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Review Article

Understanding and treating hypertension in diabetic populations

Massimo Volpe[1,2], Allegra Battistoni[1], Carmine Savoia[1], Giuliano Tocci[1,2]

[1]Division of Cardiology, Department of Clinical and Molecular Medicine, Faculty of Medicine and Phycology, University of Rome Sapienza, Sant'Andrea Hospital, Rome, Italy; [2]IRCCS Neuromed, Pozzilli (IS), Italy

Correspondence to: Prof. Massimo Volpe, MD, FAHA, FESC. Chair and Division of Cardiology, Department of Clinical and Molecular Medicine, Faculty of Medicine and Phycology, University of Rome Sapienza, Sant'Andrea Hospital, Via di Grottarossa 1035-9, 00189 Rome, Italy. Email: massimo.volpe@uniroma1.it.

Abstract: Hypertension and diabetes frequently occurs in the same individuals in clinical practice. Moreover, the presence of hypertension does increase the risk of new-onset diabetes, as well as diabetes does promote development of hypertension. Whatever the case, the concomitant presence of these conditions confers a high risk of major cardiovascular complications and promotes the use integrated pharmacological interventions, aimed at achieving the recommended therapeutic targets. While the benefits of lowering abnormal fasting glucose levels in patients with hypertension and diabetes have been consistently demonstrated, the blood pressure (BP) targets to be achieved to get a benefit in patients with diabetes have been recently reconsidered. In the past, randomized clinical trials have, indeed, demonstrated that lowering BP levels to less than 140/90 mmHg was associated to a substantial reduction of the risk of developing macrovascular and microvascular complications in hypertensive patients with diabetes. In addition, epidemiological and clinical reports suggested that "the lower, the better" for BP in diabetes, so that levels of BP even lower than 130/80 mmHg have been recommended. Recent randomized clinical trials, however, designed to evaluate the potential benefits obtained with an intensive antihypertensive therapy, aimed at achieving a target systolic BP level below 120 mmHg as compared to those obtained with less stringent therapy, have challenged the previous recommendations from international guidelines. In fact, detailed analyses of these trials showed a paradoxically increased risk of coronary events, mostly myocardial infarction, in those patients who achieved the lowest BP levels, particularly in the high-risk subsets of hypertensive populations with diabetes. In the light of these considerations, the present article will briefly review the common pathophysiological mechanisms, the potential sites of therapeutic interactions and the currently recommended BP targets to be achieved under pharmacological treatment in hypertension and diabetes.

Keywords: Hypertension; diabetes mellitus; blood pressure (BP) targets; antihypertensive treatment; renin-angiotensin system (RAS)

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Introduction

Diabetes mellitus is a major public health problem of epidemic proportions and its worldwide prevalence is expected to further increase in the near future (1,2). Patients with diabetes are at high risk of developing major cardiovascular complications, mostly including myocardial infarction, ischemic stroke and congestive heart failure, but also microvascular complications, such as retinopathy, nephropathy and peripheral artery disease (3). Moreover, the presence of diabetes not only increases the risk of experiencing major cardiovascular events, but it also increases the risk of developing hypertension. On the other hand, hypertension, a clinical entity in which insulin resistance is common, is strongly associated with higher risk of developing metabolic complications, including new onset

diabetes, as compared to normotension, and it may precede the development of diabetes by several years.

Once established, the concomitant presence of diabetes and hypertension substantially affects cardiovascular prognosis, reduces the event-free survival, and influences the ability of achieving the recommended therapeutic targets, both in terms of fasting glucose and blood pressure (BP) levels. This detrimental association between diabetes and hypertension has also demonstrated to induce the development and promote the progression of hypertension-related organ damage at both cardiac, vascular and renal levels, thus leading to a further increased risk of developing major cardiovascular events.

Given the objective difficulties in achieving the recommended therapeutic targets in hypertensive patients with diabetes, BP goals to be achieved under pharmacological therapy have been recently revised. In the past, randomized clinical trials have, indeed, demonstrated that lowering BP levels to less than 140/90 mmHg was associated to a substantial reduced risk of developing macrovascular and microvascular complications in hypertensive patients with diabetes. Recent randomized clinical trials, however, designed to evaluate the potential benefits obtained with lowering systolic BP level below 120 mmHg, showed an increased risk of coronary events, mostly myocardial infarction, in those patients who achieved the lowest BP levels, particularly in the high-risk subsets of hypertensive populations with diabetes.

In the light of these considerations, the present article will briefly review the pathophysiological mechanisms shared by essential hypertension and diabetes mellitus, the potential sites of therapeutic interactions and the currently recommended BP targets to be achieved under pharmacological treatment in hypertensive patients with diabetes.

Pathophysiology of vascular alterations in hypertension and diabetes

Vascular remodelling, endothelial dysfunction and vascular stiffness are common features in hypertension and diabetes (*Figure 1*). Low-grade inflammation occurs at the vasculature level in several conditions that predispose to development and progression of cardiovascular diseases, including hypertension and diabetes (5-7). In particular, low-grade inflammation of the vascular wall participates in vascular remodelling and may contribute to the pathophysiology of hypertension (8,9). Elevated plasma levels of inflammatory mediators may be associated with increased risk of the occurrence of diabetes (10) and cardiovascular disease. Moreover, inflammation may be included in the definition of the metabolic syndrome that may in turn increase the risk of overt diabetes mellitus and cardiovascular events (11).

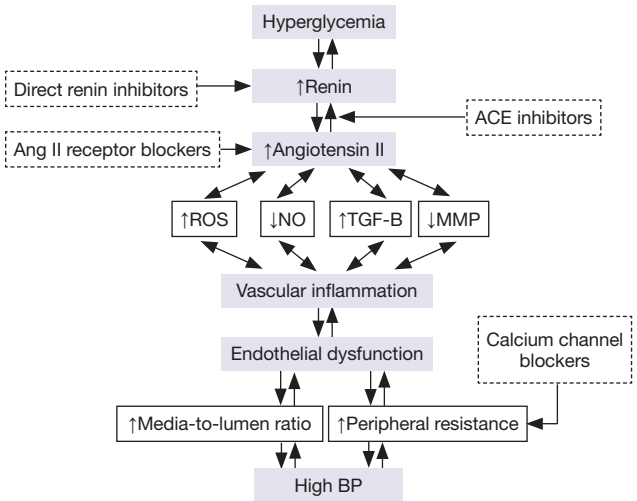

Figure 1 A schematic representation of the main pathophysiological mechanisms and potential sites of therapeutic interactions in hypertension and diabetes. ACE, angiotensin-converting enzyme; Ang, angiotensin; ROS, reactive oxygen species; NO, nitric oxide; TGF-beta, transforming growth factor-beta; MMP, matrix metalloproteinases; BP, blood pressure. Modified from reference (4).

Patients with cardiovascular disease, mostly hypertension, coronary artery disease, and congestive heart failure, show increased expression and plasma concentration of different inflammatory markers and mediators, including C-reactive protein (CRP) and several adhesion molecules (selectins, ICAM-1, VCAM-1) (12,13). In particular, high levels of inflammatory mediators, particularly IL-6, ICAM-1 and CRP have been demonstrated in patients with hypertension (14), and have been associated with the risk for developing hypertension (15,16). Also, abnormal activation of the renin-angiotensin system (RAS) may play a central role in the pathophysiology and development of cardiovascular disease in these settings (17). In particular, angiotensin II induces vascular remodeling and injury by several mechanisms including vasoconstriction, cell growth, oxidative stress and inflammation by inducing cytokine release (18) and pro-inflammatory transcription factors such as nuclear factor κB (NF-κB) (19), which regulates adhesion molecules and cytokine expression in several cell types (20).

These molecules induce and maintain inflammation within the vascular wall, stimulate deposition of extracellular matrix and promote hypertrophy and/or hyperplasia of vascular smooth muscle cells (21).

A large body of evidence underlines the pathophysiological role played by inflammation in the progression of cardiovascular and metabolic disease and in the triggering of cardiovascular events, as well as the need to oppose pharmacologically these mechanisms to improve cardiovascular outcomes. In the United Kingdom Prospective Diabetes Study (UKPDS), the incidence of complications of diabetes was strongly associated with elevated BP (22). Thus, lowering BP as well as therapeutic approaches to control vascular inflammation, particularly in patients with glucose intolerance or diabetes, may provide significant clinical benefits. However, two recently published post-monitoring follow-up studies of UKPDS (23,24) have shown that, although early and intensive treatment of hyperglycemia provides benefits for cardiovascular mortality that extend over time, the effects of a tight antihypertensive strategy in patients with diabetes did not seem to last during the following years (4).

Oxidative stress

Oxidative stress is characterized by increased reactive oxygen species (ROS) production. The major source of vascular ROS is NADPH oxidase, which is expressed in endothelial cells, vascular smooth muscle cells, fibroblasts and monocytes/macrophages (25,26). Angiotensin II, ET (endothelin)-1 and inflammatory mediators can increase synthesis of most subunits of NADPH oxidase and modulate basal NADPH oxidase-induced ROS production by the activation of several pathways (involving cSrc, PKC, PLA_2 and PLD) (27,28).

ROS are also produced by mitochondria in the vasculature (29-35). In particular, mitochondrial p66Shc is a pivotal modulator of mitochondrial ROS through oxidation of cytochrome c (36,37), and has been considered as part of a putative transduction pathway relevant to endothelial integrity (38,39). In fact, genetic ablation of Shc in mouse has been shown to reduce the production of intracellular oxidants, to protect against age-dependent endothelial dysfunction (40), and consequently to prolong life span (36). Indeed, old mice lacking p66Shc showed increased nitric oxide (NO) bioavailability in endothelium, lower ROS levels in the absence of any difference in the expression of superoxide dismutase (SOD) (40), and no age-dependent changes in iNOS. Furthermore, p66Shc expression is increased in patients with type 2 diabetes and correlates with markers of oxidative stress such as plasma isoprostane levels (41). Genetic deletion of p66Shc protects against vascular dysfunction and oxidative stress in diabetic mice (42). Moreover, p66Shc knockdown in endothelial cells from obese mice attenuated ROS production, free fatty acids oxidation and prevented dysregulation of proinflammatory pathways. *In vivo* gene silencing of p66Shc may restore endothelial insulin response by affecting the IRS-1/Akt/eNOS pathway (43). Hence p66Shc may also contribute to the pathogenesis of insulin resistance.

Enhanced angiotensin II-induced ROS is involved in the mechanisms leading to vascular remodeling in part by impairing NO bioavailability and the endothelium-dependent vascular relaxation (5-9). Moreover, ROS are responsible of vascular smooth muscle cells proliferation and hypertrophy, collagen deposition and the release of pro-inflammatory cytokine and transcription factors such as NF-κB. These processes may lead to increased vascular tone and structural changes in the circulation. Inflammation contributes to vascular remodelling promoting cell growth and proliferation of vascular smooth muscle cells. Among the mechanisms that participate in the inflammatory responses in the vascular wall important role is played by the increased expression of adhesion molecules (VCAM-1, ICAM-1) on the endothelial cell membrane, the accumulation of monocyte/macrophages, and lymphocytes (44). Also, Ang II as well as increased oxidative stress are important modulator of T-cell activation and development of vascular inflammation (45,46). Innate immunity may also be involved in the mechanisms that contribute to the low-grade inflammation in hypertension. Mice deficient in vascular macrophages as well as in T and B lymphocytes did not present vascular remodelling in response to Ang II- or DOCA-salt (47). It has been shown that an imbalance between pro-inflammatory subset of T lymphocytes (Th1, Th2 and Th17) and the anti-inflammatory T regulatory (Treg) may be responsible of the inflammatory response described in cardiac and metabolic diseases (48). Treg adoptive transfer lowered BP levels and protected from vascular remodelling mice infused with either angiotensin II (49) or aldosterone (50). Therefore, reduction of Treg and T effector up-regulation are associated to increase BP and are involved in the pathogenesis of BP-induced vascular inflammation and cardiovascular remodelling.

Ang II-induced inflammation via NF-κB and AP-1

activation involves, in part, ET receptors (51). ET-1 activates NADPH oxidase, as well as other sources of ROS, (i.e., xanthine oxidase and mitochondria) to produce increased oxidant stress in vascular smooth muscle cells and blood vessels (52-54). In turn, ROS are potent stimulators of ET-1 synthesis by endothelial cells and vascular smooth muscle cells (55). ET-A receptor antagonism decreases oxidative stress, normalizes hypertrophic remodelling, decreases collagen and fibronectin deposition, and reduces adhesion molecules levels in the vasculature of aldosterone-infused rats (56). When human preproET-1 was transgenically overexpressed in the endothelium, mice exhibited endothelial dysfunction and increased activity of NADPH oxidase, leading to enhanced oxidative stress and vascular inflammation (56).

The activation of mineralocorticoid receptors may also contribute to cardiovascular dysfunction, inflammation, fibrosis and vascular damage. In particular aldosterone increases the activity of tissue angiotensin-converting enzyme (ACE) (57) and up-regulates angiotensin receptors, thus potentiating effects of the RAS. Several animal models have confirmed that aldosterone and other mineralocorticoids can cause injury of the vasculature of several organs including heart and brain, ROS formation and endothelial dysfunction (58). Aldosterone may induce endothelial dysfunction and inflammation through activation of COX-2 (cyclo-oxygenase-2) in normotensive and hypertensive rats (59).

BP reduction per se may influence inflammation, since antihypertensive drugs such as calcium channel blockers not only decreased BP in patients with hypertension, but also reduced plasma concentrations of ICAM-1, E-selectin and vWF (60). However, it has been shown that despite effective antihypertensive treatment, resistance arteries from hypertensive diabetic patients showed marked remodelling, greater than that of vessels from untreated, non diabetic, hypertensive subjects (61). Thus, considering the pro-inflammatory effects of Ang II and aldosterone, drugs that interfere with the components of RAS, such as ACE inhibitors, angiotensin II receptor blockers (ARBs) and mineralocorticoid receptor antagonists represent suitable therapeutic tools to reduce vascular inflammation and result in reduced cardiovascular events in randomized clinical trials (62-64). The addition of ARBs to antihypertensive medications resulted in an improvement in resistance artery remodelling in diabetic hypertensive patients (65). Mineralocorticoid antagonism may attenuate these deleterious effects by reducing directly the pro-inflammatory and pro-fibrotic effects of aldosterone (66,67). Moreover, eplerenone treatment was also associated with reduced stiffness, decreased collagen/elastin ratio, and a reduction in circulating inflammatory mediators in hypertensive patients (65).

Treating hypertension in diabetes

BP reduction is one of the most powerful and effective pharmacological interventions to reduce cardiovascular morbidity and mortality, particularly in the presence of diabetes mellitus. Evidence derived from randomised clinical trials have consistently demonstrated significant benefits obtained by lowering high BP levels in different clinical settings, including elderly patients with isolated systolic hypertension (68-71), essential hypertension (72-74), high cardiovascular risk profile (75-77), coronary artery disease (78,79), previous stroke (80,81), and mostly diabetes mellitus (82,83). The results of these trials have been used for supporting the evidence to define optimal BP targets to be achieved and effective therapeutic strategies to be adopted in patients with hypertension and diabetes.

Blood pressure (BP) targets in hypertension and diabetes

Previous sets of international guidelines for the clinical management of hypertension have gradually affirmed and systematically promoted the achievement of ambitious BP targets in hypertensive patients at high or very high cardiovascular risk profile, such as those with diabetes mellitus (84-88). This therapeutic strategy was summarized by the paradigm “the lower, the better”, that characterized the clinical management of hypertension and diabetes until the early 2010’s, and was predominantly applied in hypertensive patients with diabetes. The same guidelines, however, acknowledged the fact that definite evidence in favour of more ambitious BP targets (i.e., <130/80 mmHg) compared to traditional BP goals (i.e., <140/90 mmHg) was missing. In fact, a closer analysis of trials performed in patients with hypertension at different cardiovascular risk profile, including those with diabetes, demonstrated that effective BP control (defined as <140/90 mmHg in general hypertensive patients and <130/80 mmHg in hypertensive patients with diabetes mellitus or renal disease) was achieved only in a few of these trials (89,90).

In order to overcome this limitation, several randomized controlled clinical trials have been designed in the recent years. These trials were aimed to demonstrate the potential

benefits derived by more intensive BP reductions in patients with hypertension and diabetes compared to those obtained by conventional BP reductions. Results from these trials, however, dramatically failed to demonstrate any potential cardiovascular (or renal) advantage, particularly for extreme BP reductions (91-93). These findings, in fact, have somehow revitalized the concept of the J-curve (94), showing an increased risk of coronary events, mostly myocardial infarction, in those patients who achieved the lowest BP levels, particularly in high-risk subsets of hypertensive populations, such as those with multiple risk factors, diabetes, chronic kidney disease (CKD) or previous history of coronary artery disease.

Quite consistently, in sub-analyses derived from relatively old randomized clinical trials, including the Systolic Hypertension in the Elderly Program (SHEP) (95), the Systolic Hypertension in Europe (Syst-Eur) (96), the International Verapamil-Trandolapril Study (INVEST) (97), the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) (98), the risk of myocardial infarction increased in high-risk patients achieving on-treatment lower systolic BP levels. A large, albeit predominant proportion of patients included in these trials were diabetics with hypertension.

More recently, several other trials have tested the hypothesis of potential benefits derived from an intensive therapy compared to a conventional therapy in terms of achieving strict or usual systolic BP control. For example, the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD-BP) trial (91) was designed to verify the potential benefits obtained with target systolic BP levels below 120 mmHg (intensive therapy) compared to those obtained with target systolic BP levels below 140 mmHg (conventional therapy) on major cardiovascular events among high-risk patients with type 2 diabetes (91). The large and significant systolic BP fall did not result in a reduction of the incidence of the primary composite cardiovascular endpoint (non-fatal MI, non-fatal stroke and death from cardiovascular causes) (91). No benefits on major cardiovascular events, no significant changes of cardiovascular and non- cardiovascular mortality (both actually showed a slight tendency to increase), a significant reduction of fatal and non-fatal stroke (an event more directly linked to BP reduction), and a significant worsening of renal function were reported (91). Also, in the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) (99) and the Treating to New Targets (TNT) (100) trials, a paradoxically increased risk of myocardial infarction (not stroke) and renal impairments were observed in those patients at very high global cardiovascular risk profile, which achieved extremely low systolic BP reductions. More recently, in the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial (101), which demonstrated that new onset of microalbuminuria can be effectively prevented in type 2 diabetic patients with high-normal BP levels by a high dose antihypertensive therapy, it has been also described a five-fold increase in the risk of developing fatal myocardial infarction in the active group as compared to placebo group, though absolute numbers of events were small.

Table 1 shows the evolution of recommended BP therapeutic goals and thresholds to be achieved in patients with hypertension and diabetes from former to more recent hypertension guidelines. On the basis of the currently available clinical evidence, latest set of European guidelines recommend the BP targets of <140/90 mmHg also in hypertensive patients with diabetes. In these patients, lower diastolic BP levels (85 mmHg) might be achieved, if tolerated and not contraindicated (104).

Antihypertensive drug strategies in hypertension and diabetes

Guidelines recommend initiating drug treatment when systolic BP is more than 140 mmHg in diabetic patients (111). To achieve these goals, the pharmacological strategy may include any antihypertensive drug class, although those agents able to counteract the RAS, including ACE inhibitors and ARBs, should be preferred (111). A proposed therapeutic platform for choosing the most effective therapeutic strategy to be applied in high risk patients with hypertension and diabetes is reported in *Table 2* (112).

Conclusions

Despite the impressive improvement in the clinical management of hypertension and diabetes, the achievement of effective control of therapeutic targets in this high risk population remain a major clinical challenge. Clinical studies continuously reported a very low rate of control in both hypertensive and diabetic patients, independently by age and clinical setting. In addition, recently available evidence has questioned the traditional therapeutic interventions proposed in the past, which recommended rigorous and unconditioned therapeutic targets. On the basis of these findings, more prudent targets have been proposed for both hypertension and diabetes, especially when these

Table 1 Different BP therapeutic goals and thresholds to be achieved in patients with hypertension and diabetes from former to more recent hypertension guidelines

Guidelines	BP targets to be achieved in Hypertension (mmHg)	BP targets to be achieved in hypertension and diabetes (mmHg)	Ref.
1999 WHO/ISH hypertension	<140/90	<130/85	(102)
2003 ESH/ESC hypertension	<140/90	<130/80	(85)
2007 ESH/ESC hypertension	<140/90	<130/80	(88)
2009 ESH reappraisal	<140/90	<140	(103)
2013 ESH/ESC hypertension	<140/90	<140/85	(104)
2003 JNC VII	<140/90	<130/80	(86)
2014 JNC VIII	<140/90	<140/90	(105)
2004 Canadian hypertension	<140/90	<130/80	(106)
2010 Canadian hypertension	<140/90	<130/80	(107)
2011 Canadian hypertension	<140/90	<130/80	(108)
2012 Canadian hypertension	<140/90	<130/80	(109)
2013 Canadian hypertension	<140/90	<130/80	(110)
1999 BHS guidelines	<140/90	<140/90	(84)
2004 BHS guidelines	<140/90	<140/90	(87)

BP, blood pressure; ESH, European Society of Hypertension; ESC, European Society of Hypertension; JNC, Joint National Committee; BHS, British Society of Hypertension.

Table 2 A proposed therapeutic platform for choosing the most effective therapeutic strategy to be applied in high risk patients with hypertension and diabetes. Modified from reference (104)

Hypertension with	Grade 1 HT (SBP 140-159 mmHg or DBP 90-99 mmHg)	Grade 2 HT (SBP 160-179 mmHg or DBP 100-109 mmHg)	Grade 3 HT (SBP ≥180 mmHg or DBP ≥110 mmHg)
Metabolic syndrome	RAS-i (medium dose), if not at target, →	RAS-i/CCB (medium dose), if not at target, →	RAS-i/CCB (full dose)
Diabetes	RAS-i (full dose), if not at target, →	RAS-i/CCB (medium dose), if not at target, →	RAS-i/CCB (full dose)

RASi, renin-angiotensin system inhibitors (including ACE inhibitors and angiotensin II receptor blockers); SBP, systolic blood pressure; DBP, diastolic blood pressure; CCB, calcium-channel blockers; HT, hypertension.

conditions are associated with other relevant comorbidities. A further improvement should be the adoption of different therapeutic targets on the basis of individual age, beyond global cardiovascular risk stratification. Future studies will help to answer these questions and provide useful evidence for improving the clinical management of hypertension and diabetes in the clinical practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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