Diagnosis and management of hypertension in patients with Cushing's syndrome: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension

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Endogenous/exogenous Cushing's syndrome is characterized by a cluster of systemic manifestations of hypercortisolism, which cause increased cardiovascular risk. Its biological basis is glucocorticoid excess, acting on various pathogenic processes inducing cardiovascular damage. Hypertension is a common feature in Cushing's syndrome and may persist after normalizing hormone excess and discontinuing steroid therapy. In endogenous Cushing's syndrome, the earlier the diagnosis the sooner management can be employed to offset the deleterious effects of excess cortisol. Such management includes combined treatments directed against the underlying cause and tailored antihypertensive drugs aimed at controlling the consequences of glucocorticoid excess. Experts on endocrine hypertension and members of the Working Group on Endocrine Hypertension of the European Society of Hypertension (ESH) prepared this Consensus document, which summarizes the current knowledge in epidemiology, genetics, diagnosis, and treatment of hypertension in Cushing's syndrome.

Keywords: adrenocorticotrophic hormone, adrenal cortex, cardiovascular, consensus, cortisol, Cushing, glucocorticoid, hypertension, pituitary, position statement

Abbreviations: 11β-HSD1, 1β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; 1mg DST, 1mg dexamethasone suppression test; 24h UFC, 24h urinary free cortisol; ABPM, ambulatory blood pressure monitoring; ACE-I, angiotensin-converting enzyme inhibitor; ACS, autonomous cortisol secretion; ACTH, adrenocorticotrophic hormone; AII, angiotensin II; AIP, aryl hydrocarbon receptor interacting protein; ARB, angiotensin receptor blocker; ARMC5, armadillo repeat containing 5; ATRRX, alpha thalassemia/mental retardation syndrome X-linked chromatin remodeler; BP, blood pressure; BRG1,

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brahma-related gene-1; CABLES1, Cdk5 and Abl enzyme substrate 1; cAMP, cyclic adenosine monophosphate; CD, Cushing's disease; CRH, corticotropin-releasing hormone; CS, Cushing's syndrome; CT, computerized tomography; DICER1, Dicer 1, ribonuclease III; ENaC, epithelial sodium channels; GIP, gastrointestinal peptide; GNAS, guanine nucleotide-binding protein G(S) subunit alpha; HSP90, heat shock protein 90; HU, Hounsfield units; KDM1A, lysine demethylase 1A; LC-MS/MS, liquid-chromatography tandem mass spectrometry; LNSC, late-night salivary cortisol; LV, left ventricle; LVH, left ventricular hypertrophy; MEN, multiple endocrine neoplasia; MR, mineralocorticoid receptor; NR3C1, nuclear receptor subfamily 3 group C member 1; OSA, obstructive sleep apnea; p27/Kip1, cyclin-dependent kinase inhibitor 1B; PDE11A, phosphodiesterase 11A; PKA, protein kinase A; PMAH, primary macronodular adrenal hyperplasia; POMC, pro-opiomelanocortin; PRKACA, protein kinase cAMP-activated catalytic subunit alpha; PRKAR1A, protein kinase cAMP-dependent type I regulatory subunit alpha; TP53, tumor protein p53; USP48, ubiquitin-specific peptidase 48; USP8, ubiquitin-specific peptidase 8; VHL, Von Hippel Lindau

INTRODUCTION

Cushing's syndrome is characterized by a cluster of systemic manifestations of hypercortisolism, which cause increased cardiovascular risk. Hypertension is a common feature of Cushing's syndrome and paramount to its cardiovascular morbidity and mortality. Experts on endocrine hypertension and members of the Working Group on Endocrine Hypertension of the European Society of Hypertension (ESH) prepared this Consensus document, which summarizes the current knowledge in epidemiology, genetics, diagnosis, and treatment of hypertension in Cushing's syndrome.

EPIDEMIOLOGY AND NATURAL HISTORY OF HYPERCORTISOLISM

Cushing's syndrome is a condition that summarizes the consequences of prolonged exposure to excessive exogenous or endogenous glucocorticoids [1]. Exogenous or iatrogenic Cushing's syndrome is far more common than endogenous Cushing's syndrome and is because of the wide use of systemic and topical glucocorticoids [2]. Development of exogenous Cushing's syndrome depends on several factors, including cumulative dose, modes of delivery, and potency of glucocorticoids, as well as the individual sensitivity to glucocorticoids and concomitant use of agents potentially increasing their bioavailability [3]. Although the onset of the features related to the excess of glucocorticoids is usually rapid in iatrogenic Cushing's syndrome, high inter-individual variability in the sensitivity to glucocorticoids has been observed, making it difficult to predict the effects of chronic corticosteroid treatment in each patient [4]. This consensus statement, however, focuses primarily on endogenous Cushing's syndrome.

Endogenous Cushing's syndrome is usually caused by excessive adrenocorticotrophic hormone (ACTH) release from a pituitary corticotroph tumor (Cushing's disease) and, less frequently, by ectopic ACTH or CRH production, the latter extremely rare. In around 20% of cases, Cushing's syndrome can also be ACTH-independent, caused by adrenocortical tumors or hyperplasia [1].

The incidence of endogenous Cushing's syndrome in the general population is low [0.7–2.4 per million population per year), although the prevalence may be higher (2–5%) in special populations, including patients with difficult to control type 2 diabetes or hypertension] [5–8]. An adrenal incidentaloma may be detected in 0.2–7% of patients undergoing abdominal imaging, of whom between 5 and 50%, depending on the diagnostic criteria used, may have evidence of autonomous cortisol secretion (ACS) [9,10].

A female preponderance (female-to-male ratio of 4–5 : 1) has been reported for pituitary and benign adrenal Cushing's syndrome but the clinical picture may be worse in male individuals [11]. Mean age at diagnosis is 44 years, and patients with adrenal Cushing's syndrome are slightly older than those with Cushing's disease [11].

A two to five times increase in mortality has been described in untreated Cushing's syndrome, especially in those with type 2 diabetes and/or hypertension, as compared with the general population [5,12,13]. Although most deaths occur within the first year after the diagnosis because of infections and cardiovascular disease, mortality rate remains elevated in Cushing's syndrome even for long time after resolution of hypercortisolism [12,14,15]. Indeed, 'cured' Cushing's syndrome patients show sustained systemic problems, including an impaired quality of life [16], the severity of which is associated with the length of prior exposure to glucocorticoid excess, often reflected by a delay in diagnosis of at least 2–3 years [16,17].

COMORBIDITIES, OVERALL CARDIOMETABOLIC RISK, AND MORTALITY

Hypercortisolism causing Cushing's syndrome has detrimental systemic effects that result in increased risk for several serious comorbidities, including cardiocerebrovascular and metabolic diseases, osteoporotic fractures, severe infections, pulmonary embolism, and major depression [18,19].

The majority (80–85%) of patients with Cushing's syndrome have hypertension at diagnosis [11,20], and 9% may have required hospital admission because of hypertensive crisis before they were diagnosed with Cushing's syndrome [21]. Diabetes mellitus is also commonly observed (35–50% of the patients) [11,20,22], as is dyslipidaemia (40–70%) [19,20,22,23]. Furthermore, patients with active Cushing's syndrome have left ventricular hypertrophy (LVH) and diastolic dysfunction [24], as well as increased carotid intima–media thickness, and smaller systolic lumen diameter compared with controls [23]. Atherosclerotic plaques in the common carotid artery are present in one-third of patients with Cushing's syndrome, compared with 6% of controls matched for age and BMI [23]. Following treatment for Cushing's syndrome, the prevalence of hypertension and diabetes mellitus decreases, dyslipidemia improves, intima–media thickness decreases, and LV structure and

function is often restored [22–24]. However, despite these improvements, patients with Cushing's syndrome in remission for 1 year still have ongoing adverse cardiometabolic risk profiles compared with controls [22,23], and coronary calcifications and noncalcified plaques are more prevalent than in controls at long-term follow-up (mean 11 years) [25]. Two nationwide studies from Scandinavia illustrate the clinical impact of hypercortisolism and the burden of multisystem comorbidities in patients with Cushing's syndrome. In Denmark, patients with active Cushing's syndrome had a seven-fold increased risk of venous thromboembolism because of hypercoagulable state, a six-fold increased risk of heart failure, a four-to-five-fold risk of stroke and a three-fold risk of fractures, compared with the background population [12]. Also, during long-term follow-up after treatment, a three-fold increased risk of acute myocardial infarction was observed. Similar results were found in a recent study from Sweden where the risk for pulmonary embolism, deep vein thrombosis, and sepsis remained five to six times higher after treatment, whereas a three-fold increased risk for stroke was observed [26].

Given the above data, it is not surprising that patients with Cushing's syndrome have more than two-fold increased mortality compared with the general population [13,15,27]. The mortality rate is the highest in patients who are not in remission following treatment (five-fold to seven-fold increase) but is also increased during long-term follow-up in patients in remission [15,27]. Both hypertension and diabetes mellitus have been found to be independent factors associated with increased mortality in some studies [13,28], as well as the rapidity to control the disease [29]. The commonest cause of death in the perioperative period is severe infections [14,30]; however, all cause of death is mainly related to cardiovascular disease. In a large nationwide Swedish study including 502 patients with Cushing's disease, 133 deaths were observed, compared with 54 expected from the general population, giving a standardized mortality rate of 2.5 (95% confidence interval 2.1–2.9) [15]. Of the 133 deaths, 63 were because of cardiovascular diseases, including 32 deaths because of ischemic heart disease and nine because of ischemic stroke [15].

Patients with exogenous Cushing's syndrome seem to have the same adverse cardiometabolic risk profile as patients with endogenous Cushing's syndrome [31]. Remarkably, that data from iatrogenic Cushing's syndrome patients, even without diabetes, suggest that metformin treatment is effective to reduce cardiovascular and metabolic risk factors [32].

ETIOLOGY AND NEW GENETIC ASPECTS

Pituitary tumors

Corticotroph tumors of the pituitary gland are monoclonal neoplasms that are mainly sporadic; rarely they are part of genetic syndromes, including multiple endocrine neoplasia (MEN)1 and AIP-negative familial isolated pituitary adenoma [33–35]. Patients with DICER1 syndrome may develop ACTH-secreting pituitary blastomas with very low penetrance [36]. Case reports described patients with Carney complex and Lynch syndrome with corticotroph adenomas and patients with corticotroph adenomas with somatic *GNAS* gene mutation [37,38,35]. Partial resistance to negative glucocorticoid feedback is a hallmark of Cushing's disease [39]. The *NR3C1* gene that encodes for glucocorticoid receptor is mutated in around 6% of corticotroph tumors [40] and the expression of factors facilitating and mediating glucocorticoid feedback, including HSP90, BRG1, p27/Kip1, and CABLES1 are dysregulated at the posttranscriptional/posttranslational level [41–45]. More than half of corticotroph tumors carry somatic mutations in the genes encoding for the USP8 (∼50%) and USP48 (∼10%) deubiquitinases [46–48]. Patients with *USP8* mutant tumors not only have a distinct clinical profile characterized by smaller and less invasive tumors but also increased incidence of recurrence [47,49,50]. *USP8* wild type macroadenomas and aggressive corticotroph tumors may carry *TP53* and *ATRX* mutations [48,51,52]. The role of additional germline or somatic genetic alterations remains to be further studied [53,54].

Ectopic Cushing's syndrome

Ectopic Cushing's syndrome could be because of ACTH or rarely CRH secretion from lung or thymic neuroendocrine tumors, pheochromocytoma, medullary thyroid carcinoma, olfactory neuroblastoma [55], or, in a few cases, as part of MEN1, MEN2, MEN4 (rarely), and Von Hippel Lindau (VHL) syndromes [38]. *USP8* mutations were not detected in tumors causing ectopic Cushing's syndrome [56].

Adrenocortical tumors

ACTH-independent adrenocortical sources of cortisol excess include cortisol-producing adrenal adenomas, adrenocortical carcinomas, and bilateral micronodular and macronodular adrenal hyperplasia. In cortisol-producing adenomas, up to two-thirds of these tumors bear a somatic recurrent mutation p.L206R in the *PRKACA* gene, encoding the catalytic subunit α of protein kinase A (PKA) [57–59]. In contrast, *PRKACA* negative cortisol-producing tumors are genetically less defined [60]. Similarly, cortisol production of adrenocortical carcinoma is not associated with the presence of a specific genetic fingerprint [61,62]. The particular importance of cAMP-PKA-dependent pathways in the regulation of adrenocortical glucocorticoid production is further substantiated by the presence of germline mutations in the PKA regulatory subunit gene, *PRKAR1A,* in adrenal Cushing's syndrome associated with Carney complex [63] and mutations in phosphodiesterases (*PDE11A*) that contribute to a variety of adrenal lesions [64]. Loss-of-function mutations in the *ARMC5* gene are the most common genetic cause of Cushing's syndrome because of primary macronodular adrenal hyperplasia (PMAH) with a combination of germline and somatic mutations [65]. Cortisol excess in patients with PMAH may be mediated by ectopic hormone receptors in adrenal glands [66], with inactivation of *KDM1A* gene being recently identified in the gastrointestinal peptide (GIP)-dependent Cushing's syndrome [67,68].

CLINICAL FEATURES

(a) Phenotype of overt Cushing's syndrome

The spectrum of the Cushing's syndrome phenotype varies from mild to severe, and this depends on duration and

severity of hypercortisolism, age and sex of the patient, and underlying cause. In moderate or severe cases, signs and symptoms of Cushing's syndrome are invariably present [69–71] (Supplementary Table 1, http://links.lww.com/HJH/C37).

Clinical features include weight gain with centripetal distribution of the body fat (with or without obesity), dorsocervical fat pad ('buffalo hump'), round ('moon') face, and facial plethora. The most specific features of Cushing's syndrome phenotype are because of the increased protein catabolism and include purple abdominal striae, skin thinning, proximal muscle weakness with severe fatigue, easy bruising, and osteoporosis resulting in increased fracture risk. Gonadal dysfunction is common in both sexes with female patients presenting with menstrual irregularities, loss of libido, hirsutism and acne, and with male patients presenting low libido and erectile dysfunction. Neuropsychiatric symptoms include cognitive impairment, major depression, and psychosis, including risk of suicide. Moreover, because of immunosuppression, Cushing's syndrome patients are prone to infections. In addition, cortisol excess predisposes to less-specific signs and comorbidities commonly encountered in the general population, such as hypertension, prediabetes, and diabetes, a hypercoagulable state and dyslipidemia. From a clinical standpoint, the most discriminatory clinical features facilitating a diagnosis of Cushing's syndrome are easy bruising, muscle weakness, facial plethora, and purple abdominal striae [11,69,72,73].

In general, the clinical phenotype has only minor differences amongst patients with various causes of Cushing's syndrome. However, the presentation of patients with malignant tumors causing the ectopic ACTH syndrome, for example, ACTH-producing small-cell lung carcinomas, differ from those observed in typical pituitary or adrenal forms of Cushing's syndrome: the dominant clinical features are a rapidly progressive appearance of weight loss, physical wasting, and myopathy accompanied by skin hyperpigmentation, hypokalemia with metabolic alkalosis, and glucose intolerance. In cases of well differentiated neuroendocrine tumors, however, symptoms may develop more slowly and resemble typical symptoms of CD [74–77]. In children, a most discriminating manifestation is growth retardation and delayed or pseudoprecocious puberty, caused by cortisol and androgen excess [78].

(b) Adrenal incidentaloma and autonomous cortisol secretion

ACS is the most frequent hormonal alteration in adrenal incidentalomas, affecting up to 40–50% of patients [79]. As these patients do not present with classic features of excess cortisol, diagnosis is predominantly biochemical and is mainly based on the inadequate cortisol suppression by the 1 mg overnight dexamethasone suppression test [9]. Notably, clinical progression to overt Cushing's syndrome is extremely low; a recent study showed that only 0.2% of patients with ACS developed overt cortisol hypersecretion [80].

Despite the absence of typical Cushing's syndrome symptoms and signs, several but not all retrospective cross-sectional and follow-up studies demonstrated that ACS is associated with an increased cardiovascular and all-cause mortality proportional to the degree of cortisol excess [71,80–86]. A higher prevalence of hypertension, impaired glucose tolerance and type 2 diabetes, dyslipidemia, osteoporosis, and vertebral fractures along with decline in the quality of life has also been described in comparison to the general population [87–90]. However, at the individual level, the likelihood of developing certain comorbidities varies, and is associated with the degree and duration of exposure to mild cortisol excess, as well as with tissue sensitivity to glucocorticoids, partly related to polymorphisms of the glucocorticoid receptor gene [91]. Moreover, the steroid secretory profile may also affect the clinical phenotype. The concomitant secretion of corticosterone depicted by the analysis of steroid profiles by liquid-chromatography tandem mass spectrometry (LC-MS/MS), along with ACS, resulted in a more aggressive presentation in terms of resistant hypertension phenotype [92].

Hypertension is the commonest comorbidity associated with ACS, being found in 64% of patients at baseline, of whom roughly 13% experience further worsening of blood pressure values on subsequent follow-up evaluations. Of note, 8.4% of patients developed new-onset hypertension after a mean follow-up of 59.8 months [80]. Such an increased prevalence of hypertension along with an increased prevalence of type 2 diabetes and dyslipidemia contributes to the higher cardiovascular risk observed among patients with ACS. Accordingly, several long-term follow-up studies demonstrated a higher rate of cardiovascular disease in patients with ACS [71,93].

(c) Hypertension phenotype, pathophysiology, and assessment of organ damage

On the basis of epidemiological studies, the prevalence of hypertension in endogenous Cushing's syndrome is estimated to range up to 85% [11,20,73,94]. Synthetic glucocorticoids may also lead to iatrogenic Cushing's syndrome with higher risk of hypertension, by inducing weight gain or lipodystrophy [95].

Hypertension phenotype

Hypertension usually occurs early in the course of the disease, equally in both genders, and may persist even after achieving clinical and hormonal remission [96,97]. A nondipping blood pressure (BP) profile, which mirrors the disrupted cortisol circadian rhythm, is observed in more than 50% of patients, whether normotensive or hypertensive, and in patients with adrenal causes, there is more blunted nocturnal decline [98–100]. Mechanisms underlying this cause-related difference may be worth mentioning. Ambulatory blood pressure monitoring (ABPM)-derived short-term BP variability is also increased in Cushing's syndrome, independent of BP elevation, and it may represent an additional cardiovascular risk factor per se [101]. An altered BP circadian rhythm has been also observed in patients treated with long-term glucocorticoids [102]. Most studies have not demonstrated dependence of BP values on the duration and degree of hypercortisolism [20,22]. Hypertension is usually mild to moderate. Ectopic Cushing's syndrome patients, however, present more frequently with severe hypertension and hypokalemia, because of the mineralocorticoid effect of excess cortisol, which is not

completely inactivated by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) at renal level, and show end-organ damage [77,103].

Pathophysiology

The pathophysiology of Cushing's syndrome-related hypertension is complex and includes a variety of impairments in BP regulatory systems with multiple contributing factors (Fig. 1).

Enhanced mineralocorticoid activity

The mineralocorticoid receptors are expressed predominantly in the distal nephron and have equal affinity for to aldosterone and cortisol. Under physiological conditions, however, cortisol is unable to exert its mineralocorticoid action as renal 11β-HSD2 catalyzes its conversion to cortisone, which is not a MR-ligand [104,105]. Supraphysiological cortisol levels in patients with severe Cushing's syndrome exceed the capacity of 11β-HSD2, leading to cortisol mineralocorticoid receptor-binding and activation, and results in sodium and water retention, so increasing plasma volume but with increased potassium excretion causing hypokalemia [106]. 11β-HSD1, the isoenzyme catalyzing the cortisone-to-cortisol conversion, and the activated epithelial sodium channels (ENaC) are additional contributors to the enhanced mineralocorticoid activity in Cushing's syndrome [105,107].

Renin–angiotensin system

Hypercortisolism leads to an increased hepatic synthesis of angiotensinogen. However, despite angiotensin II formation is expected to be higher because of increased renin substrate, plasma renin activity and circulating angiotensin II (AII) levels are usually normal. Vascular pressor response to AII is reported to be enhanced by cortisol-induced up-regulation of AII-receptors type 1 [108–110].

Sympathetic nervous system

Glucocorticoids modulate the synthesis of neurotransmitters and the vascular response to catecholamines. Nevertheless, circulating catecholamine concentrations are within the normal range and adrenergic receptors seem intact in patients with Cushing's syndrome, but an enhanced pressor response to beta-adrenergic agonists and impaired cardiac sympathetic autonomic modulation have been demonstrated in some studies [107,109,111,112].

Vasoregulatory system and vascular remodeling

Glucocorticoid excess induces enhanced vascular responsiveness to vasoconstrictors (via down-regulation of the

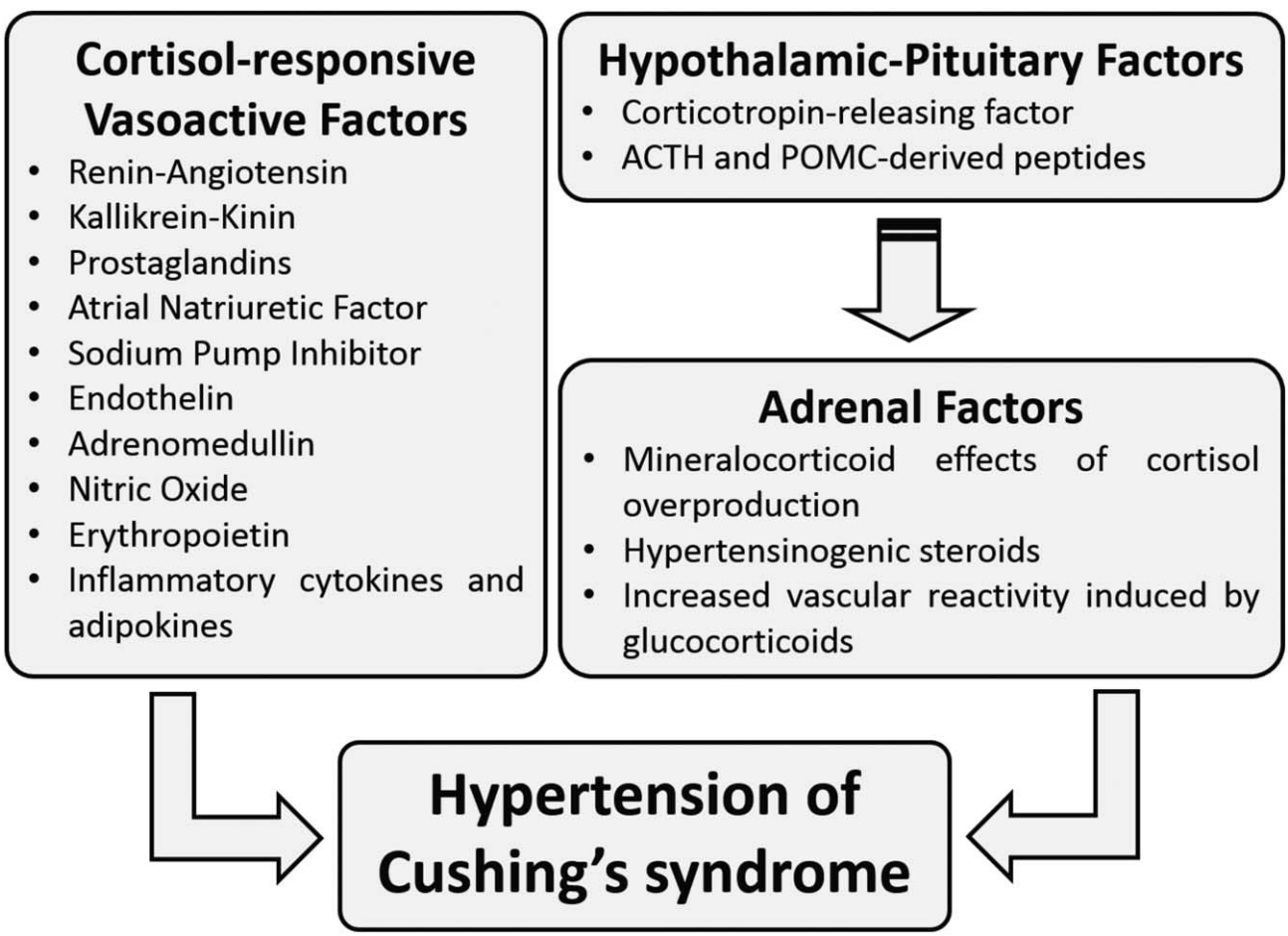

FIGURE 1 Summary of the main pathogenetic mechanisms of hypertension in Cushing's syndrome.

plasma membrane Na/Ca-exchanger), elevation of the vasoconstrictor endothelin-1, inhibition of nitric oxide signaling pathways at multiple levels and impaired synthesis of vasodilators (e.g. prostacyclin and/or kallikrein–kinin system), leading to generalized vasoconstriction. Vascular remodeling and dysfunction present with hypertrophic changes in the wall of small-resistance arteries as a result of increased vascular endothelial growth factor and insulin resistance [94,113–115].

Metabolic abnormalities

Dyslipidemia, prediabetes, or overt diabetes mellitus with visceral adiposity and insulin resistance associated with Cushing's syndrome are additional pathogenic factors [116,117].

Obstructive sleep apnea

Obstructive sleep apnea (OSA), which significantly correlated with visceral obesity, activated sympathetic nervous system, and nocturnal hypercortisolemia, has been observed in approximately one-third of the patients with Cushing's syndrome and may be a major contributor to hypertension [118,119].

Assessment of cardiovascular damage

Cardiac structural changes

Signs of cardiovascular damage are commonly observed in a high proportion of hypertensive patients but may also be seen in normotensive patients with Cushing's syndrome. This indicates that factors other than high BP *per se* are involved in the pathogenesis of cardiovascular complications. LVH and LV systolic and diastolic dysfunctions have been described, as assessed by standard trans-thoracic echocardiography [120]. In addition to confirming LVH, echocardiography documented a characteristic alteration of LV geometric pattern in Cushing's syndrome (concentric remodeling), which was unrelated to BP levels [120]. LV mass and the concentric LV pattern are relatively independent from 24-h BP load and profile (dipping/nondipping) in Cushing's syndrome patients [100], further suggesting a deleterious effect of hypercortisolism directly on the cardiac mass [121]. Novel echocardiographic techniques, such as speckle tracking echocardiography and tissue Doppler imaging, have been used as sensitive tools for evaluating LV performance in patients with Cushing's syndrome. LV global longitudinal strain, assessed by speckle tracking echocardiography, was able to detect low LV contractility and high prevalence of LV subclinical diastolic dysfunction, even with well controlled BP, in patients with hypercortisolism [122,123]. In obese patients with Cushing's syndrome, cardiac MRI mapping seems to be the most informative method for assessment of subclinical systolic alteration [124,125]. The reversibility of some of these abnormalities did not relate to BP changes after disease treatment in echo/MRI-based clinical studies [24,125].

Coronary artery disease

According to the current guidelines, noninvasive functional imaging for myocardial ischemia or coronary computerized tomography (CT) angiography is recommended as the initial test for diagnosing coronary artery disease, in symptomatic patients in whom coronary artery disease cannot be excluded by clinical assessment alone [126]. Noninvasive imaging methods, such as transthoracic Doppler echocardiography, multislice CT, and MRI have been applied in patients with Cushing's syndrome [25,125,127]. Invasive coronary angiography with the availability of invasive functional evaluation may be considered for confirmation of the diagnosis of coronary artery disease in patients with an uncertain diagnosis after noninvasive testing, in those with severe symptoms refractory to medical therapy, or typical angina at a low level of exercise and clinical evaluation that indicates high event risk [126].

Hypertensive vasculopathy

The assessment of hypertensive vasculopathy may be performed by carotid artery duplex with measurement of the intima–media thickness in the common carotid artery, and by measurement of the pulse-wave velocity. Increased carotid intima–media thickness is a strong predictor of systemic atherosclerosis and cerebral vascular accidents and is reported in Cushing's syndrome patients and remained abnormal even after disease remission, indicating a persistent cardiovascular risk [23]. The intima–media thickness in different vascular territories was found to be higher in Cushing's syndrome patients than in a population matched for cardiovascular risk factors, including hypertension [128]. Endothelium-dependent flow-mediated vasodilation is impaired in Cushing's syndrome, but the clinical relevance for cardiovascular risk of blood markers of endothelial dysfunction and/or inflammation remains unclear [129]. Cushing's syndrome has also been associated with increased arterial stiffness [130].

A clear relationship between hypercortisolism and cardiovascular morbidity and mortality has been recently confirmed in Cushing's disease [131]. In addition to prompt treatment of hypercortisolism according to current guidelines, it is highly recommended that evaluation, monitoring, and treatment should be performed according to the general cardiovascular risk prevention guidelines, individualized for presence of complications and risk factors [132,133]. On the basis of the current evidence of the cardiovascular effects of excess cortisol, a comprehensive assessment by 24-h ambulatory blood pressure monitoring, echocardiogram, and carotid ultrasound is recommended in Cushing's syndrome both at baseline and after hypercortisolism is cured. Whenever necessary, this will involve the collaboration of primary care physicians, cardiovascular specialists, and endocrinologists. Even when clinical signs of overt hypercortisolism are not present, patients with ACS showed an increased cardiovascular risk. However, more data are needed to state definitive recommendation about the cardiovascular risk assessment of these patients.

BIOCHEMICAL SCREENING AND SUBTYPING

(a) Screening for hypercortisolism in hypertensive patients: clinical features that should prompt biochemical assessment

Secondary hypertension accounts for 5–15% of all hypertension [133]. The few published series investigating the

causes of secondary hypertension report that the prevalence of Cushing's syndrome ranges from 0 to 1%, increasing to 6.2 and 7.7% when the analysis is limited to patients with early-onset hypertension (before the age of 40 years) or those harboring adrenal masses (Supplementary Table 2, http://links.lww.com/HJH/C37) [6,134–140]. The differences in prevalence also reflect variations in regional, ethnic, or diagnostic criteria. Although hypertension because of the Cushing's syndrome contributes to cardiovascular impairment, screening all hypertensive patients for Cushing's syndrome is neither feasible nor cost-effective [141]. Therefore, screening for Cushing's syndrome should be considered in those hypertensive patients with features suggesting an increased likelihood of hypercortisolism [39,133] (Table 1). Generally, young onset, sudden development of severe or worsening hypertension, or treatment-resistant hypertension are all features that should prompt screening for secondary causes [133]. Presentations that favor Cushing's syndrome are the combination of any of the above, especially if 24-h ambulatory BP profiles do not show nocturnal dipping, with other clinical features specific for hypercortisolism: easy bruising, facial plethora, proximal myopathy or proximal muscle weakness, wide violaceous striae, or osteoporosis in young male individuals. Predictive models exist based on these clinical features, which, if present, should prompt biochemical evaluation [142–144]. Whilst weight gain and obesity are common in Cushing's syndrome, by themselves they have poor discriminatory value for the diagnosis. Thus, obesity alone should not prompt assessment for Cushing's syndrome.

In summary, identification of Cushing's syndrome in hypertensive patients requires a high clinical index of suspicion but if suggestive features are present (Table 1), then biochemical testing for hypercortisolism is warranted.

(b) Screening of Cushing's syndrome and autonomous cortisol secretion

The diagnostic flow-chart for hypercortisolism is shown in Fig. 2. Three main hormonal tests are currently used for biochemical screening of Cushing's syndrome in patients with a suspicious clinical picture (after excluding glucocorticoid intake): overnight 1 mg dexamethasone suppression test (1 mg DST), 24-h urinary free cortisol (24-h UFC), and late-night salivary or serum cortisol [39]. Late-night salivary cortisol (LNSC) is preferred over midnight serum cortisol as it does not require hospitalization and is less invasive (see Supplementary Material and Supplementary Table 3, http://links.lww.com/HJH/C37 for test details). Initial biochemical screening for Cushing's syndrome is done by performing one of those three tests. If normal, hypercortisolism is excluded. However, further hormonal assessment may be considered in patients with a high pretest probability of Cushing's syndrome (see previous paragraph), or who, in the 6 months following initial testing, show progression of symptoms that could potentially be driven by hypercortisolism. Additionally, if 1 mg DST results are not in line with the clinical suspicion, it might be worthwhile to measure also dexamethasone levels, as suggested by recent studies [145,146]. In the case of an abnormal initial result, positivity of at least one of the remaining screening tests is required to establish the diagnosis of Cushing's syndrome, especially given that cyclicity/variability in Cushing's syndrome is not an infrequent phenomenon, with a prevalence in Cushing's disease above 15% [147]. Cut-offs and accuracy of the screening tests for Cushing's syndrome are reported in Table 2.

In patients with adrenal incidentalomas without a clinical phenotype suggesting overt Cushing's syndrome, the 1 mg DST is recommended for screening [9]. To maximize sensitivity and specificity, a double cut-off for cortisol has been proposed. In case of serum cortisol greater than 138 nmol/l (5 μg/dl), the diagnosis of ACS (formerly known as 'subclinical Cushing's syndrome') is confirmed. Serum cortisol levels between 50 and 138 nmol/l (1.8 and 5 μg/dl) indicate 'possible autonomous cortisol secretion' and, especially, in the presence of potential cortisol-related comorbidities, further assessments may be required to confirm hypercortisolism including low/undetectable basal plasma ACTH or abnormal 1 mg DST after 3–12 months [9]. The other screening tests recommended for Cushing's syndrome are of little use in patients with adrenal incidentalomas without clinical signs of hypercortisolism, given the poor and contrasting data on the diagnostic performance of 24-h UFC and LNSC in this clinical context [150]. However, alternative diagnostic strategies have to be considered when patients with adrenal incidentalomas also present with conditions responsible for false-positives on the 1 mg DST (Supplementary Table 3, http://links.lww.com/HJH/C37) [39,151], like the use of oral contraceptive therapy [152]. In this regard, simultaneous assay of cortisol and dexamethasone in serum or saliva has been shown to improve diagnostic accuracy of 1 mg DST in patients with overt Cushing's syndrome or ACS [146,153].

(c) Subtyping of Cushing's syndrome

Once hypercortisolism is established, further subtyping is required to establish the cause of Cushing's syndrome. First, morning plasma ACTH is measured following immediate

TABLE 1. Main characteristics of hypertensive patients who should be screened for Cushing's syndrome

Age	Young patients (<40 years) with grade 2 hypertension or onset of any grade of hypertension in childhood
Onset	Acute worsening hypertension in patients with previously documented chronically stable hypertension
Severity	Resistant hypertension
Hypertension phenotype	Blood pressure nondipping profile – Presence of extensive hypertension-mediated organ damage
Radiological findings	Adrenal lesions
Clinical features specific for hypercortisolism	Easy bruising, facial plethora, *striae* Proximal myopathy or proximal muscle weakness – Osteoporosis at young age – Unusual features for age or multiple and progressive features

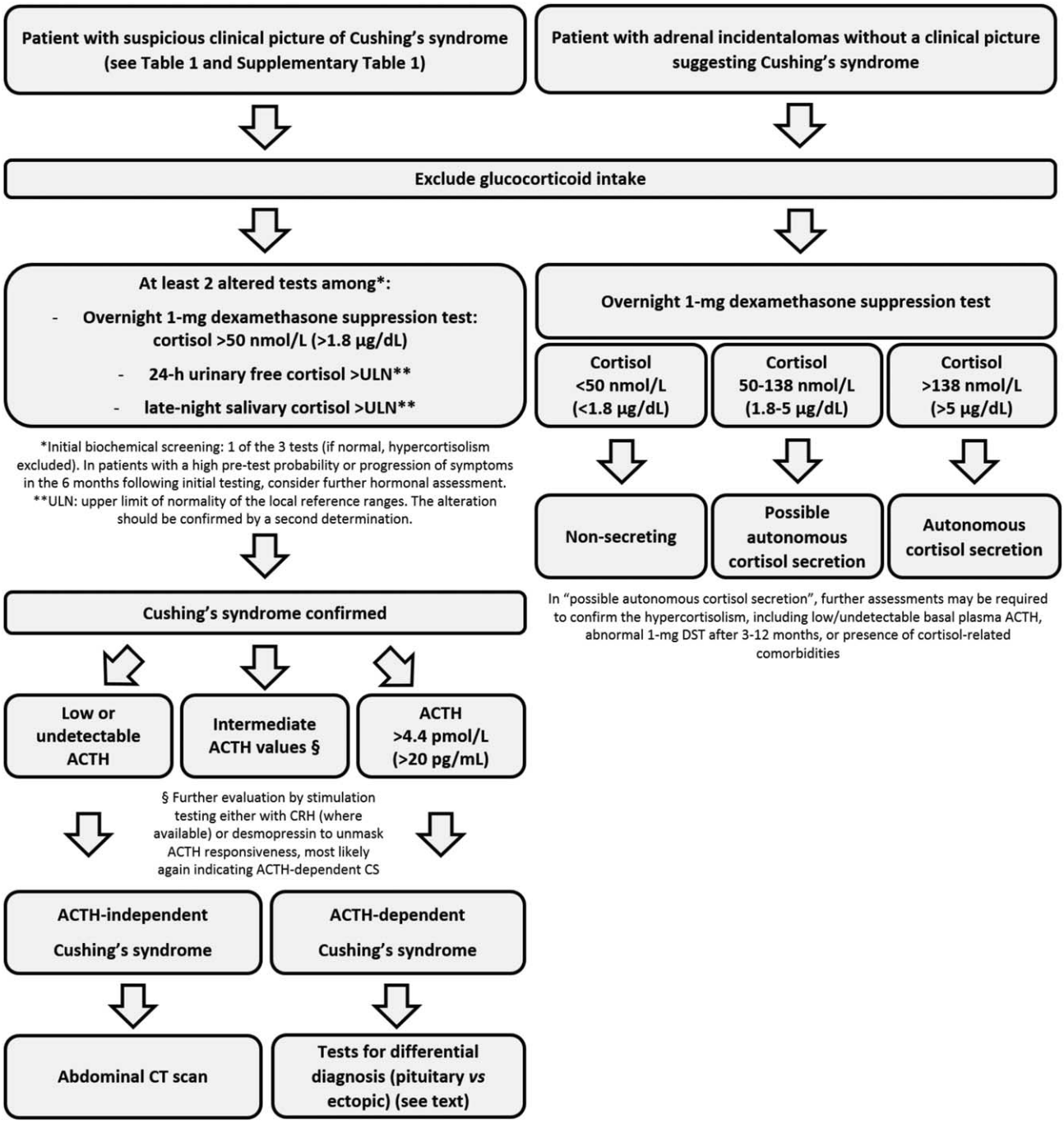

FIGURE 2 Diagnostic flow-chart for hypercortisolism.

blood sample centrifugation at low temperature (to avoid degradation) on at least two separate days to differentiate ACTH-dependent from ACTH-independent Cushing's syndrome [72]. ACTH values below the lower detection limit of the assay reliably indicate ACTH-independent Cushing's syndrome, whereas ACTH levels greater than 20 pg/ml are highly suggestive of an ACTH-dependent source. Intermediate ACTH levels are almost always reflective of

TABLE 2. Cut-offs and accuracy of the screening tests for Cushing's syndrome

Type of test	Diagnostic cutoff for Cushing's syndrome	Sensitivity[b]	Specificity[b]
Overnight 1 mg dexamethasone suppression test	Serum cortisol >50 nmol/l (1.8 µg/dl)	99%	93%
24-h urinary-free cortisol[a]	Above the upper limit of normal of the local reference ranges	94%	93%
Late-night salivary cortisol[a]		96%	93%

[a]Elevation of 24-h UFC and LNSC should be confirmed by a second determination.
[b]On the basis of ref. [148]. Slight differences have been reported in relation to the use of different hormonal assays [149].

ACTH-dependent Cushing's syndrome but often need further imaging and dynamic functional evaluation, that is, ACTH stimulation by CRH or desmopressin [154], within expert centers.

Adrenocorticotrophic hormone-dependent Cushing's syndrome

Cushing's disease is considerably more frequent than ectopic sources of ACTH, and more common in women than men. Ectopic Cushing's syndrome usually presents with more severe symptoms of shorter duration, greater hypercortisolemia and plasma ACTH levels, and higher frequency of hypokalemia, but features may rarely resemble CD [155]. Unfortunately, differential diagnosis of ACTH-dependent Cushing's syndrome has many potential pitfalls. Therefore, it is essential that evaluation is performed in centers with sufficient experience. Many centers consider a sufficient evidence to proceed with pituitary surgery the following conditions: visualization of a pituitary adenoma larger than 6 mm in diameter by MRI and/or congruent positive results by CRH and/or desmopressin test and high-dose dexamethasone suppression testing (the latter being less accurate and less frequently used in major centers). In all other patients, bilateral inferior petrosal venous sinus catheterization is used to differentiate Cushing's disease from ectopic Cushing's syndrome. Whole-body imaging by CT or MRI, with or without functional imaging using ^{68}Ga DOTA-somatostatin analogues-PET, may also be considered to differentiate Cushing's disease from ectopic Cushing's syndrome [156,157]. Functional imaging by PET scan may improve correct detection of corticotropic pituitary adenomas in the future, using ^{11}C-methionine as a tracer [158] or targeting the CRH receptor [159].

Adrenocorticotrophic hormone-independent Cushing's syndrome

Imaging by CT or MRI will demonstrate the cause of ACS, in most cases, a cortisol-secreting adrenal adenoma. A tumor with homogenous content and unenhanced Hounsfield units (HU) less than 10 on CT imaging is consistent with an adrenal adenoma [9,160,161], and if this is not the case, evaluation in expert adrenal centers is recommended, especially for tumors bigger than 4 cm. Multiple nodules bigger than 1 cm in diameter or rarely diffuse enlargement of both adrenals indicate PMAH, which may be further evaluated by screening for aberrant receptor expression, germline mutations in *ARMC5* and other genes [162], and potentially by MS-based steroid profiling [163]. In contrast, multiple small nodules less than 1 cm in diameter ('bead-like' nodules on high-resolution CT) characterize primary pigmented nodular adrenocortical disease where genetic testing and screening for other manifestations of Carney complex is indicated [162].

TREATMENT

(a) Control of endogenous hypercortisolism

Although the control of hypercortisolism does not necessarily lead to remission of hypertension, obtaining rapidly eucortisolism in patients with Cushing's syndrome is a mandatory step because of the increased morbidity and mortality in patients with uncontrolled hypercortisolism [164]. Most of the causes of Cushing's syndrome require surgery as a first-line treatment. This is true for Cushing's disease (removal of the pituitary tumor), ectopic Cushing's syndrome (excision of ACTH-secreting tumors), or ACTH-independent hypercortisolism (adrenalectomy for benign adrenal adenoma or malignant adrenocortical carcinoma) [132]. Pituitary surgery for Cushing's disease is associated with immediate remission rate in 82% of the patients (47–94%) with microadenomas (in experienced hands), and 60% (17–91.7%) in those with macroadenomas [165]. Unilateral adrenalectomy for benign adrenal adenomas associated with Cushing's syndrome is curative in nearly 100% of the cases [132]. In rare forms of Cushing's syndrome and malignancy, the results of surgical approach depend on the clinical condition of the patients and on the severity of disease [132,155,165].

Additional therapeutic modalities (drugs, radiotherapy, bilateral adrenalectomy) can also be used to control hypercortisolism usually after failed surgery, and their roles in the therapeutic algorithms of Cushing's syndrome depend on the cause. Hypercortisolism may be controlled by drugs aimed at lowering cortisol levels [166–173]. It is important to emphasize that these drugs will not lead to cure, and thus will have to be maintained on a long-term basis. They may be used after failure or contraindications to surgery, in patients with cortisol-secreting metastases, or while waiting for the effects of pituitary radiation in patients with Cushing's disease.

Drugs targeting the pituitary bind to somatostatin receptors (mainly type 5) or dopamine receptors (type 2), which are expressed by the pituitary tumor [169,170]. The biochemical control of hypercortisolism is limited, being reported in 30–50% of the cases of ACTH-dependent Cushing's syndrome. Drugs targeting the adrenals block one or more enzymes of the steroidogenesis: they can be used in all causes of Cushing's syndrome, and several are available depending on the countries (ketoconazole, metyrapone, osilodrostat, and mitotane). Metyrapone and olisodrostat, because of their prevalent inhibition of the enzyme 11beta-hydroxylase/aldosterone synthase, may increase the levels of 11-deoxycorticosterone, a precursor of aldosterone with mineralocorticoid activity, worsening hypertension and inducing hypokalemia, which tend subsequently to improve when cortisol levels normalize [172].

Drugs targeting the adrenals are more effective than those targeting the pituitary gland and usually control cortisol secretion in 50–80% of the cases [166,168,169]. Additionally, mitotane, which is specifically used in adrenocortical carcinoma, also has an adrenolytic effect [174]. As each of these drugs has a specific tolerance profile including risks of adrenal insufficiency, their use should be carefully monitored, ideally in expert centers. In selected cases, patients with severe hypercortisolism might be treated by a combination of drugs before surgery to obtain rapid control of hypercortisolism, and therefore, to improve the clinical state in preparation for surgery [175–177].

Mifepristone, a progesterone receptor antagonist with glucocorticoid receptor antagonistic activity at higher concentrations (still off label in Europe), has also been reported to induce hypertension and hypokalemia in some patients

with Cushing's syndrome, likely because of the noncomplete inactivation of excess cortisol by 11β-HSD2 in the kidney, leading to binding and activation of mineralocorticoid receptors [178].

Another therapeutic option to control hypercortisolism, especially in Cushing's disease, is radiotherapy, which can be used after failed transsphenoidal surgery, when a tumor remnant is visualized on pituitary MRI. Although the efficacy is reported in 50–80% of the cases, the main drawbacks of radiotherapy are the time to reach maximal efficacy (usually 2–5 years), requiring an effective antisecretory treatment during this period, and the occurrence of pituitary secretory deficits [179].

Bilateral adrenalectomy leads to control of hypercortisolism in virtually 100% cases. Although the control of hypercortisolism is immediate, it is still considered as a third-line treatment by the majority of teams as it leads to permanent adrenal insufficiency [180]. However, some expert groups suggest that it should be performed earlier when curative surgery fails, thanks to its efficacy and safety [181]. Nevertheless, bilateral adrenalectomy in patients with Cushing's disease carries the risk of development of corticotroph tumor progression (Nelson's syndrome) in up to 53% of the patients [182].

In patients with ACS, the efficacy of the surgical treatment has been investigated in a few, mostly retrospective studies, showing that hypertension improved in 60.5% of patients undergoing adrenalectomy, with a mean decrease of 12.7 mmHg in SBP and 9.3 mmHg in DBP [183]. Moreover, patients with ACS treated by adrenalectomy showed a significant improvement in hypertension when compared with those under conservative management [183].

(b) Control of blood pressure

Given the high prevalence of alterations in the circadian BP profile in Cushing's syndrome patients, assessment of BP control by treatment should include performance of 24-h ambulatory BP monitoring, which allows to explore the achievement of a smooth reduction of BP over the 24-h, including nocturnal BP control [184]. As the increase in BP levels in Cushing's syndrome patients is related to the chronic exposure to excessive circulating cortisol levels [93], the ideal way to reach BP control in Cushing's syndrome patients is the biochemical control of hypercortisolism. After surgical remission, Cushing's syndrome patients experience normalization of BP levels in around 40% of cases and an overall improvement in hypertension in up to 90% of cases [94,97,116], being the time of exposure to excess cortisol the determinant of residual hypertension [185]. An improvement in BP levels are also observed during specific medical therapy for hypercortisolism, regardless of the specific drug used [172,186,187]. Addition of ketoconazole normalized BP in 11 of 12 Cushing's syndrome patients with mild-to-moderate hypertension resistant to combined antihypertensive therapy [188]. However, in larger cohorts of Cushing's syndrome patients, hypertension was an adverse event of treatment with ketoconazole alone, metyrapone alone, or with their combination in 48% of the cases overall [189], with osilodrostat in 12% [171], and with mifepristone in 24% [190]. Therefore, these drugs may potentially complicate the treatment of normotensive or hypertensive patients with active hypercortisolism. Although normalization of cortisol levels may improve hypertension, around one-third of Cushing's syndrome patients in remission still experience abnormal BP levels [191,192]. Moreover, definitive long-term biochemical control of hypercortisolism may be difficult to achieve in Cushing's disease recurrence after pituitary surgery is reported in up to 33% of patients [186], whilst for those on medical treatment, there is the potential development of escape or adverse events during medical therapy, requiring treatment up-titration or discontinuation, respectively [186,187]. In addition, it should be considered that most patients treated with cortisol-lowering drugs display disrupted circadian rhythm of cortisol secretion despite having a quantitively normal 24-h cortisol production (as assessed by 24-h UFC). Some studies suggest that a persistently increased late-night cortisol may participate to the maintenance of hypertension despite apparent control of hypercortisolism by measurement of 24-h UFC [193]. Any recurrence of hypercortisolemia may then lead to a new increase in BP levels. Therefore, alongside with biochemical control of hypercortisolism, specific treatment with antihypertensive drugs is required for Cushing's syndrome patients (Fig. 3).

Currently, specific studies focusing on the treatment of hypertension in Cushing's syndrome patients are lacking. However, considering the pathophysiology of hypertension in Cushing's syndrome patients and the currently available guidelines on the treatment of hypertension [133], some therapeutic suggestions may be made. As Cushing's syndrome patients experience an increased cardiovascular risk because of the Cushing's syndrome-related metabolic comorbidities, including visceral obesity and glucose and lipid metabolism impairment [18], strict control of BP levels ($\leq$130/80 mmHg) is needed [94]. As a generalized up-regulation of the renin–angiotensin–aldosterone system is observed in Cushing's syndrome patients, angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) could be preferred as first-line approach to lower BP levels in Cushing's syndrome patients, also given their better cardioprotective effects [94,192,194]. If BP control is not achieved with ACE-Is/ARBs monotherapy, calcium channel blockers should be considered as a second-line treatment, because of their high efficacy in reducing BP levels and the higher efficacy in both monotherapy and combined therapy with ACE-Is/ARBs in preventing cardiovascular events as compared with other antihypertensive drugs [94,194]; however, in case of preexisting moderate or severe peripheral edema, they should be considered with caution. If the addition of calcium channel blockers is not effective or contra-indicated, mineralocorticoid receptor-antagonists should be considered as a third-line or second-line treatment [94,191]; moreover, they should be considered as a first-line treatment in persistent Cushing's syndrome patients with both hypertension and hypokalemia, to favor control of both BP and potassium levels [94,192]. As male Cushing's syndrome patients may experience hypogonadism and gynecomastia during spironolactone treatment [18,195], eplerenone is a reasonable alternative [94]. In case of further lack of BP control, alpha-blockers or NO donors may be considered as additional therapies [94]. Conversely, beta-blockers and

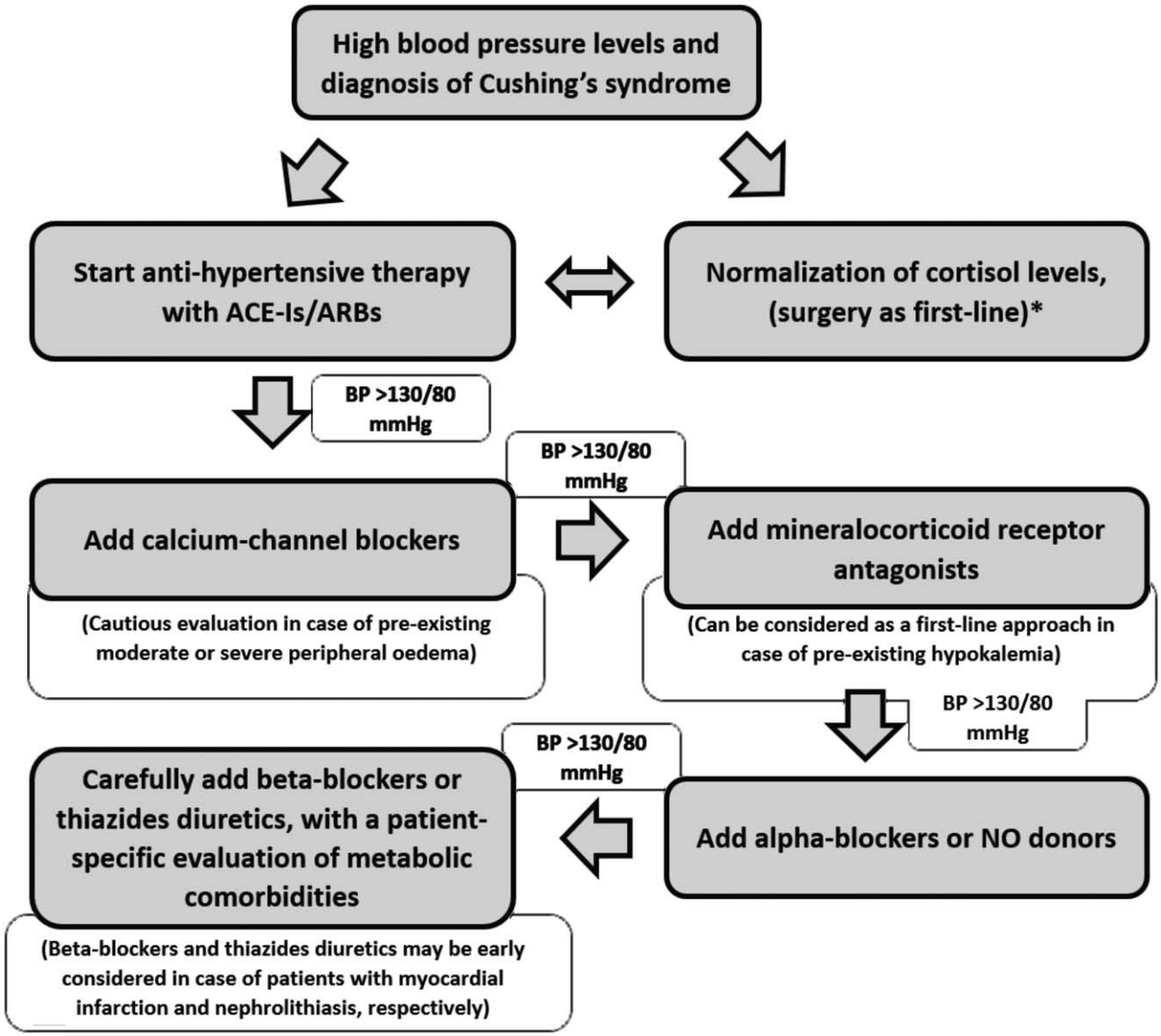

FIGURE 3 Treatment algorithm of hypertension in Cushing's syndrome.
ACE-Is, angiotensin conversion-enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; NO, nitric oxide. *In the case of failure or contra-indications to surgery, in patients with cortisol-secreting metastases, or in Cushing's disease patients waiting for the effects of pituitary radiation, cortisol-lowering drugs can be considered. Worsening of hypertension has been described using metyrapone, osilodrostat, or mifepristone.

thiazide diuretics should be used with caution in patients with Cushing's syndrome as both may worsen Cushing's syndrome-related metabolic comorbidities and, in case of thiazide, preexisting hypokalemia [94,191]. However, vasodilating beta-blockers, including labetalol, nebivolol, celiprolol, and carvedilol, may be considered in Cushing's syndrome patients with previous myocardial infarction, as they may improve myocardial infarction-related morbidity and mortality, whereas hydrochlorothiazide may be considered in Cushing's syndrome patients with kidney stones as they may prevent cortisol-induced hypercalciuria [191].

CONCLUSION

A summary of the main messages of this consensus is reported in Table 3. There is a strong association of Cushing's syndrome with increased cardiovascular risk. The biological link is cortisol overproduction acting on various pathogenetic processes and resulting in cardiovascular damage. This pertains also to patients with ACS, in whom a similar risk profile is found. A comprehensive biochemical and clinical work-up for renal, cardiac, and vascular comorbidities is required, and allows tailoring of the most suitable therapy for any given patient. Cortisol normalization by surgery or specific medications directed against the cause of hypercortisolism is the mainstay of treatment of hypertension in Cushing's syndrome. Patients not achieving control of BP and awaiting correction of hypercortisolism need tailored antihypertensive therapy. Cardiovascular status should accurately be assessed during both the active phase of disease and the postoperative follow-up as cardiovascular risk persists for a long time after cure.

TABLE 3. Consensus bulleted points

Three tests are currently recommended for the diagnosis of endogenous Cushing's syndrome: 1 mg dexamethasone suppression test, 24 h urinary free cortisol, and late night salivary (or serum) cortisol.
In patients with clinical suspicion of Cushing's syndrome, the diagnosis of endogenous hypercortisolism is made upon the finding of two out of three positive screening tests.
In patients with adrenal incidentalomas without a clinical picture of Cushing's syndrome, 1 mg dexamethasone suppression test is the recommended screening test to rule out autonomous cortisol secretion.
As a first step, in patients with a confirmed diagnosis of endogenous Cushing's syndrome, morning ACTH levels in plasma are determined to distinguish ACTH-dependent from ACTH-independent Cushing's syndrome.
In ACTH-independent Cushing's syndrome, unenhanced computerized tomography or MRI of the abdomen will most likely demonstrate a cortisol-producing adrenal adenoma.
In ACTH-dependent Cushing's syndrome, noninvasive stimulation tests and pituitary MRI may be sufficient for the diagnosis of Cushing's disease. In all other patients, bilateral inferior petrosal venous sinus catheterization and/or cross sectional and functional imaging may allow differentiation of a pituitary from an ectopic source of autonomous ACTH secretion.
Hypertension in Cushing's syndrome is linked to cortisol overproduction. However, cardiovascular damage seems to be unrelated to high blood pressure per se and may persist after resolution of hypercortisolism.
A comprehensive assessment by 24 h ambulatory blood pressure monitoring, echocardiogram, and carotid ultrasound is recommended in Cushing's syndrome both at baseline and after hypercortisolism is cured. Further search for end-organ damage is mandatory in complicated hypertension.
Normalization of cortisol levels should be the first-line approach to hypertensive patients with Cushing's syndrome
Surgery should be the first-line option in the majority of cases, whatever the etiology of Cushing's syndrome
After failed surgery, different therapeutic options (drugs, radiotherapy, bilateral adrenalectomy) should be discussed in expert centers.
While waiting for normalization of cortisol levels, start angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as a first-line therapy, aiming at strict control of blood pressure levels (≤130/80 mmHg)
In case of lack of blood pressure control, consider addition of calcium channel-blockers or, in case of hypokalemia, mineralocorticoid receptor antagonists
Beta-blockers and thiazide diuretics should be considered as a third-line or fourth-line treatment because of the potential exacerbation of Cushing's syndrome metabolic comorbidities

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Conflicts of interest

There are no conflicts of interest.

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