complicates medication management in the aged, as health care practitioners currently lack a systematic method to integrate age-related complexities into standard clinical practice.[8]

A literature search was conducted across major scientific databases, including Google Scholar, ResearchGate, PubMed and Scopus, covering publications up to May 2025. Articles that directly addressed the pharmacological treatment of hypertension and diabetes co-morbidity were identified and analysed for inclusion in this review. Only 117 articles were adapted for this review. Excluded articles included those outside the scope of this study, not in English, or whose full texts were unavailable and not retrievable. The keywords that directed our literature searches included: hypertension, diabetes, ageing, co-morbidities of hypertension and diabetes, and pharmacotherapy.

Prevalence of hypertension and diabetes co-morbidity in elderly populations

Several epidemiologic studies have indicated that the prevalence of hypertension in patients with diabetes mellitus is approximately 1.5 to 2.0 times greater than in a suitably matched non-diabetic population.[9] In individuals with insulin-dependent diabetes mellitus (IDDM), hypertension is typically absent at the time of diagnosis.[10] As renal insufficiency progresses, blood pressure increases, potentially accelerating the transition to end-stage renal failure. In non-insulin-dependent diabetes mellitus (NIDDM), numerous patients exhibit hypertension at the time of diagnosis. The prevalence of hypertension in NIDDM correlates with the extent of obesity, advanced age, and significant atherosclerosis commonly observed, likely encompassing many individuals with essential hypertension.

Multiple supplementary pathophysiological mechanisms contribute to the initiation and maintenance of hypertension in individuals with diabetes. Hyperglycaemia and elevated total body exchangeable sodium may result in extracellular fluid buildup and plasma volume expansion. In certain cases, modifications in the functionality of the renin-angiotensin-aldosterone system and vascular responsiveness to vasoactive hormones may also contribute. Recent suggestions indicate that hyperinsulinaemia and insulin resistance may

contribute to sustained increased blood pressure, as insulin is recognised for promoting salt retention and augmenting sympathetic nervous system activity. However, the pathogenetic relationship between these two common disorders remains elusive. The investigation of the complex interaction between hypertension and diabetes has proceeded along two distinct but interrelated lines. Physicians whose primary area of investigation was hypertension observed a high frequency of diabetes or abnormal glucose tolerance among their hypertensive patients and suggested that hypertension was a prediabetic state.[11] Conversely, diabetologists focused on the heightened incidence of hypertension in their patients and its potential adverse effects on the long-term microvascular and macrovascular complications of diabetes.[12] Recently, these two lines of inquiry have merged to discover a common pathophysiologic underpinning for both disorders.

The incidence of hypertension and diabetes markedly escalates with advancing age. The World Health Organization (WHO) reports that around 1.28 billion adults globally are affected by hypertension, with a significant increase in prevalence among individuals aged 60 years and older.[13] Diabetes impacts over 537 million adult individuals worldwide, with the statistics expected to project to 643 million in the next five years, with significant prevalence among the elderly population.[14,15]

In several elderly folks, these two illnesses frequently coexist. Research demonstrates that more than 70% of elderly individuals with diabetes also suffer from hypertension.[4] This co-morbidity is especially concerning because of the cumulative impact these diseases have on the cardiovascular system, significantly increasing the risk of myocardial infarctions, cerebrovascular accidents, and renal failure.[16] Older persons are more likely to have both illnesses due to the cumulative effects of ageing, extended exposure to cardiovascular risk factors, and sedentary lifestyles.[17]

Physiological changes in ageing and their impact on risk for hypertension and diabetes

As individuals age, numerous physiological alterations transpire that elevate the risk of obtaining hypertension and diabetes. These will include:

i. *Vascular stiffening*: As individuals age, arteries often become rigid, resulting in a loss of elasticity and suppleness. This vascular stiffening enhances peripheral resistance, resulting in higher blood pressure levels. Older persons also have a decrease in the sensitivity of baroreceptors, which regulate blood pressure.[18] This may result in inadequate blood pressure regulation, hence exacerbating hypertension.

ii. *Insulin resistance:* Ageing correlates with a decline in insulin sensitivity. The body's cells exhibit diminished sensitivity to insulin, leading in a less efficient removal of glucose from the bloodstream. The reduction in insulin sensitivity, exacerbated by diminished physical activity and alterations in body composition (including increased fat mass and reduced muscle mass), heightens the chance of developing Type 2 diabetes.[19]

iii. *Decline in pancreatic function*: The pancreas, responsible for producing insulin, also undergoes functional decline with age.[20] This reduction in pancreatic beta-cell function means that even if insulin is produced, it may not be enough to regulate blood sugar levels effectively, contributing to the onset of diabetes.

iv. *Kidney function decline*: Both hypertension and diabetes exert pressure on the kidneys.[4] The

age-related deterioration of renal function renders elderly patients more sensitive to the detrimental effects of hypertension and hyperglycaemia, hence hastening the advancement of both illnesses.

Importance of managing co-morbidities in the elderly

The simultaneous presence of hypertension and diabetes in elderly adults poses distinct obstacles regarding treatment and management.[21] The cumulative impact of these disorders hastens the decline of the cardiovascular system, kidneys, and other essential organs.[22] Moreover, geriatric individuals are predisposed to other chronic conditions, including hyperlipidaemia and cardiovascular disease, which exacerbates the management of hypertension and diabetes.[7] One of the primary reasons for handling these co-morbidities is prevention of severe complications.[23] Untreated hypertension can result in stroke, myocardial infarction, and congestive heart failure, whereas inadequately managed diabetes heightens the risk of diabetic retinopathy, neuropathy, nephropathy, and cardiovascular disease. Collectively, these disorders substantially increase the risk of mortality and adversely affect quality of life.[24]

The management of hypertension and diabetes in the elderly is further complicated by polypharmacy, which refers to the administration of many drugs for diverse illnesses.[25] Numerous older adults concurrently administer drugs for hypertension, glycaemia, hyperlipidaemia, and various other conditions. This elevates the possibility of drug interactions and adverse consequences, complicating treatment protocols. Healthcare professionals must implement a holistic, customised strategy that effectively manages both illnesses while mitigating the dangers of over-medication.[26]

Pathophysiology and interactions between hypertension and diabetes

Pathophysiology of essential hypertension in adults

Blood pressure (BP) is the fundamental mechanism that distributes blood to all bodily organs; therefore, the regulation of BP is crucial for survival. In this background, it is unsurprising that the control of blood pressure involves a very intricate and occasionally redundant interaction among renal, neuronal, cardiac, vascular, and endocrine processes, influenced by hereditary and environmental variables.[27]

a) Role of kidneys in the pathogenesis of essential hypertension

The kidney is crucial for regulating blood pressure by managing salt and water excretion, hence preserving extracellular volume homeostasis.[28] Blood pressure and salt homeostasis are closely connected through the pressure natriuresis mechanism, which aids in maintaining blood pressure at a specific fixed point.[29] An augmentation in renal perfusion pressure results in an increase in renal sodium excretion and a decrease in extracellular fluid volume, causing blood pressure to return to its baseline level.[30] This hypothesis asserts that hypertension results from a shift in the blood pressure set point due to a dysfunction in the pressure-natriuresis mechanism.[31] The regulation of sodium excretion in the pressure natriuresis phenomenon primarily occurs in the proximal nephron areas, with changes in medullary blood flow being crucial for the pressure-natriuresis interaction. Furthermore, additional endocrine factors, including as the renin-angiotensin-aldosterone system, nitric oxide, and prostaglandins, might modify the pressure-natriuresis relationship to increased or decreased set points. Significant evidence demonstrates that sodium management by the distal nephron segments is crucial for maintaining sodium equilibrium in reaction to variations in

blood pressure. Moreover, elements including the sympathetic nervous system, localised intrarenal inflammation, and the generation of reactive oxygen species (ROS) can affect the pressure-natriuresis association.[32]

b) Sympathetic nervous system and renin-angiotensin-aldosterone system

Multiple neuroendocrine systems also increase blood pressure and maintain the hypertensive condition, partly due to their impact on renal function. The two most critical systems are undoubtedly the renin-angiotensin-aldosterone system and the sympathetic nervous system.[33] The renin-angiotensin-aldosterone system (RAAS), activated by renin secretion from the juxtaglomerular cells of the kidney, plays a significant role in the pathophysiology of hypertension via its vascular, endocrine, central, and renal processes. Recent years have demonstrated that the RAAS operates not only as a circulatory system but also as a localised tissue system.[33] Thus, renal angiotensin II serves as a potent vasoconstrictor and a growth-promoting peptide, modulating blood pressure via affecting renal haemodynamics and glomerular filtration rate, as it alters the tone of both afferent and efferent arterioles.[34] There is substantial evidence that the sympathetic nervous system has a role in blood pressure regulation and the pathogenesis of hypertension. Numerous animal models of hypertension exhibit heightened sympathetic activity.[35,36] Furthermore, in the initial phases of clinical hypertension, a conjunction of sympathetic hyperactivity and parasympathetic dysfunction has been noted in young individuals exhibiting an elevated heart rate.[37] The sympathetic system significantly affects renin secretion, renal haemodynamics, and tubular salt management in the kidney.[31] The involvement of the sympathetic nervous system and baroreflex regulation in the onset of hypertension has prompted the creation of novel interventional approaches for managing resistant hypertension, such as renal denervation and baroreflex sensitisation.[38]

c) *Prostaglandins*

Prostaglandins are a class of molecules that regulate blood pressure and may play a role in the onset of hypertension. Prostaglandins originate from the metabolism of arachidonic acid. Their production involves multiple stages: initially, the release of arachidonic acid from membrane phospholipids, facilitated by phospholipase A_2; subsequently, the enzymatic transformation of arachidonic acid by cyclooxygenases (COX-1, COX-2, or COX-3) to yield PGH_2; and finally, the synthesis of specific prostaglandins, mediated by prostaglandin synthases, such as prostacyclin synthase, leading to the formation of prostacyclin (PGI_2), or thromboxane synthase, which produces thromboxane A_2. This cascade leads to the synthesis of several prostaglandins with distinct biological activities, including vascular, renal, and inflammatory actions.[39]

Phospholipase A_2 is stimulated by various factors, including angiotensin II, norepinephrine, and bradykinin. Prostaglandins primarily operate around their release sites due of their rapid breakdown by local metabolism into inactive metabolites. Prostaglandins can elicit either vasoconstriction (thromboxane A_2, $PGF_2\alpha$) or vasodilation (PGE_2, prostacyclin) at the vascular level.[40] A notable feature of vasodilatory prostaglandins is their ability to modulate vasoconstriction induced by potent vasoactive drugs such as angiotensin II. In the average adult kidney, both COX-1 and COX-2 are expressed continuously. COX-1 is located in the glomerulus, afferent arteriole, and tubular cells, whereas COX-2 is found in the afferent and efferent arterioles, podocytes, macula densa, and some tubular and interstitial cells. Intrarenal

prostaglandins are essential in regulating renal perfusion and glomerular filtration rate. They also participate in the maintenance of sodium, potassium, and chloride homeostasis, along with the regulation of renin secretion.[41]

The impact of prostaglandins on vascular function, renal electrolyte balance, and renin secretion may be especially relevant to the onset of hypertension.[42] Data demonstrate that mice devoid of the PGI_2 receptor show resistance to the development of renovascular hypertension, a renin-dependent form of hypertension.[43] Individuals with hypertension demonstrate a deficiency in vasodilatory prostaglandins[44], although an increase in thromboxane A_2 has been noted in essential hypertension.[45] The data indicate a possible imbalance between anti-hypertensive and pro-hypertensive prostaglandins in hypertension.[46] The three proposed functions of prostaglandins in hypertension are highlighted by the observation that both selective and nonselective COX-1 and COX-2 inhibitors increase blood pressure, encourage salt retention, and may trigger hypertension in some patients.[46] However, the hypertensive effect of non-steroidal anti-inflammatory drugs is more pronounced in patients with hypertension than in normotensive individuals.

Pathophysiology of diabetes in the elderly

The aetiology of diabetes entails a disturbance in the feedback mechanisms governing insulin action and production, resulting in increased blood glucose levels.[47] In cases of β-cell failure, insulin synthesis is reduced, limiting the body's capacity to maintain physiological glucose levels. Conversely, insulin resistance (IR) results in increased glucose production in the liver and reduced glucose uptake in muscle, liver, and adipose tissue. While both processes arise early in pathophysiology and facilitate disease progression, β-cell dysfunction is generally more evident than insulin resistance. However, the simultaneous presence of β-cell dysfunction and insulin resistance intensifies hyperglycaemia, promoting the progression of type 2 diabetes mellitus (T2DM).[48]

Pancreatic β-cells are accountable for the generation of insulin, which is generated as pre-proinsulin. During maturation, pre-proinsulin has a structural alteration facilitated by several proteins in the endoplasmic reticulum (ER), resulting in proinsulin.[49] Subsequently, proinsulin is transported from the endoplasmic reticulum to the Golgi apparatus, where it enters immature secretory vesicles and is broken into C-peptide and insulin.[50] Upon maturation, insulin is sequestered in granules until its release is activated. The secretion of insulin is predominantly stimulated by elevated glucose levels. It is important to acknowledge that additional variables, including amino acids, fatty acids, and hormones, can also stimulate insulin release. As circulation glucose levels rise, β-cells absorb glucose mostly via the glucose transporter 2 (GLUT2), a solute carrier protein that functions as a glucose sensor for β-cells. Following glucose entry, glucose catabolism commences, increasing the intracellular ATP/ADP ratio[47], which activates the closure of ATP-sensitive potassium channels in the plasma membrane. This leads to membrane depolarisation and the activation of voltage-gated Ca^{2+} channels, permitting Ca^{2+} influx into the cell. The elevation of intracellular Ca^{2+} concentration triggers the priming and fusion of insulin-containing secretory granules with the plasma membrane, resulting in insulin exocytosis.

β-cell dysfunction has traditionally been associated with β-cell mortality.[51] Recent studies suggest that the dysfunction of β-cells in T2DM may arise from a complex interaction between

environmental variables and many molecular pathways in cell biology.[52] In a condition of overconsumption, similar to obesity, hyperglycaemia and hyperlipidaemia often arise, fostering insulin resistance and chronic inflammation. Beta cells, because to differences in their genetic vulnerability, are subjected to toxic stimuli including inflammation, inflammatory stress, endoplasmic reticulum stress, metabolic/oxidative stress, and amyloid stress, which may ultimately lead to the degradation of islet integrity. Excess free fatty acids and hyperglycaemia lead to β-cell dysfunction by inducing endoplasmic reticulum stress through the activation of apoptotic unfolded protein response pathways.[53] Lipotoxicity, glucotoxicity, and glucolipotoxicity linked to obesity elevate metabolic and oxidative stress, leading to β-cell death.[53]

Insufficient synthesis of insulin precursors or insulin, along with disruptions in the secretion pathway, can lead to insulin secretory dysfunction, which are the primary cause of β-cell failure and a critical component of T2DM. The reduced expression of the GLUT2 glucose transporter may affect the ensuing signalling cascade[54], while misfolding of proinsulin is another frequently noted factor linked to insufficient insulin production and diabetes.[55]

Interactions between hypertension and diabetes

The interplay between hypertension and diabetes is intricate, and these two illnesses frequently coexist, especially in older adults. Both exhibit shared risk factors, including obesity, a sedentary lifestyle, and advanced age. The coexistence of hypertension with diabetes produces a synergistic impact, exacerbating the risk of cardiovascular disease, stroke, and renal impairment. Multiple mechanisms elucidate the robust interplay between these two diseases:

i. Insulin resistance and hypertension: Insulin resistance, a hallmark of Type 2 diabetes, is closely linked to the development of hypertension. Insulin frequently induces vasodilation, promoting the relaxing of blood vessels and improving blood circulation.[56] In individuals with insulin resistance, the vasodilatory response is impaired, resulting in heightened peripheral resistance and higher blood pressure.[57] Moreover, insulin resistance leads to increased salt retention by the kidneys, so elevating blood volume and further raising blood pressure.[58]

ii. RAAS activation in both conditions: The RAAS is excessively active in both hypertension and diabetes. In diabetes, hyperglycaemia and insulin resistance stimulate the RAAS, leading to increased concentrations of angiotensin II and aldosterone. These hormones promote vasoconstriction, sodium retention, and inflammation, all of which contribute to hypertension.[5] The simultaneous dysfunction of the RAAS explains the high incidence of hypertension in diabetic people.[59]

iii. Endothelial dysfunction: Endothelial dysfunction is a common pathophysiological mechanism in hypertension and diabetes. In diabetes, chronic hyperglycaemia damages the endothelial cells of blood vessels, leading to reduced nitric oxide production.[60] Inadequate nitric oxide hinders proper vasodilation, leading to increased peripheral resistance and hypertension. Hypertension exacerbates vascular damage, creating a harmful cycle of endothelial injury and elevated blood pressure.[61]

iv. Inflammation and oxidative stress: Chronic inflammation and oxidative stress are pivotal contributors to the onset of hypertension and diabetes.[62] Hyperglycaemia in diabetes prompts the production of reactive oxygen species (ROS), leading to oxidative damage to cells, including endothelial and smooth

muscle cells in blood vessels.[63] Oxidative stress causes arterial stiffness and inflammation, both of which lead to hypertension.[64] Hypertension similarly increases oxidative stress in the vascular system, hence accelerating the progression of diabetes-related complications.[65]

v. *Obesity as a common risk factor*: Obesity represents a significant risk factor for hypertension and diabetes, as excess body fat exacerbates the pathophysiology of both conditions.[66] Adipose tissue, particularly visceral fat, secretes pro-inflammatory cytokines that exacerbate insulin resistance and vascular inflammation.[67] Furthermore, obesity increases cardiac workload and hypertension, hence complicating the management of diabetes and hypertension in obese patients.[68]

Complications arising from hypertension and diabetes co-morbidity

The simultaneous presence of hypertension and diabetes markedly elevates the risk of serious consequences, predominantly concerning cardiovascular health. These encompass:

i. *Cardiovascular disease (CVD):* Individuals with hypertension and diabetes are at a markedly increased risk of acquiring cardiovascular diseases, such as coronary artery disease, myocardial infarctions, and cerebrovascular accidents.[69] The combined consequences of insulin resistance, hyperglycaemia, and hypertension accelerate the advancement of atherosclerosis, or arterial stiffening. This may lead to plaque buildup, narrowing of blood vessels, and ultimately, blockages that trigger heart attacks or strokes.[69]

ii. *Diabetic nephropathy and hypertension-induced renal damage*: Diabetes and hypertension both contribute to renal impairment, potentially culminating in chronic kidney disease (CKD).[70] In diabetes, elevated blood glucose levels damage the small blood vessels in the kidneys, leading to diabetic nephropathy.[71] Hypertension intensifies this damage by increasing pressure within the kidneys' filtration units, so further diminishing their function.[72] This combination significantly elevates the risk of end-stage renal disease (ESRD), requiring dialysis or kidney transplantation.[73]

iii. *Retinopathy and microvascular complications*: Diabetes is a key factor in microvascular problems, particularly diabetic retinopathy, which affects the retinal blood vessels and can lead to blindness.[74] Hypertension accelerates the progression of retinopathy by increasing pressure in the retinal arteries, leading to rupture or leaking. The combined impact of hyperglycaemia and hypertension leads to increased retinal damage and visual impairment.[75]

iv. *Neuropathy*: Diabetes-induced neuropathy constitutes a substantial complication that may be exacerbated by hypertension.[76] Both conditions hinder circulation, depriving nerves of the oxygen and nutrients essential for proper function.[77] This leads to nerve damage, particularly in the peripheral nervous system, resulting in pain, numbness, and functional deficits in the limbs.[77]

Clinical guidelines for treatment for hypertension and diabetes co-morbidity

Managing elderly people with hypertension and diabetes necessitates a sophisticated, interdisciplinary strategy, since both ailments markedly elevate the danger of cardiovascular incidents, renal failure, and other critical complications.[78] Clinical guidelines are formulated based on comprehensive research and expert consensus to guarantee that patients receive optimal care while reducing unfavourable consequences.[78] The primary objectives in

managing hypertension and diabetes are to regulate blood pressure and glucose levels, mitigate the risk of complications, and enhance overall quality of life.[79] In geriatric patients, specific considerations are addressed due to characteristics including frailty, polypharmacy, and the existence of several comorbidities.[80]

The broadly referenced clinical guidelines for managing hypertension and diabetes co-morbidity in the elderly include recommendations from the American Diabetes Association (ADA), the American Heart Association (AHA), the European Society of Hypertension (ESH), and the European Society of Cardiology (ESC).[81] These guidelines emphasise a comprehensive, individualised approach, which includes lifestyle interventions, pharmacological therapy, and regular monitoring of both blood pressure and blood glucose levels.[81]

Blood pressure targets for elderly patients with diabetes

Managing hypertension in elderly diabetic patients necessitates meticulous evaluation of blood pressure objectives to mitigate cardiovascular disease risk while avoiding adverse effects.[78] Excessive lowering of blood pressure, especially in elderly individuals, may result in negative consequences including dizziness, falls, and diminished renal function.[82] Clinical guidelines often advocate for a more cautious strategy in managing blood pressure among elderly adults relative to younger demographics. Current recommendations from organisations such the ADA, ESH, and ESC indicate that a goal systolic blood pressure (SBP) below 140 mmHg is suitable for the majority of older adults with diabetes. Certain guidelines advocate for even more personalised aims, especially for old or weak patients.[81]

Optimal blood pressure target: For elderly patients with diabetes, most guidelines suggest a blood pressure target of 130-140/80-90 mmHg. This range mitigates the risk of cardiovascular events while minimising the likelihood of unfavourable therapeutic effects.[83]

Consideration for frail elderly patients: Guidelines advocate for more lenient blood pressure objectives in frail elderly adults or those with restricted life expectancy.[84] A systolic blood pressure target of 140-150 mmHg may be deemed acceptable, particularly if lower targets induce symptoms like dizziness or exhaustion.[85] The determination of particular blood pressure targets must consider individual patient characteristics, including age, overall health, co-morbidities, and patient preferences.[86] The blood pressure targets must be attained progressively to avert abrupt declines that may result in problems like hypotension and falls.[87]

Glycaemic control goals for elderly patients with hypertension

Glycaemic control is critical in the management of Type 2 diabetes in the elderly, as hyperglycaemia contributes to cardiovascular disease, kidney damage, and other complications.[88] However, like blood pressure targets, glycaemic goals should be individualised based on the patient's overall health, risk of hypoglycaemia, and co-existing conditions.[89]

HbA1c target: Glycated haemoglobin (HbA1c) is the primary measure used to assess long-term glycaemic control.[90] For most elderly patients with diabetes, guidelines recommend an HbA1c target of 7.0-8.0%.[91] This range helps prevent the development of diabetic complications while reducing the risk of hypoglycaemia, which can be particularly dangerous in older adults.[91]

Relaxed glycaemic targets for frail patients: In elderly patients who are frail, have multiple co-morbidities, or a limited life expectancy, a more

relaxed HbA1c target of 8.0-8.5% may be appropriate. This approach reduces the risk of hypoglycaemia and other treatment-related complications that could negatively impact quality of life.[92]

Avoiding hypoglycaemia: In elderly patients, hypoglycaemia poses a serious risk, particularly if they are on medications such as insulin or sulphonylureas, which increase the risk of low blood sugar.[93] Clinical guidelines emphasise the importance of avoiding hypoglycaemia by choosing medications with a lower risk of this side effect and by setting appropriate, individualised glycaemic targets.[89]

Pharmacological management of hypertension and diabetes co-morbidity

The simultaneous occurrence of hypertension and diabetes, especially in senior individuals, poses a considerable difficulty for healthcare professionals. Both illnesses independently elevate the chance of cardiovascular diseases (CVD), stroke, renal failure, and other consequences.[94] When these conditions coalesce, the risk of negative outcomes escalates, rendering pharmacological intervention essential for alleviating long-term harm and enhancing quality of life.

Managing both conditions simultaneously requires a careful selection of medications that not only control blood pressure and blood glucose but also protect vital organs such as the heart and kidneys.[95] However, the presence of co-morbidity in elderly patients introduces additional complexities. Factors like polypharmacy, age-related decline in organ function, frailty, and drug interactions need to be carefully considered to avoid adverse outcomes, such as hypoglycaemia or hypotension.[17,96]

Therapeutic goals for managing co-morbid hypertension and diabetes

The primary goals in pharmacological management of co-morbid hypertension and diabetes are[97]:

i. Reduction of blood pressure to target levels, minimising cardiovascular risk without causing harm (e.g., hypotension, falls).[98]
ii. Achieving optimal glycaemic control to prevent diabetic complications, while avoiding hypoglycaemia, especially in elderly patients.[99]
iii. Minimisation of polypharmacy risks, including drug interactions, side effects, and the burden on elderly patients, who may be dealing with multiple medications for various conditions.[100]

Antihypertensive medications in diabetic patients

Choosing antihypertensive agents for diabetic patients requires an understanding of the interplay between hypertension, diabetes, and the patient's overall health status. Specific drug classes are favoured for their ability to manage both blood pressure and complications related to diabetes. (Table 1)

Table 1: Antihypertensive agents for diabetic patients

Drugs	Notes	Therapeutic effects	Adverse effects	References
Angiotensin-Converting Enzyme (ACE) Inhibitors	ACE inhibitors, such as lisinopril and enalapril, are widely considered first-line therapy for managing hypertension in patients with diabetes. They work by inhibiting the renin-angiotensin-aldosterone system (RAAS), which is often overactive in diabetic patients. This not only lowers blood pressure but also reduces the progression of diabetic nephropathy by decreasing proteinuria (the presence of protein in urine) and slowing kidney damage	ACE inhibitors have been shown to reduce cardiovascular risk and protect the kidneys, making them ideal for elderly diabetic patients who are at increased risk of both cardiovascular and renal complications	ACE inhibitors may cause side effects such as hyperkalemia (high potassium levels) and a persistent cough, and they are contraindicated in patients with advanced renal impairment or those who experience angioedema	(101)
Angiotensin II Receptor Blockers (ARBs)	ARBs, such as losartan and valsartan, provide similar benefits to ACE inhibitors but are often prescribed when patients cannot tolerate ACE inhibitors due to side effects.	ARBs reduce proteinuria, slow the progression of kidney disease, and are well - tolerated by m ost patients.	Similar to ACE inhibitors, ARBs can cause hyperkalemia and must be used with caution in patients with renal insufficiency	(102, 103)

Drugs	Notes	Therapeutic effects	Adverse effects	References
	They work by blocking the angiotensin II receptor, leading to vasodilation and reduc ed blood pressure. Like ACE inhibitors, ARBs have nephroprotective effects and are crucial for diabetic patients who may be progressing toward diabetic nephropathy			
Calcium Channel Blockers (CCBs)	Calcium channel blockers, like amlodipine and diltiazem, are frequently prescribed for aged people, especially those with isolated systolic hypertension. These drugs facilitate the relaxation of blood vessels, diminishing vascular resistance and decreasing blood pressure.	Calcium channel blockers (CCBs) effectively lower blood pressure without negatively impacting glucose metabolism, rendering them a suitable choice for diabetic individuals. They also mitigate the risk of stroke, a prevalent issue in individuals with both hypertension and diabetes	CCBs may cause peripheral edema, particularly in elderly patients, and should be monitored in patients with heart failure	([104])

Drugs	Notes	Therapeutic effects	Adverse effects	References
Thiazide Diuretics	Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone, help manage hypertension by reducing fluid retention and decreasing bl ood volume. They are often included as part of combination therapy in diabetic patients to achieve optimal blood pressure control	Thiazides are effective at decreasing blood pressure and have been reported to lower the danger of stroke in hypertensive patients	In diabetic patients, thiazides may increase blood glucose levels and potentially worsen insulin resistance. They should be used cautiously in aged patients with a history of diabetes, and potassium levels must be monitored due to the possibility of hypokalemia	([105])
Beta-Blockers	Beta-blockers, such as metoprolol and carvedilol, are occasionally used in hypertensive patients with diabetes, particularly in those with co-existing coronary artery disease or heart failure. They work by slowing heart rate and reducing myocardial oxygen demand	Beta-blockers provide cardiovascular protection, particularly for patients with a history of myocardial infarction or heart failure	Beta-blockers can mask the symptoms of hypoglycemia, such as tachycardia, making them a less favorable option for patients who are at high risk for low blood sugar episodes. Additionally, non-selective beta-blockers can potentially worsen glucose tolerance, making cardio-selective agents preferable	([106])

Antidiabetic drugs in Hypertensive Patients

In patients with diabetes and hypertension, blood glucose control is critical to prevent microvascular complications, such as retinopathy, neuropathy, and nephropathy, as well as macrovascular complications like heart disease and stroke. The pharmacological options for diabetes management must take into account the presence of hypertension to avoid adverse effects and drug interactions.[4] (Table 2)

Table 2: Pharmacological options for diabetes management in hypertensive patients

Drugs	Notes	Therapeutic effects	Adverse effects	References
Metformin	Metformin is the first-line treatment for Type 2 diabetes in most patients. It works by reducing hepatic glucose production and improving insulin sensitivity. It is particularly useful in hypertensive patients with diabetes because it does not cause weight gain or hypoglycemia, two major concerns in elderly populations	Metformin has cardiovascular benefits and helps with weight management, making it a strong choice for elderly patients who are overweight or at risk for cardiovascular diseases.	Metformin should be used with caution in elderly patients with renal impairment due to the risk of lactic acidosis. Monitoring renal function is essential in this population	[107, 108]
Sulfonylureas	Sulfonylureas, such as glipizide and glyburide, work by stimulating the pancreas to release insulin. These drugs are effective at lowering blood glucose but have a higher risk of causing hypoglycemia, particularly in elderly patients	Sulfonylureas are effective at controlling blood glucose levels in the short term, and their relatively low cost makes them accessible	The risk of hypoglycemia, particularly in elderly patients with declining kidney function or irregular eating patterns, makes sulfonylureas less ideal. Newer agents with a lower risk of hypoglycemia are generally preferred in elderly populations	[109]

Drugs	Notes	Therapeutic effects	Adverse effects	References
Dipeptidyl peptidase-4 (DPP-4) Inhibitors	DPP-4 inhibitors, such as sitagliptin and saxagliptin, are a newer class of drugs that increase insulin release and decrease glucagon levels. These drugs are generally well-tolerated and have a low risk of causing hypoglycemia, making them suitable for elderly patients with co-morbid hypertension and diabetes	DPP-4 inhibitors are weight-neutral, have a low risk of hypoglycemia, and can be safely combined with other antihypertensive and antidiabetic medications	DPP-4 inhibitors, while typically well-tolerated, may pose a somewhat elevated risk of heart failure in certain patients, particularly those with pre-existing cardiovascular problems	(110)
Glucagon-like peptides-1 (GLP-1) Receptor Agonists	GLP-1 receptor agonists, such as liraglutide and exenatide, are injectable medications that enhance insulin secretion, suppress glucagon release, and promote weight loss. These agents have shown cardiovascular benefits, making them an attractive option for patients with both diabetes and hypertension	GLP-1 receptor agonists not only improve glycemic control but also promote weight loss and provide cardiovascular protection, reducing the risk of adverse outcomes in hypertensive patients with diabetes	The main drawbacks of GLP-1 receptor agonists are gastrointestinal side effects, such as nausea, and the need for injections, which may be less desirable for elderly patients	(111)

Drugs	Notes	Therapeutic effects	Adverse effects	References
Sodium-glucose transporter protein-2 (SGLT-2) Inhibitors	SGLT -2 inhibitors, such as empagliflozin and canagliflozin, lower blood glucose by promoting the excretion of glucose in the urine. These drugs also offer significant cardiovascular and renal benefits, making them a valuable addition to the treatment regimen for patients with both hypertension and diabetes	SGLT -2 inhibitors have demonstrated efficacy in diminishing the chance of heart failure and decelerating the advancement of renal disease in diabetic individuals, rendering them a robust option for aged patients with concomitant hypertension	SGLT -2 inhibitors can cause urinary tract infections and dehydration, particularly in elderly patients. Proper hydration and monitoring of renal function are important when using these medications	([112])

Special considerations for elderly patients

Elderly patients present unique challenges in the pharmacological management of hypertension and diabetes.[113] Age-associated alterations in drug metabolism, polypharmacy, frailty, and comorbid conditions must all be considered to avoid adverse outcomes.[113] Strategies for managing these complexities include:

i. Dose adjustments: Lower starting doses and slower titration of medications to avoid adverse effects.[114]

ii. Monitoring for drug interactions: Given the likelihood of polypharmacy, careful attention must be paid to potential drug-drug interactions that could exacerbate side effects or reduce the effectiveness of therapy.[115]

iii. Minimising the risk of hypoglycaemia: Elderly patients, particularly those with declining renal function or irregular meal patterns, are at higher risk of hypoglycaemia.[116] Medications with a lower risk of hypoglycaemia should be prioritised.

iv. Promoting medication adherence: Simplifying drug regimens and using combination therapies can reduce pill burden and improve adherence in elderly patients, who may struggle with complex treatment plans.[117]

Conclusion and Future prospects

Ageing is a natural physiological process experienced by all individuals, and with advancements in healthcare and living standards, the average old population is anticipated to rise over time. The rise in the older population also correlates with a higher prevalence of non-communicable diseases, such as hypertension and diabetes mellitus. Indeed, there is a correlated rise in co-morbidity between these two disorders. Physiological alterations associated with ageing,

including vascular rigidity, heightened insulin resistance, and diminished pancreatic and renal function, contribute to the elevated susceptibility to diabetic hypertensive co-morbidity. Moreover, the activation of the renin-angiotensin-aldosterone system, endothelial dysfunction, inflammation, oxidative stress, and obesity are pivotal in the pathogenesis of both disorders. This co-morbidity presents considerable hurdles in therapeutic management and, if not properly handled, may result in heightened mortality and the emergence of sequelae such as retinopathy, neuropathy, and nephropathy, among others. Managing older people with concurrent hypertension and diabetes necessitates a sophisticated, interdisciplinary strategy. Age-associated alterations in drug metabolism, polypharmacy, frailty, and comorbid conditions must all be considered to avoid adverse outcomes and promote adherence while ensuring optimal efficacy. Attempts must also be made to shift management patterns towards personalised medicine with genetic profiling and telemedicine with remote monitoring.

As the world's population ages, the prevalence of hypertension and diabetes among the elderly is expected to increase. This necessitates ongoing research into novel techniques to managing these co-morbid conditions, with a particular emphasis on personalised medicine, emerging technology, and more integrated care models.

1. *Personalised Medicine and Genetic Profiling:* Advances in genetic profiling and personalised medicine hold the potential of enabling more targeted therapy in hypertension and diabetes treatment. Understanding an individual's genetic propensity enables healthcare providers to tailor pharmacological treatments and lifestyle suggestions to improve outcomes and avoid complications.
2. *Telemedicine and Remote Monitoring:* Telemedicine and remote monitoring technologies are increasingly vital instruments for controlling chronic diseases in the senior demographic. Remote surveillance of blood pressure, glucose levels, and other health parameters facilitates more proactive interventions, diminishing the necessity for frequent clinic visits while enhancing patient outcomes through early treatment.
3. *Integrated Care Models*: Future care for elderly people with co-morbid hypertension and diabetes is expected to take a more integrated, multidisciplinary approach. Coordination of therapy among physicians, dietitians, physical therapists, mental health professionals, and social workers ensures that all aspects of a patient's health are addressed, leading to better overall outcomes.

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