Doxazosin in metabolically complicated hypertension

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Metabolic syndrome, a cluster of metabolic abnormalities with visceral obesity and insulin resistance as its central component, is highly prevalent among hypertensive patients. Hypertension complicated by metabolic syndrome is associated with an increased risk of cardiovascular disease and new-onset Type II diabetes mellitus that further aggravates the prognostic outlook. Such a complex condition requires a multifactorial intervention including blood pressure lowering, improvement of the adverse metabolic profile and delayed onset of new diabetes. In this respect, doxazosin and other α-1 adrenoceptor blocking agents are of interest given their effect on the lipid profile in dyslipidemic, obese hypertensive patients, either diabetic or not. Doxazosin improves insulin sensitivity, apparently by accelerating insulin and glucose disposal through vasodilatation of skeletal muscle vascular beds. Whether long-term treatment with the drug might delay, or possibly prevent, incident Type II diabetes in hypertension complicated by metabolic syndrome is an intriguing possibility to be tested in appropriately designed clinical trials.

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Hypertension & metabolic syndrome

Hypertension is a well-recognized cardiovascular risk factor that is often associated with metabolic abnormalities that increase cardiovascular morbidity and mortality exponentially [1]. This well-recognized cluster of noxious biological factors has led to the development of the term metabolic syndrome (MS) [2–5], a constellation of cardiovascular risk factors that predicts an approximately threefold increased risk for new-onset Type II diabetes (FIGURE 1) [6] and an approximately twofold increased incidence of cardiovascular events [6]. Among the different diagnostic criteria formulated by several professional organizations and agencies (TABLE 1) [2–4], the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III definition [4] is the most widely employed, with hypertension and central adiposity as the most common coexisting traits [7]. Not unexpectedly, therefore, MS is widely prevalent among hypertensive subjects. For example, its prevalence was sixfold greater in hypertensive as compared with normotensive individuals in the care of primary care physicians (24 vs 4%, respectively) [8]. Moreover, MS was diagnosed in approximately a third of patients referred to specialized hypertension units [9], a figure twofold higher than that reported in demographically and geographically comparable population samples [10]. Hypertension complicated by MS also associates with other cardiovascular risk factors, such as microalbuminuria, left ventricular hypertrophy, carotid thickening [11], low-grade inflammation, increased prothrombotic proteins [7] and endothelial dysfunction [12]. Hypertension complicated by MS also features an augmented sympathetic activity [13] that contributes to blood pressure (BP) elevation by increasing renin secretion and tubular sodium reabsorption, and worsens the overall risk profile by promoting left ventricular hypertrophy and vessel remodeling. Sympathetic-mediated vasoconstriction also impairs insulin sensitivity by reducing muscle blood flow with less efficient insulinization of metabolically active tissues, reduced glucose delivery and lesser glucose uptake in skeletal muscle. The ensuing progressive deterioration of insulin action favors impaired glucose tolerance and Type II diabetes, which hypertension predisposes individuals to, independent of body weight [14].

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In summary, hypertension complicated by multiple metabolic alterations is frequent in the general population and is often associated with increased cardiovascular risk, particularly if it coexists with diabetes and abdominal adiposity [15]. Although the rational approach to this complex condition is by necessity multifactorial, effective BP lowering is at the core [16]. However, antihypertensive treatments should be metabolically neutral or, even better, improve the overall metabolic picture [16]. Great emphasis has been given in the past few years to the role of inhibition of the renin–angiotensin system [16], but other drugs may also have favorable metabolic effects. In this context, doxazosin, an α-1 adrenoceptor inhibitor, may represent an useful option as suggested by its effect in hypertension complicated by dyslipidemia, obesity and Type II diabetes.

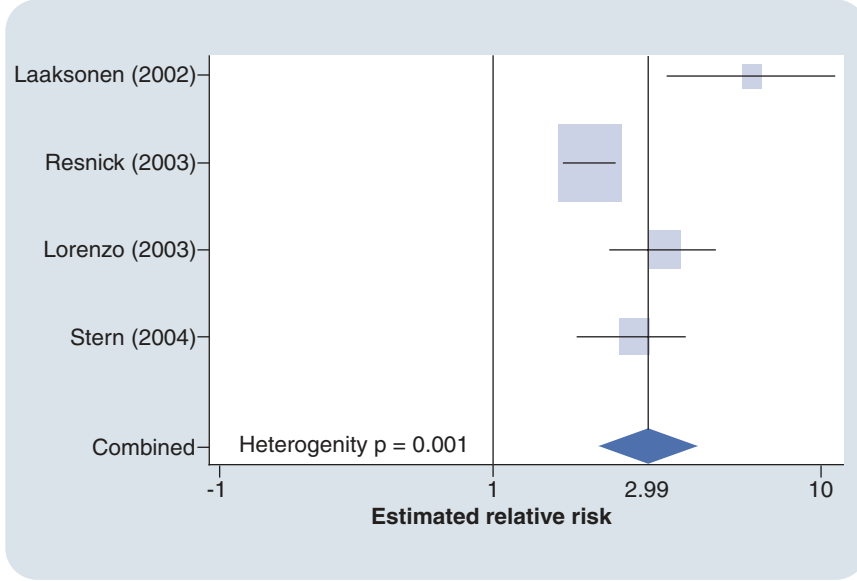

Figure 1. Associations between metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III) and diabetes.
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Overview of doxazosin in hypertension

Doxazosin, and other chemically unrelated compounds, were made available for hypertension treatment a few years after the release of the prototype prazosin in 1976 [17]. Although less lipid-soluble than prazosin and with lower receptor affinity (see TABLE 2 for a list of the available α-1 antagonist compounds), doxazosin is appropriate for once-daily administration because of a longer half-life extending over a 22 h period [17]. Doxazosin reduces BP as a function of the prevailing level of α-1-mediated sympathetic vasoconstrictor tone with more marked BP drops in hypertensive subjects and scarce or no hypotensive effect in those with normal BP [18]. Owing to preserved presynaptic α-2-mediated negative feedback on norepinephrine release [19] and in contrast to nonselective α-blockers (e.g., phentolamine), doxazosin does not – or less than proportionally – increase cardiac output, heart rate and renin release. The drug is an effective antihypertensive agent, approximately comparable with other antihypertensive drugs and can often control BP in patients resistant to two or more drugs [20]. Doxazosin does not adversely affect renal function [20] and reduces left ventricular hypertrophy, although to a somewhat lesser extent than hydrochlorothiazide, captopril or atenolol [21]. The drug also reduces urinary albumin excretion in hypertensive patients, whether they are diabetic or not [22,23]. Clinical side effects compared favorably with other major drug classes in the Treatment of Mild Hypertension Study (TOMHS) [24], although, as for other vasodilators, doxazosin may slightly expand body fluid volume and retain urinary sodium [25]. Orthostatic hypotension may occur in volume-depleted patients or in diabetic subjects with

Table 1. Comparison of some of the most widely used definitions for metabolic syndrome.

WHO	EGIR	ATP III	IDF
Diabetes, impaired fasting glucose, glucose intolerance or insulin resistance (hyperinsulinemic, euglycemic clamp) plus two or more of the following: – BMI >30 kg/m^2, or waist-to-hip ratio >0.9 (M) or >0.85 (F) – TG ≥1.7 mmol/l or HDL-C <0.9 (M) or <1.0 mmol/l (F) – BP >130/90 mmHg – Albuminuria >20 µg/min	Insulin resistance by fasting insulin values, plus two or more of the following: – Central obesity with WC ≥94 cm (M) or ≥80 cm (F) – TG >2.0 mmol/l or HDL <1.0mmol/l – BP ≥140/90 mmHg or on antihypertensive medication – FBG ≥6.1 mmol/l	Three or more of the following: – WC >102 cm (M), >88cm (F) – HDL-C <1.03 mmol/l (M), <1.29 mmol/l (F) – TG >1.7 mmol/l – BP ≥135/85 mmHg or antihypertensive medication – FPG ≥6.1 mmol/l ≥5.6 mmol/l	Central obesity (ethnic specific values), plus any two of the following: – TG >1.7 mmol/l or on specific treatment – HDL-C <1.03 mmol/l (M), <1.29 mmol/l (F) or on specific treatment – BP ≥130/85 mmHg or on antihypertensive treatment – FPG ≥5.6 mmol/l or treated Type II diabetes

ATP: Adult Treatment Panel; BMI: Body mass index; BP: Blood pressure; EGIR: European Group for the Study of Insulin Resistance; F: Female; FBG: Fasting blood glucose; FPG: Fasting plasma glucose; HDL-C: High-density lipoprotein cholesterol; IDF: International Diabetes Federation; M: Male; TG: Triglyceride; WC: Waist circumference.
Data from [2–5].

Table 2. List of selective α-1 adrenoceptor blocking drugs available for human use.

Compounds	α-1 adrenoceptor subtype	Plasma half-life (h)	Dose (mg)	Dosing
Alfuzosin	1a, 1b, 1d	~9	10	Once daily
Bunazosin	1a, 1b, 1d	~12	3–12	Once daily
Doxazosin	1a, 1b, 1d	~22	4–8	Once daily
Indoramin	1a, 1b, 1d	~5	25–75	Twice daily
Prazosin	1a, 1b, 1d	~3	10	Twice daily
Tamsulosin	1a, 1d	~14–15	0.4–0.8	Once daily
Terazosin	1a, 1b, 1d	~12	2–10	Once daily
Urapidil	1a, 1b, 1d		10–50	Intravenous use

autonomic neuropathy although, rather uncommonly due to its slow onset of action [25]. In women, doxazosin may trigger urinary incontinence, a side-effect reversible on drug withdrawal. Doxazosin may also positively influence hemorheology by reducing blood viscosity and increasing red blood cell deformability. Proapoptotic, α-1-independent effects have been claimed to exert positive effects in medical treatment of pituitary adenomas [26].

A specific area of use for doxazosin is in patients with benign prostatic hyperplasia (BPH) in whom the drug improves both symptoms and urinary flow by blocking α-1 adrenergic receptors in the bladder neck and prostatic capsule [18]. Therefore, doxazosin represents a rational treatment in hypertensive patients with comorbid BPH, a clinical condition associated with sympathetic overactivity, overweight with visceral abdominal fat distribution, dyslipidemia, hypertension, impaired glucose metabolism and subclinical inflammation (i.e., the typical features of MS) [27].

Doxazosin in metabolically complicated hypertension

Mechanisms of α-1 adrenoceptor-mediated metabolic effects

α-1 adrenoceptors are G-protein-coupled, norepinephrine-binding transmembrane receptors biochemically distinguished in three distinct but highly homologous subgroups (1a, 1b and 1d). Activated α-1 receptors transduce intracellular signals through phospholipase C stimulation and phosphatidylinositol bisphosphate hydrolysis, triggering intracellular Ca^{2+} release from nonmitochondrial pools and activating protein kinase C [28].

Although local vasodilatation in response to doxazosin appears to play an important role in the metabolic effects of the drug (see later), blockade of hepatic α-1-adrenoceptors may modulate glycogenolysis and gluconeogenesis [29], decrease triglyceride output from the liver [30], reduce cholesterol synthesis and accelerate binding of low-density lipoproteins (LDLs) to their hepatic receptors [31].

Effects of doxazosin on lipids & blood glucose in man

The identification of the metabolic effects of doxazosin and other α-1 adrenoceptor blocking drugs dates back to the early 1980s. In 1986, Cox, in pooling the results of 13 placebo-controlled, double-blind studies performed in doxazosin-treated nondiabetic patients, showed a mean change of triglycerides and high-density lipoprotein (HDL) of -9.1 and +7.6%, respectively, with minor, clinically irrelevant changes (-2.9%) in LDL cholesterol [32]. Comparable results were reported by Grimm a few years later (median triglycerides decrease of 9.1%; median HDL increase of 6.3%) [33]. The overview by Glanz *et al.* on doxazosin in Type II diabetes again showed mean decrements of 8.8% in triglycerides and increments of 10.8% in HDL, respectively, accompanied by decreased fasting plasma glucose [34]. The mechanisms responsible for these effects are not completely understood, but vasodilatation, by accelerating lipid and glucose disposal, may contribute to both, while a direct effect on lipoprotein lipase activity, the enzyme responsible for triglyceride hydrolysis at the surface of endothelial cells, is unlikely. In fact, increased removal of plasma triglyceride-rich lipoproteins after a fatty meal was not accompanied by changes in tissue lipoprotein lipase activity in patients treated with doxazosin (FIGURE 2) [35].

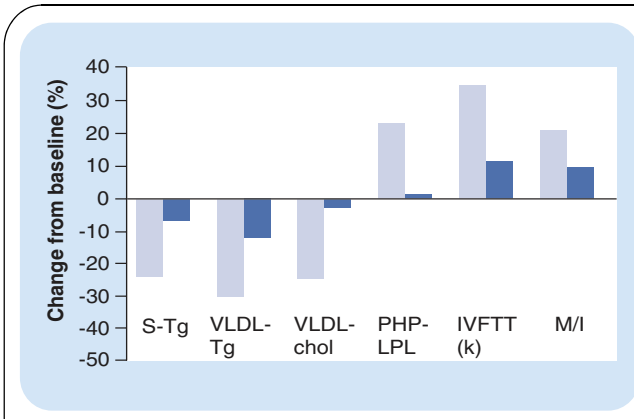

Figure 2. Metabolic effects of doxazosin (light bars) and enalapril (dark bars) on S-Tgs, VLDL-Tg and VLDL-chol concentration, activity of PHP-LPL, elimination rate constant at the IVFTT (k) and M/I.
Chol: Cholesterol; IVFTT: Intravenous fat tolerance test; M/I: Insulin sensitivity index; PHP-LDL: Lipoprotein lipase in postheparin plasma; Tg: Triglycerides; VLDL: Very low-density lipoprotein.
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Effects of doxazosin on insulin sensitivity

As reported in TABLE 3, which summarizes most of the available studies carried out by reliable techniques for quantification of its action [36–41], doxazosin consistently improves insulin sensitivity (FIGURE 2). That effect, also confirmed by studies using homeostasis model assessment (HOMA) as an indirect index of insulin sensitivity [42–45], cannot be ascribed to changes in hepatic glucose production as measured using the tracer dilution technique [39]. Thus, the drug is likely to act by vasodilating skeletal muscle vasculature, thereby expanding the tissue area exposed to insulin. Although plausible, this hypothesis may not be exhaustive, however, since nonspecific arteriolar vasodilators, such as hydralazine, are either neutral or detrimental for insulin sensitivity [46]. Any further speculation is, however, impossible in the absence of specific mechanistically oriented studies. Importantly, the metabolic effect of doxazosin is more evident in insulin-resistant states, as shown by Andersson *et al.*, who reported an effect of doxazosin only in insulin-resistant, hypertriglyceridemic, overweight hypertensive patients (i.e., the MS phenotype) [35]. Results did not change when other metabolic variables, such as low HDL cholesterol or high plasma insulin concentrations, were used to categorize the study population [35]. Similar findings have been reported by Jeng *et al.* in using the insulin suppression test [40] and by Zehetgruber *et al.* by measuring fasting insulin concentrations [47]. Consistent with the overall picture, doxazosin did not change insulin sensitivity when used in lean, glucose-tolerant subjects [41].

α-1-blocking drugs also seem to decrease fasting and postmeal free fatty acids [48] and to protect from the adverse impact of salt restriction on serum lipids and insulin sensitivity [49]. This observation is relevant because diuretics or severe salt restriction can boost sympathetic activity and, therefore, aggravate insulin resistance [13]. Doxazosin exerted its effect on HOMA even in glucose-intolerant subjects on hypoglycemic treatment with acarbose, an α-glucosidase inhibitor [43].

In head-to-head comparisons with other drugs, doxazosin increased insulin sensitivity while enalapril, an angiotensin-converting enzyme (ACE) inhibitor (FIGURE 2) [35] or irbesartan, an angiotensin II receptor blocker [44] had no metabolic impact. In insulin-resistant, hyperinsulinemic nondiabetic hypertensive patients with chronic renal failure, 12-month doxazosin treatment was associated with reduction of the HOMA index and fasting plasma insulin levels, while no effect was found in response to amlodipine, a dihydropiridine calcium channel blocker [45]. In Type II hypertensive diabetics, doxazosin, but not captopril or nifedipine, improved glucose tolerance, free fatty acid concentrations, insulin-mediated glucose uptake, glucose oxidation and nonoxidative glucose disposal [39].

Table 3. Synopsis of studies evaluating the effects of doxazosin on insulin sensitivity.

Study	Dose	Patients	Design	Outcome	Method	Ref.
Kageyama (1993)	3.3 ± 0.4 mg/day × 12 weeks	Ten essential hypertensive patients	Comparison vs baseline	Increased sensitivity	Euglycemic glucose clamp technique	[36]
Yamasaki (1994)	1–8 mg × 1 month	11 nonobese essential hypertensives	Comparison vs baseline	Increased sensitivity	Euglycemic glucose clamp technique	[37]
Giorda (1995)	2–12 mg/day × 6 weeks	12 Type II diabetics	Single blind cross-over design	Increased insulin sensitivity No change in hepatic glucose production	Euglycemic glucose clamp technique + ^{3}H glucose infusion	[38]
Giorda (1995)	2–8 mg × 12 weeks	Type II diabetic hypertensive patients on doxazosin (n = 9), captopril (25–50 mg/twice daily; n = 10) and nifedipine (30–60 mg/day; n = 11)	Group comparison	Increased insulin sensitivity, glucose oxidation and nonoxidative glucose disposal in doxazosin-treated patients	Euglycemic glucose clamp technique	[39]
Andersson (1996)	1–8 mg doxazosin (n = 23) vs 5–20 mg enalapril (n = 23) × 6 months	Hypertriglyceridemic, overweight, nondiabetic hypertensives	Comparison of doxazosin vs enalapril	Increased insulin sensitivity on doxazosin No change on enalapril	Euglycemic glucose clamp technique	[35]
Jeng (1996)	1–16 mg × 4–6 months	Ten insulin-resistant vs ten insulin-sensitive essential hypertensive patients	Comparison of insulin-resistant vs insulin-sensitive patients	Reduced steady-state plasma glucose and insulin only in insulin-resistant patients	Modified insulin-suppression test	[40]
Courtney (2003)	1–16 mg × 12 weeks	13 lean, normolipidemic, glucose-tolerant essential hypertensives	Double-blind, placebo-controlled crossover study	No difference vs placebo	Euglycemic glucose clamp technique	[41]

In British South Asians, an ethnic group at high coronary risk with strong predisposition to Type II diabetes, insulin resistance and MS, doxazosin reduced glucose, total and LDL cholesterol, triglycerides, and increased HDL cholesterol. Bendrofluazide, a thiazide diuretic, showed the opposite metabolic effects [50].

Results obtained in diabetic patients on carvedilol, a combined β- and α-1-blocking agent, further support the beneficial effects of α-1 blockade on insulin sensitivity. Carvedilol, in fact, improved insulin sensitivity, while metoprolol tartrate, a β-1-selective blocker without ancillary pharmacological properties, did not impede progression to microalbuminuria and worsening of hemoglobin A1c [51].

Effects of doxazosin on MS-related cardiovascular risk factors

In obese, hyperinsulinemic, hypertensive patients, doxazosin treatment lowered plasma insulin levels and increased tissue plasminogen activator (t-PA) mass, an effect reversible after cessation of therapy [47]. Since t-PA is a fibrinolytic, endothelial-derived product and endothelial function is defective in hypertension complicated by MS [12], the finding is compatible with an improvement in endothelial function during doxazosin treatment. This hypothesis is compatible with an increased NO-dependent vasodilation during intrabrachial acetylcholine infusion in hypertensive patients with MS [52]. In parallel, the drug also decreased postischemic minimum forearm vascular resistance (FIGURE 3) [52], an index of structural arteriolar remodeling [53]. Modulation of α-1-mediated sympathetic activation typical of MS [13] may have participated in this effect but additional studies are required to ascertain this possibility.

Other MS-related parameters sensitive to doxazosin include adiponectin [54], small and dense LDL and remnant lipoproteins [55], and C-reactive protein [56]. In experimental animals, doxazosin decreased TNF-α production [57], a key factor in the genesis of insulin resistance in MS [15]. Doxazosin, but not amlodipine, also reduced mean platelet volume, a marker of abnormal platelet activation and a correlate of insulin resistance in hypertensive patients with MS [58].

Strengths & weaknesses of doxazosin

Although new therapeutic targets will emerge for management of MS and new therapeutic approaches may become available in the near future, the choice of 'metabolically friendly' antihypertensive drugs will remain a cornerstone of the therapeutic strategy. In this context, doxazosin is a drug of interest in hypertension complicated by MS, at least to the extent that improved insulin sensitivity may delay new-onset Type II diabetes, a primary cardiovascular risk modifier and a coronary-equivalent state [4]. As an additional contributing mechanism, the α-1-blocking properties of doxazosin may counteract the enhanced sympathetic hyperactivity in MS [13]. Of interest, imidazoline agonists, a group of centrally acting sympathetic modulators, share with α-1-blockers favorable metabolic effects in dyslipidemic and insulin-resistant hypertensive patients [47]. By contrast, conventional β-blockers induce weight gain, worsen diabetes control and plasma lipid profile, promote incident diabetes [59], and

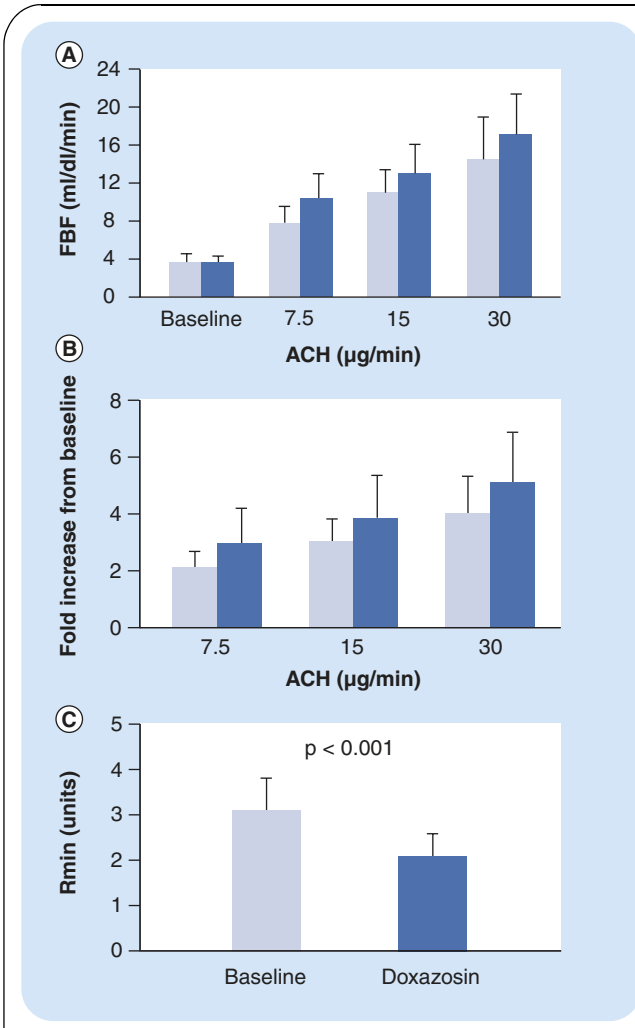

Figure 3. (A) Absolute and **(B)** relative FBF changes to graded ACH infusion in nondiabetic, hypertensive patients with National Cholesterol Education Program-Adult Treatment Panel III-defined metabolic syndrome. **(C)** reports the behavior of post-ischemic minimum vascular resistance before (light gray bar) and after (dark gray bar) doxazosin treatment in those same patients. ACH: Acetylcholine; FBF: Forearm blood flow.
Reproduced with permission from [52].

oppose effective weight loss in obese patients [60]; their use as first-choice antihypertensive drugs is doubtful at this point [61]. Thiazide diuretics, another major antihypertensive class, can worsen glucose tolerance and increase lipid levels [47] and promote a diabetogenic effect, particularly when compared with ACE inhibitors or angiotensin II receptor blockers. These latter compounds have neutral effects on lipids and body weight and can improve insulin action through vasodilatation and other direct actions on the insulin receptor signaling pathways [62]. For these reasons, both ACE inhibitors and angiotensin II receptor blockers are currently considered first-line antihypertensive drugs in the hypertensive subset with comorbid MS [16]. However, the available data are difficult to interpret since incident diabetes was seldom a prespecified primary end point and diagnosis was mainly self-reported, or based on single fasting glucose measurements. In fact, in contrast to claims about their effectiveness in

diabetes prevention [63], ramipril, an ACE inhibitor, did not reduce the conversion toward Type II diabetes in subjects with impaired glucose tolerance compared with placebo [64].

In spite of their beneficial metabolic effects, the main weakness of α-1-blockers is that, despite hundreds of studies focusing on surrogate end points, only one randomized clinical trial has evaluated the long-term cardiovascular effect of doxazosin in hypertensive patients [65]. Based on its negative outcome, doxazosin and other α-1-blockers were withdrawn from the list of first-line therapies in hypertensive patients. However, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) results, albeit highly relevant in several respects, deserve some further discussion.

Doxazosin & ALLHAT: a fair trial?

ALLHAT, the only randomized clinical study testing the long-term effects of doxazosin on cardiovascular events in elderly high-risk hypertensive patients, was interrupted prematurely owing to an increased incidence of clinically diagnosed congestive heart failure and nonfatal stroke in α-1-blocker- versus chlorthalidone-treated patients [65]. Congestive heart failure, however, was not diagnosed by instrumental assessment nor was it externally adjudicated. More importantly, perhaps, lack of preliminary cardiological screening allowed recruitment of an unknown but certainly sizable number of patients with asymptomatic left ventricular dysfunction, a quite common abnormality among elderly hypertensive patients [66]. In this condition, doxazosin could have probably unmasked a preexisting subclinical disease rather than cause its *de novo* appearance. Quite peculiarly, congestive heart failure did not generate an increased mortality rate during follow-up [65] in spite of the ominously poor prognosis of that condition [67]. Notably, the higher incidence of nonfatal stroke in the doxazosin group [65] emerged in approximately 30% of patients on atenolol as per-protocol add-on therapy [65], a drug that does not protect efficiently from stroke [60]. Reserpine, clonidine and hydralazine were the other drugs available as add-on step two and step three agents, a choice practically absent from the present prescription trends. Therefore, the results of the doxazosin arm of the ALLHAT study raise important doubts about their external validity.

Expert commentary & five-year view

Presently, the main indication for doxazosin and other α-1 adrenoceptor blockers is add-on therapy in hypertensive patient not at target on other antihypertensive drugs or in the presence of BPH. In this context, the drugs will most likely retain a small but consistent share of the market [68]. A potentially more relevant but still unexplored question is whether the favorable metabolic effects may make these drugs particularly useful in hypertensive patients with MS. Unfortunately, long-term head-to-head comparison with drugs that are considered metabolically effective, such as ACE inhibitors or angiotensin II receptor blockers are not available. It is also not known whether long-term doxazosin, through its effect on insulin sensitivity, may prevent or delay diabetes development in hypertensive subjects independent of coexisting MS. This information could, however, be easily retrieved from ALLHAT like the *post hoc* analysis of the other treatment arms of the study [69]. Quite interestingly, the ASCOT trial database could also allow a similar opportunity, since, albeit not further commented on in the published report, approximately half of the study population received doxazosin as add-on step three treatment [70]. However, until specifically designed trials address the pending safety concerns raised by the ALLHAT study, it is unlikely that doxazosin will become a first-choice drug in patients at high cardiovascular risk, such as those with hypertension and MS.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Metabolic syndrome (MS), a constellation of conventional and nonconventional risk factors, associates with increased cardiovascular risk and new-onset diabetes.
- In this highly prevalent subset of hypertensive patients, pharmacological treatment should not only reduce blood pressure but also ameliorate metabolic abnormalities and possibly prevent or at least delay new-onset diabetes.
- Doxazosin, an antihypertensive drug with α-1 adrenoceptor blocking properties, affects beneficially atherogenic dyslipidemia typical of MS. The drug also improves insulin sensitivity by increasing glucose and insulin disposal, probably through vasodilatation in skeletal muscle.
- The metabolic effect of doxazosin is most evident in insulin-resistant, obese and dyslipidemic patients, and, in that respect, proved superior to other drug classes including renin–angiotensin system inhibitors.
- To the extent that improved insulin sensitivity may contribute to prevent new-onset diabetes, doxazosin might be particularly useful in hypertension complicated by MS. However, that possibility is unknown at the present time and is an important issue to be assessed in future studies.

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