The hypertension of Cushing's syndrome: controversies in the pathophysiology and focus on cardiovascular complications

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Cushing's syndrome is associated with increased mortality, mainly due to cardiovascular complications, which are sustained by the common development of systemic arterial hypertension and metabolic syndrome, which partially persist after the disease remission. Cardiovascular diseases and hypertension associated with endogenous hypercortisolism reveal underexplored peculiarities. The use of exogenous corticosteroids also impacts on hypertension and cardiovascular system, especially after prolonged treatment. The mechanisms involved in the development of hypertension differ, whether glucocorticoid excess is acute or chronic, and the source endogenous or exogenous, introducing inconsistencies among published studies. The pleiotropic effects of glucocorticoids and the overlap of the several regulatory mechanisms controlling blood pressure suggest that a rigorous comparison of *in-vivo* and *in-vitro* studies is necessary to draw reliable conclusions. This review, developed during the first 'Altogether to Beat Cushing's syndrome' workshop held in Capri in 2012, evaluates the most important peculiarities of hypertension associated with CS, with a particular focus on its pathophysiology. A critical appraisal of most significant animal and human studies is compared with a systematic review of the few available clinical trials. A special attention is dedicated to the description of the clinical features and cardiovascular damage secondary to glucocorticoid excess. On the basis of the consensus reached during the workshop, a pathophysiology-oriented therapeutic algorithm has been developed and it could serve as a first attempt to rationalize the treatment of hypertension in Cushing's syndrome.

Keywords: antihypertensive treatment, blood pressure, corticosteroids, Cushing's syndrome, hypercortisolism, hypertension, metabolic syndrome, vascular system

Abbreviations: 11β-HSD, 11beta-hydroxysteroid dehydrogenase; ACCOMPLISH, Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension; ACEi, angiotensin I-converting enzyme inhibitor; ACTH, adreno-cortico-tropic hormone; AMI, acute myocardial infarction; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BP, blood pressure; CD, Cushing's disease; cGMP, cyclic guanosine 3'-5' monophosphate; CS, Cushing's syndrome; DBP, diastolic blood pressure; ECS, ectopic Cushing's syndrome; EH, essential hypertension; ENaC, epithelial sodium channel; eNOS, endothelial nitric oxide synthase; EPO, erythropoietin; ET-1, endothelin-1; HPA, hypothalamus–pituitary–adrenal axis; IMT, intima–media thickness; IRS-1, insulin receptor substrate-1; LXR, liver X receptor; PDE5, phosphodiesterase type 5; PI3-K, phosphatidylinositol 3-kinase; PKB, protein kinase B; RAS, renin–angiotensin system; SBP, systolic blood pressure; UFC, urinary free cortisol; VEGF, vascular endothelial growth factor

INTRODUCTION

Cushing's syndrome, or chronic hypercortisolism, is a severe endocrine disease due to the prolonged exposure to glucocorticoid excess [1–3]. The endogenous Cushing's syndrome, caused by the endogenous overproduction of cortisol by the adrenal glands, is secondary to an adrenocorticotrophin (ACTH)-secreting pituitary tumor [pituitary-dependent Cushing's syndrome

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(CS) or Cushing's disease (CD)] in around 70%, a cortisol-secreting adrenal lesion (adrenal-dependent Cushing's syndrome) in 15–20%, and an ACTH-secreting extra-pituitary tumor [ectopic Cushing's syndrome (ECS)] in 10–15% of the cases [1–3]. The chronic administration of exogenous corticosteroids for different clinical conditions may induce the development of an exogenous CS [1–3]. CS is associated with a 2–5-fold increase in mortality compared to the general population, mainly due to cardiovascular complications [1–3]. CS is indeed characterized by a peculiar clinical picture complicated by several comorbidities, mainly including systemic arterial hypertension, together with visceral obesity, impairment of glucose tolerance and dyslipidemia, configuring a metabolic syndrome [4–6]. However, the hypertension related to CS is not simply a component of the CS-related metabolic syndrome. Indeed, CS-related hypertension displays several peculiarities, develops early and can persist several years after clinical and hormonal remission of the disease [4–6].

The hypothalamus–pituitary–adrenal axis (HPA), which is responsible for the circadian rhythm of endogenous cortisol secretion, contributes to the circadian rhythm of blood pressure (BP) [7,8], and HPA dysregulation has been suggested as one of the factors involved in the pathogenesis of essential hypertension (EH) [9,10]. Exogenous corticosteroids, which are prescribed to approximately 1% of the adult population for various clinical conditions [11], significantly affect this equilibrium [12,13], and are associated with an increased risk of cardiovascular and cerebrovascular diseases [14].

The 'Altogether to Beat Cushing's syndrome' (ABC) study group produced a systematic analysis of the peculiarities of hypertension associated with endogenous and exogenous CS, focusing on its controversial pathophysiology and long-term clinical consequences. This novel pathophysiology-oriented therapeutic approach enabled a treatment-algorithm to be proposed during the first ABC workshop held in Capri in 2012.

EPIDEMIOLOGY OF HYPERTENSION IN CUSHING'S SYNDROME

Epidemiological data on hypertension associated with CS are largely retrospective. However, the available data suggested that 70–85% of adult patients [15,16] and 50–78% of pediatric patients [17–20] with endogenous CS suffer from hypertension, compared to approximately 20% of patients long-term treated with exogenous corticosteroids [21,22]. A specific feature of hypertension associated with endogenous CS is the lack of a significant difference in gender or among the different etiologies of endogenous CS [15,16,23], as well as in the degree of hypercortisolism, as BP values were found to be not correlated with circulating cortisol levels [15,24,25]. Nevertheless, one study on pediatric patients with CS showed a difference in the prevalence of systolic hypertension in ACTH-independent (74%) and ACTH-dependent CS (44%), despite an apparently similar degree of hypercortisolism, and demonstrated a positive correlation between BP values and circulating cortisol levels [18]. Anyway, although the prevalence of hypertension is similar among various forms of endogenous CS, a tendency towards higher BP is seen in adrenal compared to pituitary tumors. Figure 1 shows the BP values reported in the largest studies, according to the different etiologies of CS. The duration of hypercortisolism seems to be correlated with the development of hypertension [15]; however, half of the pediatric patients with CS, whose time to diagnosis is short, still develop hypertension within a limited period of time [26,27].

PATHOGENESIS OF HYPERTENSION IN CUSHING'S SYNDROME

The mechanisms involved in the development of hypertension are complex and only partially understood. This review summarizes the major data regarding the renin–angiotensin system (RAS), the mineralocorticoid activity, the sympathetic nervous system, and the vasoregulatory system, together with indirect mechanisms, which contribute to the development of CS-related hypertension (Table 1). The mechanisms through which hypercortisolism induces hypertension directly or indirectly, as well as the mechanisms by which specific treatments, which could counteract directly or indirectly the hypercortisolism-induced changes that contribute to the CS-related hypertension and consequent cardiovascular damage, are discussed in this review, and reviewed in Fig. 2. The pleiotropic effects of glucocorticoids and the several regulatory mechanisms controlling BP show significant overlap, suggesting that a rigorous comparison of *in-vivo* and *in-vitro* models is necessary to identify the relative contribution of each component and draw reliable conclusions. In addition, in most experimental settings, the acute effects of glucocorticoids differ in many aspects from chronic effects of either endogenous glucocorticoids or exogenous corticosteroids. A systematic review of the mechanisms involved in the pathogenesis of hypertension induced by glucocorticoid excess in humans (Table 1) and animals (Table 1S, http://links.lww.com/HJH/A423) is described in this section of the review. This approach allowed the appraisal of both the new pathways and the old paradigms. Specific following sections of the review focus on the clinical features and cardiovascular damage associated with CS-related hypertension, and on the effect of treatment for CS on hypertension. The review terminate with statements on the pharmacological treatment of the hypertension associated with CS, driven by the available knowledge. These statements were the basis for the development of a treatment algorithm for CS-related hypertension; this proposed algorithm is displayed in Fig. 3.

The renin–angiotensin system

The RAS is the most extensively investigated system as a putative contributor to hypertension in CS. Angiotensinogen is almost invariably increased [29], due to stimulation of the hepatic synthesis, whereas renin may be suppressed, as expected [30], or often normal [29], which is inappropriate in view of the enhanced mineralocorticoid activity associated with CS. Circulating angiotensin II levels have been reported to be normal [31], but the number of angiotensin II receptors (type 1A) appears increased, and an enhanced pressor response to angiotensin II infusion has been

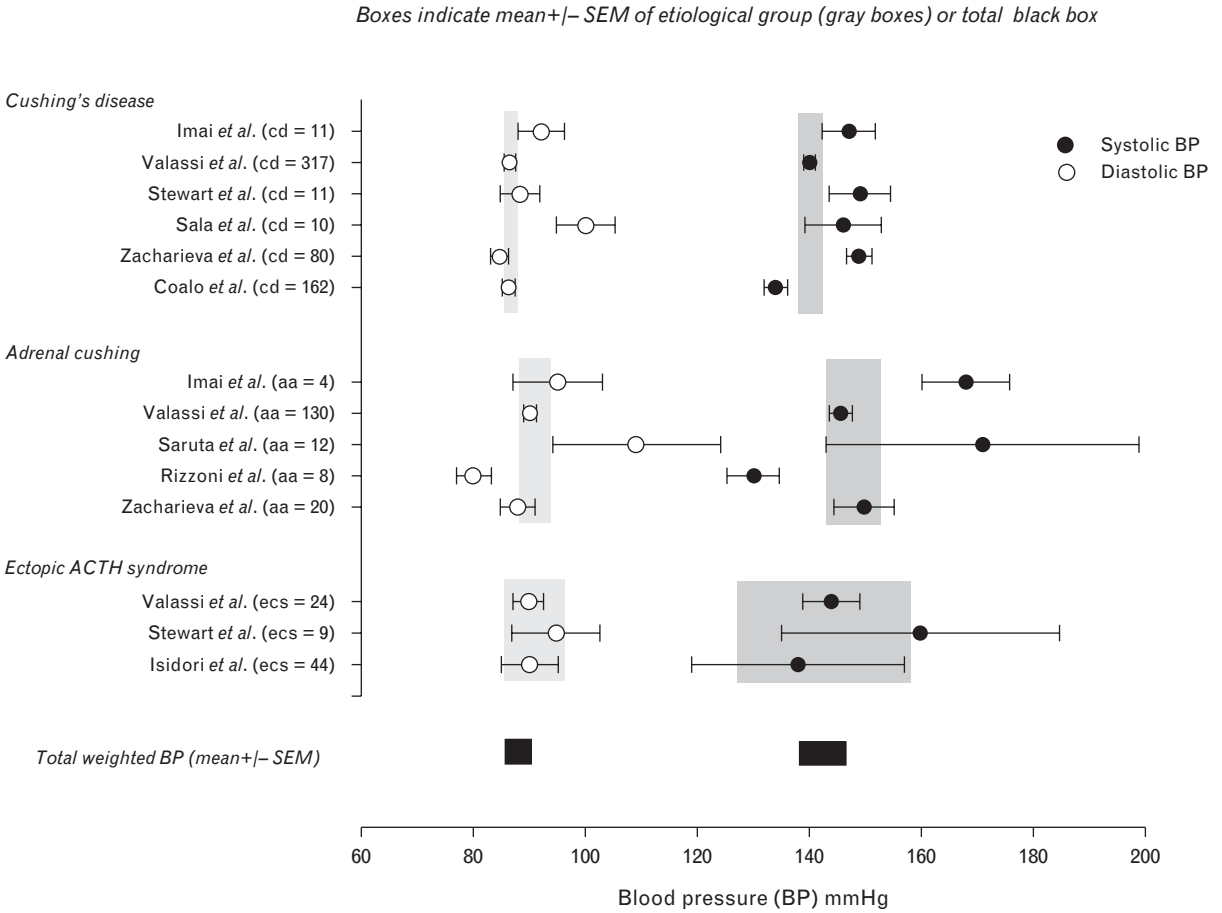

FIGURE 1 The SBP (black) and DBP (white) values (mean ±SEM) are reported for some of the largest studies, according to the different causes of Cushing's syndrome. The gray boxes summarize the mean weighted pressure value for each group of studies; the black boxes summarize the overall effect for all groups.

described in CS [32]. Confirmatory data on the involvement of the angiotensin pathways come from the acute lowering of BP obtained following oral administration of an angiotensin I-converting enzyme inhibitor (ACEi) in CS [29,33]. The fact that exogenous corticosteroids administration is more frequently associated with suppressed renin, due to a compensatory mechanism no longer observed in endogenous CS, where renin is often inappropriately normal, suggests that a long-standing hypercortisolism can induce angiotensin receptor signaling dysregulation. The clear evidence of the angiotensin pathway involvement in the development of hypertension in CS suggests that this should be the first pharmacological target. In fact, ACEi have been successfully used to counteract hypertensive

TABLE 1. Mechanisms involved in the pathogenesis of hypertension induced by glucocorticoid excess in human studies

	Human studies	Reference
Renin–angiotensin system (RAS)	↑ Angiotensinogen	[29,30,33]
	↑ DBP in response to peripheral administration of Ang II	[29,33]
	↑ AT-II 1A receptor in blood cells	[32]
Mineralcorticoid activity	↑ 11β-HSD 2 saturation	[28,36]
	↑ Plasma volume	[30,31]
Sympathetic nervous system	↑ Sensitivity to β receptor agonists	[31]
Vasoregulatory system	↑ Endothelin 1 (ET-1)	[50]
	↑ Erythropoietin (EPO) in GC-treated patients	[51]
	↑ Circulating ANP	[30,64]
	↓ ANP activity	[64,66]
	↓ Nitric oxide pathway	[56,57]
	↓ Urinary PGE2	[29]
	↓ of PGI_2 production	[67]
	↓ Urinary kallikrein	[29]
	↑ Urinary kininase I, II, NEP	[68]

11β-HSD 2,11β-Hydroxysteroid dehydrogenase type 2; Ang II, angiotensin II; ANP, atrial natriuretic peptide; AT 1A, angiotensin type 1A receptor; CS, Cushing's syndrome; MR, mineralcorticoid receptor; NEP, neutral endopepeptidase; PGE2, prostaglandin E2; PGI_2 prostacyclin; VEGF, vascular endothelial growth factor.

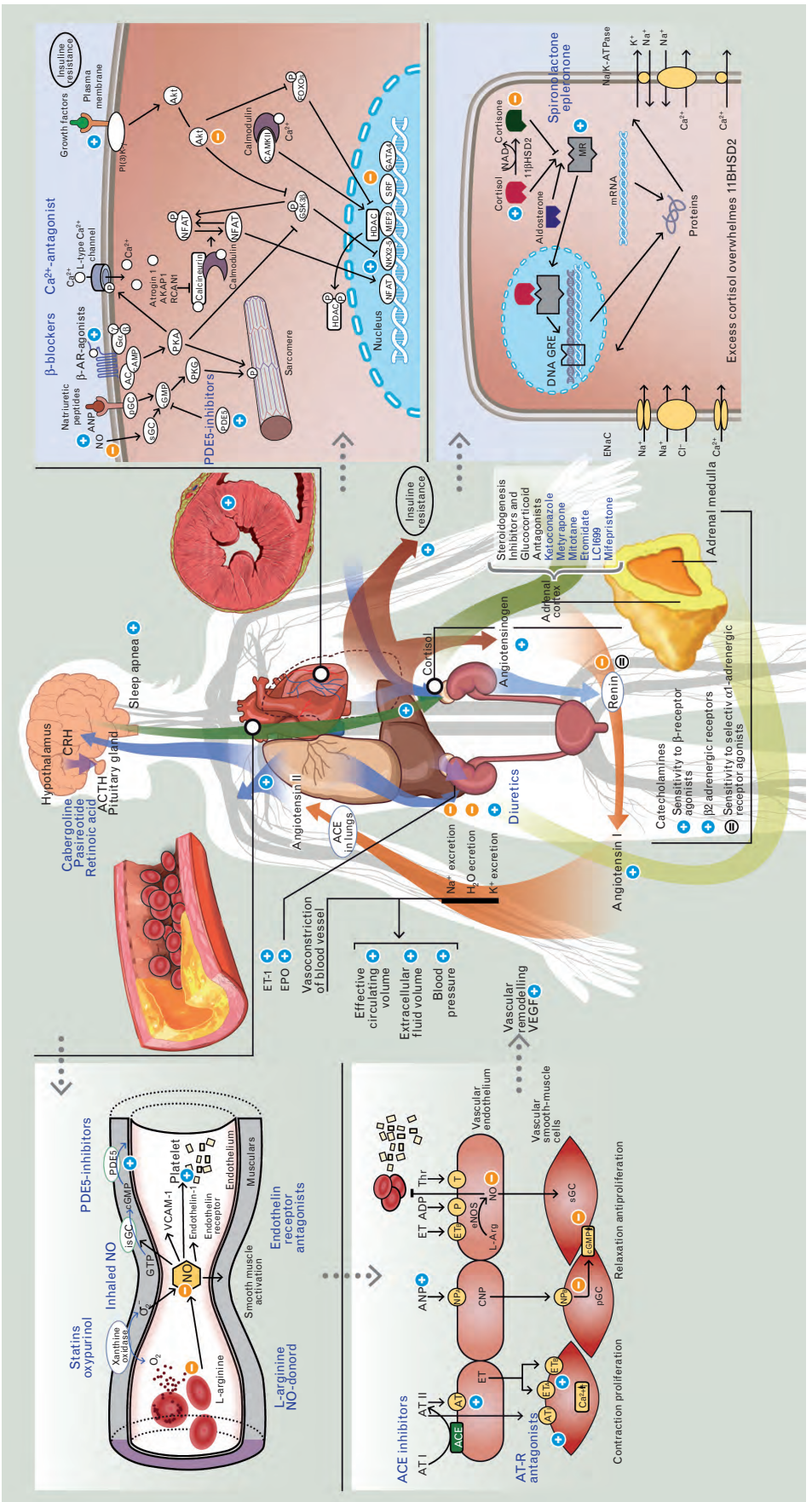

FIGURE 2 The pathophysiological mechanisms involved in the development of glucocorticoid-related hypertension. The symbols ↑, ↓ and ↔ represent, respectively, an increase, decrease and null effect for each of the affected pathway, on the basis of the studies listed in Table 1 and Table 1S (http://links.lww.com/HJH/A423). In caps blue are highlighted the drugs that can be used to counteract the pathways altered by glucocorticoid excess. AC, adenylatecyclase; ADP, adenosine diphosphate; AKAP1, A-kinase anchor protein 1; AT, angiotensin; AT_1, angiotensin type 1 receptor; AT-R antagonists, angiotensin receptor antagonists; cAMP, cyclic adenosine-monophosphate; CMKII, calcium-calmodulin-dependent protein kinase type 2; CNP, C-type natriuretic peptide; CRH, corticotropin-releasing hormone; eNOS, endothelial nitric oxide synthase; ET, endothelin; ET_A, endothelin receptor A; ET_B, endothelin receptor B; FOXOs, forkheadhomeobox type O transcription factors; GRE DNA, glucocorticoid response element-DNA; GSK3β, glycogen synthase kinase 3 Beta; GTP, guanosine triphosphate; HDAC, histone deacetylase; isGC, isoform guanylatecyclase; L-Arg, L-arginine; MEF2, myocyte enhancer factor-2; MR, mineralcorticoid receptor; NAD, nicotinamide adenine dinucleotide; NFAT, nuclear factor of activated T cells; NO, nitric oxide; NP_A, natriuretic peptide receptor type A; NP_B, natriuretic peptide receptor type B; O_2, oxygen; O_2^-, superoxide anion radical; pGC, particulateguanylate cyclase; PI3K γ, phosphatidyl inositol 3 -hydroxy kinase; PKA, protein kinase A; PKG, cGMP-dependent protein kinase; RCAN1, regulator of calcineurin 1 protein; sGC, soluble guanylatecyclase; SRF, serum response factor; Thr, threonine; VCAM-1, vascular cell adhesion molecule 1.

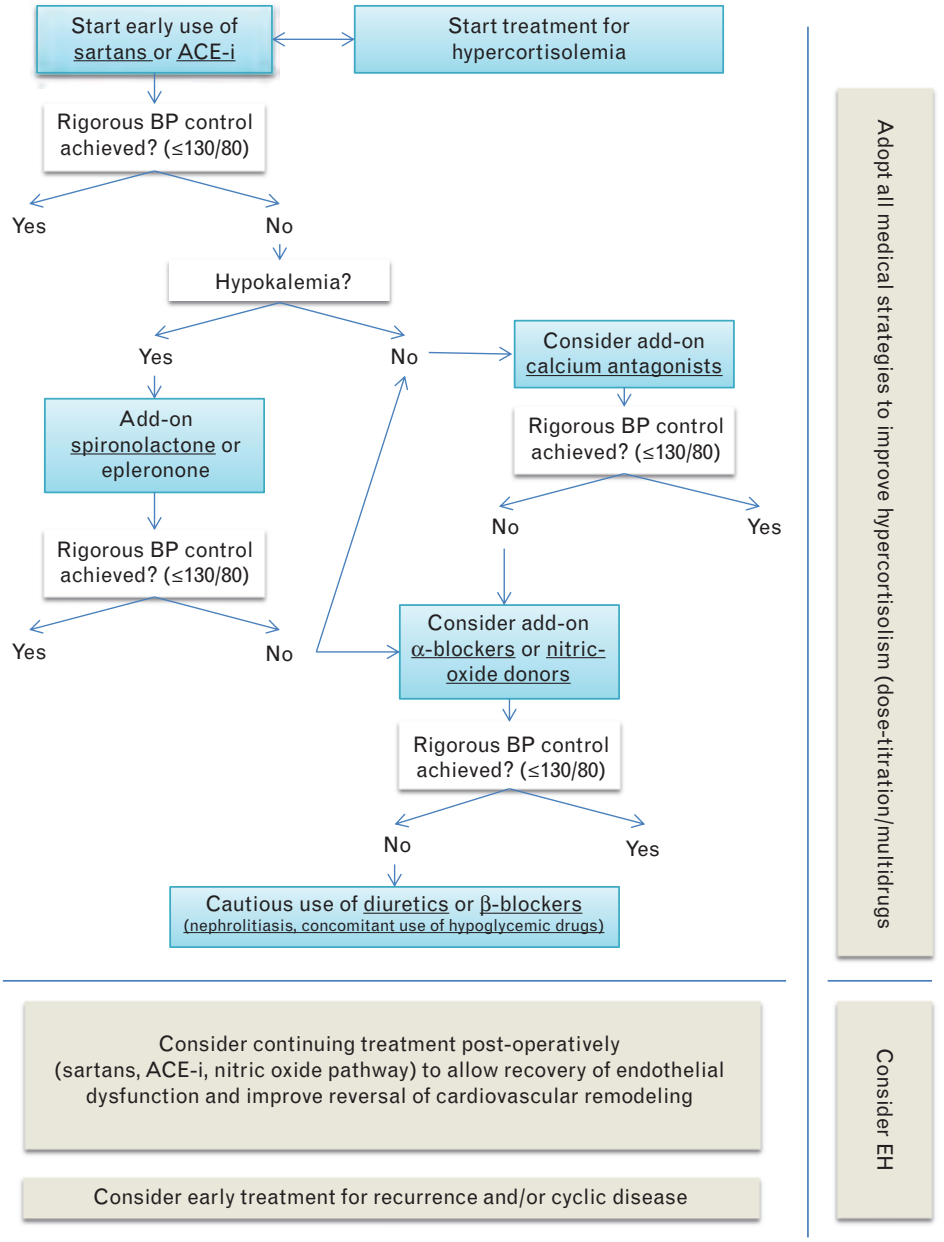

FIGURE 3 Treatment algorithm based on a pathophysiological targets of glucocorticoid excess. ACEi, angiotensin-converting enzyme inhibitor; BP, blood pressure; EH, essential hypertension.

effects of glucocorticoids [29,33], and given the enhanced sensitivity of angiotensin receptors and the cardiovascular remodeling frequently observed in CS, angiotensin receptor blockers (ARBs) also appear a reasonable first choice in the treatment algorithm (Fig. 3).

The mineralocorticoid activity

The mineralocorticoid activity has been traditionally considered a major player of hypertension secondary to glucocorticoid excess. The mineralocorticoid receptor is a nuclear receptor, mainly expressed at a renal level, which is able to bind two different corticosteroids, aldosterone and cortisol, with equal affinity [34]. Binding selectivity in the renal cortex is guaranteed by 11beta-hydroxysteroid dehydrogenase (11beta-HSD) type 2 (11beta-HSD2), which catalyzes the deactivation of cortisol to cortisone [35]. Severe CS is characterized by elevated cortisol levels that overwhelm the 'protective' role of 11beta-HSD2, leading to a functional mineralocorticoid excess, due to the binding and activation of the mineralocorticoid receptor by excessive glucocorticoids [36]. The mineralocorticoid receptor hyperactivation at the renal level is known to induce sodium retention and potassium excretion; this mechanism could explain the development in patients with CS of both hypertension, through sodium retention, and hypokalemia. However, although most studies agree that 11beta-HSD2 saturation is the major mechanism for the development of hypokalemia [37], its role in determining hypertension is less evident. Some studies suggest that hypertension induced by chronic hypercortisolism is not primarily

mediated through sodium retention [38,39], which is instead a feature of acute glucocorticoid excess [30]. In fact, chronic hypercortisolism is associated with normal circulating sodium and normal sodium excretion [30,40]. It is noteworthy that another isoform of 11beta-HSD, the type-1 (11beta-HSD1), highly expressed in the liver and the adipose tissue, and also in the heart, vascular endothelial and smooth muscle cells, catalyzes the reactivation of cortisone into cortisol, regulating local cortisol bioavailability, and complicating the role of 11beta-HSD and the enhanced mineralcorticoid activity in the development of CS-related hypertension [35]. Moreover, beyond the mineralocorticoid receptor, glucocorticoid receptor also seems to play a role in the renal regulation of sodium balance in patients with CS. Indeed, both mineralocorticoid receptor and glucocorticoid receptor have been thought to be responsible for the enhanced epithelial sodium channel activation (ENaC) and glomerular hyperfiltration, as the selective blockade of mineralocorticoid receptor or glucocorticoid receptor is insufficient to fully restore baseline conditions [40]. This is consistent with clinical observations in CS patients, whose BP improves more under mifepristone, a selective glucocorticoid receptor antagonist [41], than under spironolactone and epleronone, which are mineralocorticoid receptor antagonists [39,42]. In summary, renal mineralocorticoid receptor activation does not appear to be the main determinant of hypertension in most patients with CS, except in those with extremely elevated circulating cortisol levels where renal mineralocorticoid receptor hyperactivation contributes to additional sodium and fluid retention, beyond the increased excretion of potassium and consequent hypokalemia. However, this does not exclude the possibility that inappropriate vascular activation of mineralocorticoid receptor contributes to increased arterial wall tension, even after mild chronic cortisol elevation. In addition, a vascular mineralocorticoid receptor may exhibit different kinetics, for instance, signal transduction might be produced at different ligand concentrations from those working in the kidney [43]. Indeed, mineralocorticoid receptor blockade improves left ventricular hypertrophy and failure in rats with low-aldosterone hypertension, independently of BP-lowering, likely through an attenuation of myocardial oxidative stress and coronary vascular inflammation induced by glucocorticoid-activated mineralocorticoid receptor [44]. In conclusion, renal mineralocorticoid receptor blockade with standard doses of spironolactone or epleronone is a reasonable adjunctive treatment in patients with hypokalemia (Fig. 3). Whether higher doses are required to achieve an efficacious mineralocorticoid receptor blockade in the vasculature wall remains to be established.

The sympathetic nervous system

The sympathetic nervous system, mediated by the catecholaminergic pathway, was traditionally considered an important pathway in the development of CS-related hypertension. However, only limited controlled data support this evidence. In patients with CD, the concentrations of catecholamines, including noradrenaline and adrenaline, and adrenergic receptors seem unaltered [31], as phenylethanolamine N-methyltransferase, the enzyme responsible for noradrenaline to adrenaline methylation [45]. An enhanced pressor response to adrenergic agonists has been reported, but this evidence is controversial. In patients with CD, noradrenaline [46] and the beta-adrenergic agonists isoprenaline and isoproterenol [31] elicited a greater response than in normotensive patients. In contrast, no difference in BP increase between CS patients and control patients has been observed after infusions of the selective alpha1-adrenergic receptor agonist phenylephrine [47]. Cardiac autonomic function was also investigated and found to be impaired in CS. A recent study compared the responses of CS patients and healthy controls to various autonomic tests, finding in the former a reduced sympathetic reactivity [48]. The inconsistent findings and the fact that most CS patients also develop diabetes, requiring treatment with glucose-lowering drugs, suggest that adrenergic blockade should not be a first-line treatment for CS-related hypertension (Fig. 3). In addition, a rare, yet described, contraindication to beta-blockers as a first-line agent is represented by CS secondary to an ECS associated with pheochromocytomas [37].

The vasoregulatory system

Many substances with vasoregulatory properties have been reported to contribute to hypertension secondary to glucocorticoid excess. Endothelin-1 (ET-1), a potent vasoconstrictor, has been implicated in the pathogenesis of early hypertension and premature atherosclerosis due to glucocorticoid excess [49]. To date, only one study has found an increased ET-1 in patients with CS, although it was not correlated with BP or cortisol excretion [50]. Interestingly, in more than half of the patients, circulating ET-1 levels remained elevated even after correction of hypercortisolism [50], a finding attributed to persistent vascular damage. Erythropoietin (EPO) mediates glucocorticoid-induced vasoconstriction in a dose-dependent manner, but this phenomenon has been demonstrated only in healthy individuals acutely treated with exogenous corticosteroids [51], but no proof exists of glucocorticoid regulation of EPO gene expression. No data are presently available in endogenous CS. Enhanced vascular responsiveness to various vasoconstrictors could be explained, at least in experimental studies on murine aortic myocytes, through glucocorticoid-induced down-regulation of the plasma membrane sodium–calcium exchanger [52]. This mechanism has been advocated as a rationale for the use of calcium antagonists in the management of CS-related hypertension (Fig. 3). Most studies on vasodilators have demonstrated the detrimental effects of glucocorticoid excess on the nitric oxide pathway through different mechanisms: inhibition of nitric oxide synthase (NOS) expression [53,54], reduced availability of substrates due to inhibition of the arginine transporter, or impaired cofactor generation due to inhibition of the tetrahydrobiopterin synthesis [55]. This is confirmed by the low urinary nitric oxide metabolites [54] and reduced plasma nitrate/nitrite ratio associated with CS [56]. However, different studies demonstrated an increase in endothelial NOS (eNOS) staining in subcutaneous small-resistance arteries of CS patients; this has been interpreted as a paradoxical increase secondary to enhanced oxidative stress [57]. A beneficial transient

activation of cerebral eNOS has been reported to explain the neuroprotective effects of glucocorticoid infusion after stroke. This transient activation, apparently due to a non-genomic glucocorticoid receptor action, is responsible for increased regional cerebral blood flow [58]. The role of cyclic guanosine 3′,5′-monophosphate (cGMP), a downstream target of nitric oxide signaling, remains unexplored in CS. Its degradation is controlled by phosphodiesterase type 5 (PDE5) and regulated by steroid hormones [59] such as androgens, but data on glucocorticoids are missing. PDE5 inhibition could offer a potential treatment to prevent cardiac remodeling associated with CS [60]. cGMP is a crucial second messenger activated by G-coupled cardiac natriuretic peptide receptors [atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP)]. ANP, a hormone with natriuretic vasorelaxant and RAS-inhibiting properties, is often reported as increased in CS [61–63]. Nevertheless, there is evidence that ANP action is blunted in CS. Indeed, impaired cGMP generation was described when physiological doses of ANP were infused into patients with CD [64] or given to murine renal vascular smooth muscle cells pretreated with dexamethasone [65]. This further finding, however, was not confirmed in all studies [66]. CS might also be associated with impaired production of other powerful vasodilators including prostaglandins, prostacyclins and compounds of the kallikrein–kinin system [29,67], the latter due to accelerated renal kininase activity [68].

The metabolic factor

A metabolic derangement is a common finding in CS; it is manly characterized by an impairment of glucose and lipid metabolism, together with a catabolic state, represented by a generalized proteolysis. The effects of glucocorticoids on glucose metabolism are complex and include: increase of hepatic glucose production, reduction of glycogen synthesis, decrease of insulin-dependent glucose uptake into peripheral tissues, breakdown of proteins and lipids to provide additional substrates for glucose production, and inhibition of insulin release [69,70]. At hepatic level, glucocorticoids not only antagonize metabolic actions of insulin but also potentiate the effects of different hormones that increase glucose levels, such as glucagon and adrenaline [69,70]. The affected signaling pathways include the peroxisome proliferator-activated receptor-alpha (PPAR-alpha) [71], and the nuclear liver X receptor (LXR) [72]. The peripheral effects of glucocorticoids are mainly exerted at the level of skeletal muscle and visceral fat, where glucocorticoids reduce glucose uptake by inhibiting the expression and phosphorylation of insulin receptor substrate-1 (IRS-1), phosphatidylinositol 3-kinase (PI3-K), and protein kinase B (PKB)/Atk [69], all contributing to a decrease in intracellular glucose uptake. A randomized controlled trial in humans revealed that glucocorticoids, even at low doses, can increase fasting plasma glucose and insulin levels, and can decrease the ability of insulin to suppress endogenous glucose production and lipolysis, while increasing whole-body proteolysis [73].

The majority of patients with CS develops an overt metabolic syndrome, where the impairment of glucose tolerance and the dyslipidemia are associated with hypertension, and are strictly dependent on the visceral adiposity and insulin resistance, which are common features of the CS [4]. A study on patients with CD clearly demonstrated that circulating insulin levels were increased, suggesting a state of insulin resistance, and that an increased waist-to-hip ratio, which is a surrogate clinical marker of visceral adiposity, was significantly correlated with insulin levels and the best predictor of the increase in carotid intima–media thickness (IMT), an important preatherosclerotic lesion [74]. These evidences suggested a direct link between visceral adiposity, insulin resistance and premature atherosclerosis in CD [75]. In the long term, glucocorticoid excess can impair insulin release from the pancreatic beta cells, and this phenomenon is probably responsible for the passage from a hyperinsulinemic impairment of glucose tolerance to an overt diabetes mellitus in susceptible patients who develop CS [76,77]. Noteworthy, metabolic syndrome has been also documented in patients long-term cured from CD [78]. It is noteworthy that the metabolic derangements are likely important factors in the long-term cardiovascular outcome, by accelerating atherosclerosis and vasculature remodeling; however, in respect to the etiology of hypertension, they are more likely facilitating conditions.

The vascular factor

Vascular remodeling is a possible consequence of hypertension due to glucocorticoid excess. Hypertrophic changes in the morphology of small-resistance arteries (increased media to lumen ratio, media thickness and wall thickness) have been described in patients with CS [57]. Increased vascular endothelial growth factor (VEGF), a potent angiogenic factor, has been reported to be responsible for vasculature remodeling in various experimental models of glucocorticoid excess [79]. Hyperinsulinemia, impaired insulin signaling and insulin/IGF-I receptors hybrid formation have been claimed to play a role in vasculature smooth muscle cell dysfunction [80,81]. This vascular remodeling and dysfunction may contribute to the aggravation of hypertension associated with CS.

The sleep apnea

The obstructive sleep apnea syndrome (OSAS) is one of the most common secondary conditions associated with resistant hypertension, for which, however, a treatment is available [82]. One-third of the patients with CS develop OSAS [83,84]. The sleep disturbances are strictly correlated with the visceral obesity of patients with CD, making it unclear whether it is primarily due to a direct effect of cortisol excess or secondary to obesity. However, OSAS has been described in lean patients with ECS [85], and CD patients without OSAS exhibit an impaired sleep architecture, with fragmented sleep and an abnormal pattern in rapid eye movements, that resemble the sleep impairment of patients with major depression [84]; these evidences suggest a direct contribution of nocturnal hypercortisolemia. CS and OSAS share the activation of sympathetic nervous system and alterations of cortisol circadian rhythm [86]. Unfortunately, the effects of continuous positive airway pressure (CPAP) in lowering BP in unselected patients with OSAS turned out to be below expectation [82,87]. More recently, it has been shown that CPAP is mainly effective on nocturnal BP [87].

Therefore, a treatment of OSAS with CPAP might be useful in patients with CS, who do not have the physiological decrease of BP during the night, namely the nondipper hypertensive patients with CS.

CLINICAL FEATURES AND CARDIOVASCULAR DAMAGE ASSOCIATED WITH HYPERTENSION IN CUSHING'S SYNDROME

A near–linear relationship between hypertension and cardiovascular, renal and neurological morbid and fatal events has been repeatedly shown [88]. The relationship between hypertension and cardiovascular mortality is modified by the concomitance of other risk factors. Metabolic syndrome and glucocorticoid excess are two recognized important modifiers [89]. Hypertension is an independent predictor of mortality in patients with CD [90–92]. Most studies on CS failed to show a differential elevation between SBP and DBP, while the loss of the physiological nocturnal decrease [12] appears an early feature of both endogenous and exogenous glucocorticoid excess, with a high proportion of patients with nondipper hypertension [7,8].

Hypertension in the different subtypes of Cushing's syndrome

The prevalence of hypertension appears similar among various forms of endogenous CS; however, clinical and pathophysiological differences characterize the subtypes of CS. A tendency towards higher BP is seen in adrenal over pituitary tumors associated with CS. This difference might be related to the specific vasoactive effects of adrenal sex steroids (androgens, estrogen and their metabolites), which are generally suppressed in cortisol-secreting adrenal tumors compared to pituitary tumors responsible for CD [93,94]. Alternatively, it could be due to the retention of some circadian rhythmicity of cortisol secretion in mild CD that is lost in adrenal tumors responsible for adrenal-dependent CS. However, even in CD, over half of the patients do not present nocturnal BP-dipping, showing a lower than 10% fall in SBP and DBP at night and abnormal heart rate values [8]. Zacharieva *et al.* [95] compared the circadian BP of 100 patients with CS (80 CD and 20 adrenal CS), with 40 patients with EH, and found the blunting of nocturnal decline more severe in patients with adrenal disease. The nocturnal drop in heart rate was preserved in both groups, suggesting that the main effect was on vascular tone. In ECS, more frequently than in other subtypes of CS, patients develop severe hypokalemia, mainly due to saturation of the activity of the 11beta-HSD2. The rapidity and severity of onset of hypercortisolism in this condition is responsible for a severe organ damage [37]. A rarely recognized form of familial CS, with an insidious onset, has been recently identified [96]. Assie *et al.* [96] described 33 patients with ACTH-independent macronodular hyperplasia, most with ARMC5 mutations. Few studies describing the characteristics of hypertension in this genetic form of CS are available [96,97]; interestingly, whereas hypercortisolism is the most frequent reason for clinical presentation in families with bilateral macronodular adrenal hyperplasia positive for ARMC5 mutations, hyperaldosteronism is unusually prominent in those negative for ARMC5 mutations [97]. Future studies of the genotype–phenotype relationships in familial CS may provide an opportunity to study the very early stages of CS development. Completely different is the hypertension associated with exogenous glucocorticoid that affects about 20% of patients receiving prolonged treatment with corticosteroids. In these cases, the clinical picture is determined by the dose, route of administration, duration and type of steroid used [98].

Cardiac damage

CS is associated with an increased mortality from multisystem risk that is already elevated several years before the diagnosis, confirming that is caused by cortisol excess. Compared to matched controls, patients with active disease have a hazard ratio of 6.0 (2.1–17.1) for heart failure and of 2.1 (0.5–8.6) for acute myocardial infarction (AMI). An increased prevalence of left ventricular hypertrophy and concentric remodeling are consistently found in CS [99]. Muiesan *et al.* [99] also described important left ventricular functional alterations, such as a decrease in left ventricular systolic performance measured at the mid-wall, and a change in diastolic filling with an abnormal relaxation pattern. Toja *et al.* [100] found that CS patients presented a more severe change in left ventricular mass index and relative wall thickness than both normotensive and matched hypertensive controls. No clinically relevant diastolic dysfunction was seen in patients or controls with normal BP [100], suggesting that hypertension was involved, albeit not the only factor, in the whole range of cardiac alterations observed in CS. The most important ultrastructural abnormality in CS cardiomyopathy is myocardial fibrosis. This seems directly related to cortisol action rather than to cardiac hypertrophy or BP, exerted through an enhanced responsiveness to angiotensin II [101]. Activation of the mineralocorticoid receptor and glucocorticoid receptor also contributes to its development. It was recently shown that glucocorticoids activate cardiac mineralocorticoid receptor during experimental myocardial infarction [102], supporting the use of mineralocorticoid receptor antagonists. Yiu *et al.* [103] demonstrated that myocardial fibrosis is significantly increased in untreated CS compared to EH, and partly reversible after successful treatment of CS. On ECG, CD patients show prolonged QT and features of left ventricular hypertrophy, even if the association of CD with a prolonged QT seems to be independent of other risk factors, including hypertension. This suggests a cardiotoxic effect of hypercortisolism *per se* [104]. Moreover, in comparison with patients matched for similar cardiovascular risk factors, CS patients show a sympathovagal imbalance, characterized by relatively increased parasympathetic activity. It is still unknown whether this acts to counterbalance cortisol-induced effects on BP, and cardiac structure and function or has a different pathophysiological significance [105]. Hypertensive CS patients show impairment in all parasympathetic function parameters. The significantly different expiratory-to-inspiratory ratio might be explained by the effect of hypertension or antihypertensive medications in some patients [48].

Vasculature remodeling: large vessels

The IMT of both the carotid and aortic arteries is significantly increased in CS patients and associated with premature development of carotid atherosclerotic plaques [75,106]. Compared to matched controls, patients with active disease have a hazard ratio of 4.5 (1.8–11.1) of having a stroke [92]. Successful treatment of glucocorticoid excess decreases carotid artery IMT, which, however, remains above matched controls, respectively, 1 [74] and 5 [78] years after the cure. In untreated patients, IMT is closely correlated to central adiposity and insulin resistance, suggesting a causative link that, however, is lost after the cure, claiming into cause additional factors such as persistence of hypertension or inflammation [74,78].

Vasculature remodeling: small vessels

Cushing's syndrome is also associated with endothelial dysfunction, which precedes the development of atherosclerosis [4,74,107]. CS is associated with altered brachial flow-mediated vasodilation [108]. Endothelial dysfunction is associated with impaired microvascular reactivity, which seems to be modulated by hypertension [109], and with vascular smooth cell hypertrophy and wall fibrosis of small arteries [57]. These effects are probably due to mineralocorticoid pro-inflammatory actions. CS patients also show structural abnormalities in the resistance arteries, as indicated by an increased media-to-lumen ratio. These abnormalities are characterized by hypertrophic remodeling rather than the eutrophic remodeling usually observed in patients with EH which seems to be the consequence of cortisol growth-stimulating properties and/or vascular oxidative stress [57]. However, glucocorticoids may also activate the mineralocorticoid receptor in vascular smooth muscle cells, which involves mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK)-dependent pathways [110]. All these data suggest that glucocorticoids contribute to cardiovascular remodeling via mineralocorticoid receptor signaling, independently of sodium retention or circulating aldosterone [111].

Neither renal nor retinal damage induced by hypertension have been adequately investigated in CS patients. It has been found that more than 80% of CS patients have increased urinary albumin excretion. In general, renal proteinuria may be caused by increased glomerular filtration rate, resulting from higher intraglomerular pressure, damage to the glomerular barrier or decreased tubular reabsorption. Urinary albumin excretion is positively correlated with SBP and DBP, and fasting plasma glucose, suggesting that these factors may have contributed to the increased albumin excretion. However, it is also possible that hypercortisolemia itself increases urinary albumin excretion, although the mechanism is not clear yet [112]. An increased excretion rate of some amino acids, including cysteine, has been documented in patients with active CD, but not in cured patients [113], suggesting a specific effect of glucocorticoid excess on renal function. Renal effects of glucocorticoid also includes calcium metabolism that is responsible for hypercalciuria, increased urinary oxalate and ultimately to nephrolithiasis, a common feature of active CS [114]. Further studies are necessary to investigate both renal and retinal damage secondary to hypertension in CS patients.

EFFECT OF TREATMENT OF CUSHING'S SYNDROME ON HYPERTENSION

The definitive therapy of CS-related hypertension is the surgical removal of the tumor responsible for the disease. However, medical therapy is gaining a broader spectrum of applications [115], not only in preparation for surgery or recurrences, due to the recent development of new agents with proven efficacy in lowering ACTH secretion from pituitary tumors and antisteroidal drugs to counteract glucocorticoid excess. Interestingly, mortality data show that adequate control of hypercortisolemia does not always result in a normalization of BP. Some studies reveal a normalization of the increased cardiovascular risk after immediate surgical cure of CD [116,117], whereas others did not [90–92]. Interestingly, studies with longer follow-up tend to show a persistently elevated risk that is specific for AMI and stroke, but not for heart failure [92]. Among all CS patients, men, those with diabetes or hypertension have a significantly higher mortality risk [3].

Effect of surgical treatment

Transsphenoidal resection of pituitary tumor for CD provides a long-term cure in more than 70% of the cases [2,3,19,115]. After 5 years of cortisol normalization, however, hypertension was found in 40% of the patients, notably higher than would be expected in a sex and age-matched population [74,78]. Bilateral adrenalectomy is recommended for inoperable or occult sources of CS. A large Mayo Clinic cohort found that bilateral adrenalectomy resolved hypertension in 64% of the patients, which is a higher improvement rate than seen with parameters such as diabetes and obesity, confirming the strict association of high BP with glucocorticoid excess [118]. Magiakou *et al.* [25] evaluated 31 children with CS of different etiologies before and 1 year after surgery: 93.5% had preoperative systolic hypertension that persisted after surgical treatment in 30.7, 15.8 and 5.5% of patients at 3, 6 and 12 months, respectively. DBP completely normalized in all patients within 3 months [25]. In contrast, after successful treatment of 23 children with CS, an Italian study found a persistent significant impairment in arterial distensibility and altered 24-h BP monitoring, compared to controls [119]. This suggests that while BP improves faster in young patients, who are somewhat protected from microvascular damage, an increased cardiovascular risk persists despite cortisol and BP normalization. Recent mortality data reveal that increased hypertension can be found after 30 years of follow-up [92], independently of surgical removal of the cause of CS. The risk appears as a consequence of the length of exposure to glucocorticoid excess, with an increased mortality found in patients with symptoms lasting for more than 3 years prior to surgery, compared to those with less than a 3-year history [3].

Effect of medical therapy

Medical therapy of endogenous glucocorticoid excess includes agents that modulate pituitary or ectopic ACTH release (somatostatin analogs, dopamine agonists), inhibit steroidogenesis (ketoconazole, metyrapone, mitotane, etomidate) or block the glucocorticoid receptor (mifepristone)

TABLE 2. Recent registered clinical trials on novel treatments for Cushing's syndrome reporting effect on blood pressure and hypertension

Reference	Study: no. of patients (hypertension)	Drug dose	Primary endpoint	Effects on hypertension	Adverse effects	Follow-up
Colao *et al.*, *New Engl J Med*, 2012 [126]	Phase III, prospective, randomized, double-blind, multicenter study	Pasireotide	At 6 months, percentage of patients achieving normalization of UFC without previous dose up-titration relative to randomize dose	At 12 months	Disturbances of glucose metabolism (78%)	12 months
	Group 1: 82 CD (62 F, 20 M)	Group 1: 600 μg subcutaneously b.i.d.	Group 1: UFC normalization was achieved in 15% of the patients	↓SBP by 6.1 mmHg	Diarrhea (58%)	
	Group 2: 80 CD (64 F. 16 M)	Group 2: 900 μg subcutaneously b.i.d.	Group 2: UFC normalization was achieved in 26% of the patients	↓ DBP by 3.7 mmHg	Nausea (52%)	
					Cholelithiasis (30%)	
					Liver enzyme increase (17%)	
Feelders *et al.*, *New Engl J Med*, 2010 [127]	Prospective, open-label, multicenter study	Pasireotide: 100–250 mcg sc tds	At any set-point, percentage of patients achieving normalization of UFC	At any set-point	Disturbances of glucose homeostasis	80 days
	17 CD (13 F, 64 M mean age, 45.7 years)	If UFC not normalized added:	At day 28, pasireotide monotherapy induced UFC normalization in 5/17 patients (29%)	↓SBP by 12 ± 4 mmHg,		
		Cabergoline (day 28) 0.5–1.5 mg alternate days	At day 60, the addition of cabergoline in the remaining 12 patients normalized UFC in 4/17 patients (24%)	↓ DBP by 8 ± 3 mmHg		
		Ketoconazole (day 60) 200 mg t.i.d.	At day 80, the addition of ketoconazole in the remaining 8 patients induced normalization of UFC in 6/17 patients (35%)			
			At the end of observation, UFC nor malization was achieved in 88% of the patients			
Bertagna *et al.*, *J Clin Endocrinol Metab*, 2014 [128]	Prospective, open-label, proof-of-concept multicenter study	LCI699 (11β-hydroxylase inhibitor)	At 10 weeks, percentage of patients achieving normalization or ≥ 50% reduction in UFC	At day 70,	Fatigue (58%)	10 weeks
	12 CD (8 F, 4M, aged 25–55 years)	2–50 mg orally b.i.d.	At 10 weeks, UFC normalization or ≥ 50% reduction was achieved in 100% of patients (normalization was achieved in 92% of the patients)	↓SBP by 10 ± 4 mmHg	Nausea (42%)	
			At any time, UFC normalization was achieved in 100% of the patients	↓DBP by 6 ± 4 mmHg	Diarrhea (25%)	
					Vomiting (25%)	
					Headache (25%)	
					Hypokalemia (25%)	
Fleseriu *et al.*, *J Clin Endocrinol Metab*, 2012 [130]	Prospective, open-label, multicenter study	Mifepristone (GC receptor antagonist)	At 6 months, improvement in hyper cortisolism and its clinical features	↓ DBP 5 mmHg in 42.5%	Nausea (48%)	6 months
	50 CS (43 CD, 4 ECS, 3 AC)	300–1200 mg/day	In group 1: improvement in glucose control	↓ antihypertensive drugs in 27.5%	Fatigue (48%)	
	40 hypertensive (19 group 1, 21 group 2)		In group 2: 8/21 (38%) ↓ of 5 mmHg in DBP	↓ DBP 5 mmHg or ↓ antihypertensive drugs in 52.5% of 40 hypertensive CS	Headache (44%)	
	Group 1: C-DM cohort (diabetes and hypertension).				Hypokalemia (34%)	
	29 CS: 24 CD, 3 ECS, 2 AC				Vomiting (26%)	
	Group 2: C-HT cohort (only hypertension)				Peripheral edema (26%)	
	21 CS: 19 CD, 1 ECS, 1 AC				↑Endometrial thickness (20%) (38% of female patients)	

(*Continued*)

TABLE 2 (*Continued*)

Reference	Study: no. of patients (hypertension)	Drug dose	Primary endpoint	Effects on hypertension	Adverse effects	Follow-up
					Adrenal insufficiency	
Pecori Giraldi *et al.*, *J Clin Endocrinol Metab*, 2012 [121]	Open-label, proof-of-concept multicenter study	Retinoic acid	At any time-point, percentage of patients achieving normalization or ≥ 50% reduction in UFC	↓ SBP by 28.7 mmHg	Arthralgias (43%)	6–18 months
	7 CD (4 F, 3 M, aged 17–63 years)	Initial dose of 10 mg daily with doubling every 2 weeks up to the maximum dose of 80 mg daily	UFC normalization was achieved in 3/7 patients (43%)	↓ DBP by 26.0 mmHg	Mouth and conjuctival dryness (43%)	
	5 hypertensive		≥50% UFC reduction was achieved in 5/7 patients (71%)		Diarrhea and abdominal discomfort (29%) Transient leukocytosis (29%) Headache (14%)	

AA, adrenal adenoma; AC, adrenal carcinoma; ACTH, adrenocorticotrophin; AIMAH, ACTH-independent macronodular hyperplasia; b.i.d., twice daily; CD, Cushing's disease; CS, Cushing's syndrome; ECS, ectopic ACTH syndrome; t.i.d., thrice daily; UFC, urinary free cortisol.

[120]. Several studies which evaluated the effectiveness of these drugs on the control of hypercortisolism in patients with CS also analyzed the effect on clinical feature, including BP and hypertension. Table 2 described the outcome of recent registered clinical trials in patients with CS, detailing the effects of these compounds on BP and hypertension. Ketoconazole, an inhibitor of 17-alpha hydroxilase and 17,20 lyase activity, improved BP in over 80% of the cases [120]. Metyrapone, an inhibitor of 11-beta-hydroxylase activity, with a good response in urinary free cortisol (UFC) levels [122], is, however, associated with a potential rise in intermediates with mineralocorticoid activity, thus potentially worsening hypertension, as well as hypokalemia. Mitotane has been widely used in patients with adrenocortical carcinoma, but also in severe cases of CS, as an alternative to bilateral adrenalectomy. In particular, in ECS, UFC levels were normalized in 91% of the patients, leading to improved BP in 63% of the hypertensive patients, who were able to stop or reduce antihypertensive drugs [123]. Various novel agents have been evaluated for their possible inhibition of ACTH secretion, including the dopamine agonist cabergoline and most recently somatostatin analog pasireotide; both cabergoline and pasireotide have been demonstrated to significantly improve hypertension associated with CD [124,125]. In particular, in two different multicenter prospective clinical trial, pasiretotide was able to improve SBP and DBP by 6 and 4 mmHg, respectively, when administered alone [126], and by 12 and 8 mmHg, respectively, when administered in combination with cabergoline and ketoconazole [127]. The new compound LCI699, an orally active inhibitor of the 11-beta-hydroxylase, is being investigated in CS [128]. However, similar to metyrapone, the inhibition of 11-beta-hydroxylase activity increases cortisol and aldosterone precursors with mineralcorticoid activity, and could induce hypokalemia and worsen hypertension. The experience with mifepristone, a glucocorticoid receptor antagonist, is limited; BP was reduced in about half of the patients, although in some patients, hypertension and hypokaliemia worsened, requiring co-treatment with spironolactone [129]. In a recent multicenter, prospective, open-label study, mifepristone induced improvement in BP in a significant number of patients with CS; in particular, DBP was improved in 38% of the patients displaying only hypertension, whereas DBP and/or antihypertensive treatment was decreased in more 52% of the patients displaying hypertension alone or in association with disturbances of glucose metabolism [130]. However, despite the treatment with mifepristone, in most cases, additional antihypertensive agents were also necessary. In summary, hypertension can be difficult to control without normalization of hypercortisolemia, but this is often insufficient, suggesting the need for an integrated pharmacologic approach [131].

TREATMENT OF HYPERTENSION IN CUSHING'S SYNDROME

Table 2S (http://links.lww.com/HJH/A423) presents a systematic review of studies investigating the pharmacological treatment of hypertension in CS patients, as well as the effects of medical or surgical therapy of CS on hypertension.

This enabled a number of clinical considerations to be drawn that have been integrated with the pharmacology statements driven by experimental data to build the treatment algorithm presented in Fig. 3. First, clinical control of hypertension has been considered difficult in the presence of sustained long-standing hypercortisolism. Therefore, it is reasonable that the primary medical goal in most studies has been to control glucocorticoid excess. However, given that treatment is often surgical and the response not always successful at the first attempt, a reasonable position would be to use add-on antihypertensives to prevent cardiovascular complications. Although the prevalence of hypertension is high in CS patients, less than 50% are actually treated for hypertension prior to surgery, especially if they are young patients [19,91]. This discrepancy may be related to the evidence that, unless BP is extremely high, once the etiology of CS is established, most physicians wait for surgical cure or relay on antisteroids rather than commencing early antihypertensive treatment. This approach seems driven by empirical reasoning rather than evidence-based medicine, as the few available studies exploring the effects of antihypertensives showed consistent, reproducible effects. A different scenario is when the syndrome is not yet recognized, and the patients, especially when older, are inadequately treated for an EH. Second, use of add-on antihypertensives is supported by data on end-organ complications that seem to occur earlier and at lower BP values in CS than in EH. Such accelerated vascular remodeling and atherosclerosis should prompt aggressive treatment. Third, studies show that the antihypertensive drug is often selected according to generic guidelines for the management of EH rather than pathophysiological considerations relative to CS. This could also explain the discrepancy in results: some studies found no improvement in BP, whereas in others, even a single antihypertensive drug was effective. The proposed treatment algorithm (Fig. 3) is based on a step-up approach with different drugs specifically targeting the pathways most commonly affected by glucocorticoid excess. Fourth, persistence of hypertension after treatment of CS deserves special attention. An aggressive approach, such as with lipid-lowering drugs following ischemic heart attack, could be advocated for the treatment of residual hypertension following resolution of the glucocorticoid excess. Fifth, little attention has been paid to the impaired endothelial function, in particular, on the nitric oxide pathway, despite solid pathophysiological data and promising preliminary results. On the basis of the recent publications showing both early diastolic impairment and blunted natriuretic peptide signaling in hypercortisolism and the antiremodeling effects of chronic PDE5i in diabetic cardiomyopathy, CS patients may be excellent candidates for a dedicated study on chronic PDE5i to revert cardiovascular remodeling. Similarly, the effect of lifestyle interventions and physical activity on the outcome of CS after treatment has not been studied. Considering that myopathy and obesity both reduce the mobility of these patients, specific guidelines are needed to aid physicians in choosing a suitable rehabilitation program. Finally, the results of the recent multicenter, randomized controlled clinical trials exploring the effects of pasireotide [126] and LCI699 [128] or mifrepistone [130] allow a more precise estimate of how much BP is likely to drop following effective control of hypercortisolemia. However, these drugs have a complex mechanism of action that focuses mainly on the control of hypercortisolism. Hence, it cannot be ruled out that the effects on BP may be due to a combination of many different factors. These recent studies have shown that hypercortisolism control is very effective in lowering both systolic and diastolic pressure. Therefore, whereas the old retrospective, heterogeneous studies reviewed herein suggested that control of hypercortisolemia was insufficient to prevent end-organ disease, this may not necessarily apply to the more recent, well controlled trials, in which stricter remission/cure criteria are applied. However, even in the latest studies, only about 50% of the patients were able to discontinue antihypertensives completely. Given the data on the presence of significant cardiovascular comorbidities even after complete remission, prompt and aggressive control of BP remains desirable.

Proposed algorithm for the treatment of Cushing's syndrome-related hypertension

The European guidelines for the management of hypertension recommend to lower BP with drugs, even when hypertension is in the grade 1 range, if total cardiovascular risk is high because of diabetes, cardiac or kidney disease [89,132]. The data, herein presented, clearly show that CS represents a condition of increased risk deserving pharmacological treatment. Furthermore, although lifestyle modifications are recommended for CS patients, especially dietary control of metabolic syndrome [133], some other interventions, such as physical exercise and weight control, are more difficult in patients with CS, due to myopathy and generalized pain, which often characterize the disease. Recent guidelines indicate that diuretics, beta-blockers, calcium antagonists, ACEis and ARBs are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations [89]. However, given the pathophysiological peculiarities of CS, integrated with the recent recommendations [89], the ABC study group formulated a treatment algorithm that is specifically tailored for the management of CS-related hypertension (Fig. 3). This algorithm includes as a first-line treatment the use of any of the two blockers of the RAS, ACEi or ARB, in light of the many evidences supporting a major alteration of this pathway in CS, and for their cardioprotective effects. Conversely, beta-blockers are not considered a first-line drug, in part, because they are not superior, or even slightly worse, than calcium antagonists in reducing total mortality, cardiovascular events and stroke, but also for the possible contraindications, represented by metabolic syndrome, glucose intolerance and sleep apnea, all very frequent in patients with active CS or after the cure [134]. Calcium antagonists are powerful in lowering BP and do not present specific contraindications in respect to CS; they also have a greater efficacy than diuretics and beta-blockers in delaying atherosclerosis and IMT of the carotid artery [135] and preventing stroke [136]. Among diuretics, spironolactone should be used to control hypokalemia, when present, and has been found to have beneficial effects in heart failure [137], and, although never tested in randomized controlled studies on hypertension, can be used as a third-line drug to

lower BP. Eplerenone could be used as an alternative to spironolactone, especially in men [138]; however, it is not available as a subsidized medication in several countries, it is expensive compared to amiloride and spironolactone and, therefore, could suffer compliance in medium to long-term treatment. Thiazides should be used cautiously for the risk of aggravating hypokalemia, which is very common in CS, hyperuricemia, gout and diabetes, which may occur in CS [139,140]. Hydrochlorothiazide has been used for prevention of calcium-containing kidney stones, a frequent complication of CS, because at high dose, it can reduce urinary calcium excretion [139,140]; however, thiazides also reduce free water clearance and recent evidences questioned their use for kidney stone prevention [141,142]. Aliskiren, a direct inhibitor of renin at the site of its activation, has never been tested in CS; it can have possible complications in patients with diabetes and cannot be combined with any other drug acting on RAS. For these reasons it should not be a first choice. The alpha-blocker doxazosin has effectively been used as third-line therapy in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [143] and does not offer specific contraindications related to CS. Monotherapy is seldom sufficient to control BP in CS; however, no controlled studies on combination therapies are available in this group of patients. In non-CS patients, the Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension [414] trial documented the positive synergy an ACEi–calcium antagonist combination. This combination was superior to the combination of beta-blocker and diuretics in reducing cardiovascular events [144] that appeared to elicit more cases of new-onset diabetes in susceptible individuals, compared with other combinations [145]. Agents acting at different levels of the RAS should never be combined. New BP-lowering drugs (nitric oxide donors, vasopressin antagonists, neutral endopeptidase inhibitors, aldosterone synthase inhibitors, etc.) are all undergoing early stages of investigation [128,146].

In summary, the most appropriate approach to treat hypertension and related cardiovascular damage in patients with CS seems to commence with an ACEi or an ARB, if necessary, coupled with calcium-antagonists and/or a mineralocorticoid receptor antagonist, depending on the severity of the condition and the presence of hypokalemia. Use of other diuretics, alpha-blockers and, eventually, beta-blockers should be limited to selected cases after appropriate dose-titration of other agents taking into account the possible contraindications related to the state of hypercortisolemia.

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Conflicts of interest

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Reviewers' Summary Evaluations

Reviewer 2

This ambitious review of an important subject would have benefitted by addressing each of the various aetiologies of Cushing's separately. They differ widely in clinical and laboratory presentation, natural history, pathophysiology and appropriate treatment. Treatment priorities will also be different for each unique patient, rejecting a formalised approach. Hopefully, this review may assist choices of antihypertensive agents. The exciting recent contributions from genetics to the understanding of familial forms deserve great attention and emphasis, promising early identification of those at risk from this often insidious and late-diagnosed condition, and better understanding of pathophysiology.

Reviewer 3

The different causes of Cushing's syndrome with the attendant diversity of the pathophysiological mechanisms underlying the rise of blood pressure make it difficult to provide definitive guidelines for antihypertensive treatment in these patients. However, a careful and thorough evaluation of the present knowledge has allowed the authors to provide some major therapeutic recommendations, some of which of definite clinical relevance.