Drug-related hypertension and resistance to antihypertensive treatment: a call for action

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Several drugs can cause hypertension and/or blunt the effect of antihypertensive treatment. They can exacerbate a previously well controlled hypertension and/or render it resistant to therapy. Accordingly, drugs represent a common cause of resistance of hypertension to treatment. Identification of drug-related hypertension can be achieved with a thorough medical history targeted to ascertain concurrent therapies that are prescribed for conditions other than cardiovascular diseases. This can avoid prescribing a more aggressive antihypertensive treatment and may prevent embarking in costly and sometimes invasive diagnostic procedures. Drugs that commonly raise blood pressure include NSAIDs, steroids, oestroprogestinic agents, immunosuppressants, erythropoietin, inhibitors of angiogenesis, anti-HIV agents, and also some high-density lipoprotein-raising agents. As withdrawal of the offending drug is often impracticable, knowledge of the mechanism(s) by which each drug exerts its pressor effects may help selecting the most effective treatment. Purpose of this review is to examine the most common causes of resistant hypertension that are due to drugs or abuse of substances along with their underlying pathophysiological mechanisms. The strategy for selecting the most appropriate treatment and the reasons for 'a call of action' of research in this area are also examined. *J Hypertens* **29:2295–2309 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: angiogenesis inhibitors, anti-inflammatory drugs, cyclosporine, erythopoietin, iatrogenic hypertension, oestrogens, resistant hypertension, steroids

Abbreviations: AME, apparent mineralocorticoid excess; BP, blood pressure; COX, cyclooxygenase; COXIBs, COX-2 inhibitors; Epo, Erythropoietin; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; MAOI, monoamineoxidase inhibitor; PGI_2, prostacyclin; RHT, resistant hypertension; RTKI, receptor tyrosine kinase inhibitor; VSPI, vascular endothelial growth factor signalling pathway inhibitor

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Introduction

Resistant hypertension (RHT) [1] is diagnosed when a therapeutic plan entailing implementation of lifestyle measures and prescription of at least three drugs, including a diuretic, in adequate doses, has failed to lower SBP and DBP to goal [1,2]. It remains a major clinical problem in spite of the availability of many effective antihypertensive agents [1]. Among the several possible causes of RHT (see [2]), those attributable to drugs or abuse of substances are the majority, likely more than 58% [3]. To date, only one review has dealt with drugs causing hypertension [4], but no systematic review of drug-related RHT has appeared. We, therefore, examined RHT caused by the drugs and substances abuse and their underlying mechanisms with the aim of providing a mechanistic approach to the management of this common condition.

Boolean logic was used to select relevant literature in *PubMed*, using the terms 'blood pressure', 'hypertension', 'drug-related hypertension', and then also the drugs and substances identified to raise blood pressure (BP) that were herein examined [5]. The search was confined to articles published in the English language in peer-reviewed journals from 1990 up to February 2011. The abstracts identified through the original search were jointly evaluated by two investigators (C.M., T.M.S.) for appropriateness; for those that were held to be eligible for inclusion, the full article was obtained and used for the analysis (Fig. 1). To be included, identified publications had to meet predefined standards for eligibility and relevance which entailed a description of patients' selection criteria, blinded randomization, definition of the target condition (e.g., hypertension or RHT) and of dropouts, and use of appropriate statistical analysis. Narrative or systematic reviews on the target drugs were also examined; when they accurately reported the original data, they were quoted instead of the original articles to minimize the number of references. Case reports were quoted only when observational or prospective studies were not available. Relevant literature unravelling the molecular mechanisms underlying the BP rise was also identified, whereas articles with no focused clinical question were excluded from the analysis. Studies investigating both hypertension and other diseases were quoted only if they analysed the hypertensive population separately.

Drugs with pressor effects

Many drugs have well documented pressor effects and can, therefore, cause a raise in BP and/or render

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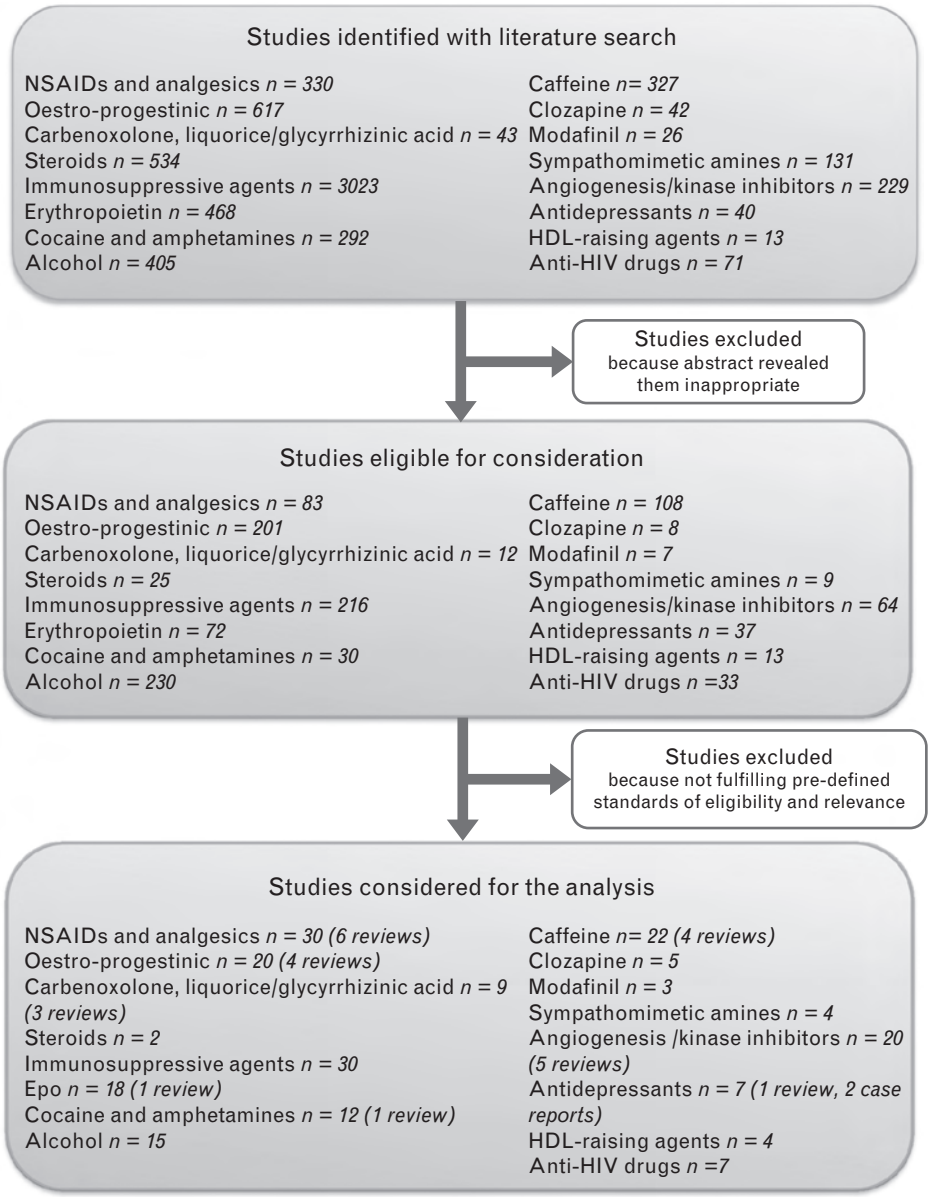
Fig. 1



Flow diagram of assessment of studies identified in the systematic review. Please see text for details. HDL, high-density lipoprotein.

hypertension resistant to antihypertensive treatment (Table 1) [6,7]. This list, which will enlarge in the future, is meant to provide a tool for diagnosing and treating drug-related hypertension.

Keys for the success of treatment of drug-related RHT are the identification of the offending drug(s) and the understanding of the underlying pressor mechanisms. In the majority of cases, removal of the culprit drug is the most rational and effective strategy, because it can allow achieving control of BP or even cure of hypertension. Unfortunately, as this is often impracticable, as discussed below, a careful assessment of the balance between the BP-lowering effect of withdrawal of the offending drug(s) and the unfavourable consequences of this action should be exploited on an individual basis.

For most of these drugs, the level of evidence supporting the choice of antihypertensive treatment is only recommendation based on expert opinion, case studies, or standard of care [6], which underlines the need for specific research in this field. In the absence of evidence-based recommendations, we will herein discuss a targeted strategy to a rational treatment when dealing with the

Table 1 Drugs that may cause hypertension and mechanistically based antidote treatment

Drugs	Proposed pressor mechanism	Mechanistically based antidote treatment
NSAIDs	Inhibition of PGE_2 and PGI_2 synthesis resulting in renal vasoconstriction, sodium, and water retention	Discontinue. If not possible, start calcium channel blockers or central adrenergic agonists, possibly associated with diuretics
Oral contraceptives and HRT	Increase in angiotensinogen synthesis, activation of RAS, aldosterone secretion, increase of plasma volume, and exchangeable sodium	In fertile women long acting calcium channel blockers, β-blockers, and methyldopa; consider diuretics. In postmenopausal women, also consider RAS inhibitors and aliskiren
HSD11B2 inhibitors Carbenoxolone Glycirrizinic acid Licorice	AME by inhibition of HSD11B2	Discontinue. If not possible, start MR antagonists.
Steroids	Increase in angiotensinogen synthesis, activation of the sympathetic nervous system, and mineralocorticoid effect	Discontinue. If not possible, start drugs blocking the RAS and the MR, along with adequate doses of diuretics to counteract sodium and water retention
Calcineurin inhibitors Cyclosporine Tacrolimus	Vasoconstriction, sympathetic activation and water and salt retention, impaired ET-1 clearance with enhanced ET_A effects.	Calcium channel blockers and RAS inhibitors
Erythropoietin	Rise of cytosolic Ca^{2+} content in vascular smooth muscle cells [67], activation of the local RAS system, increased ET-1 production, decreased NO, increased vasoconstricting response to catecholamines	Lower the dose; if unsuccessful, start calcium channel blockers or α-blockers. Diuretics and ACE inhibitors may be less effective
Sympathomimetic amines Cocaine Amphetamines Ephedrine Nasal decongestants	Cocaine and amphetamines: inhibition of the peripheral re-uptake ofNE and inhibition of baroreceptor function, thus causing sympathetic activation α-Adrenergic receptor stimulation	Discontinue offending drug if possible. If unfeasible, β-blockers
Alcohol	Stimulation of sympathetic activity, activation of the RAS, and abnormal calcium-mediated vasoconstriction	Limit intake
Caffeine	Sympathetic over-activation, antagonism of adenosine receptors, and increased norepinephrine release activation of the RAS system	Limit intake
Anti-angiogenesis and kinase inhibitors Bevacizumib RTKI	Blunted release of vasodilating factors, ET-1 stimulation, PGI_2 release, endothelial cell apoptosis, capillary rarefaction, and impaired angiogenesis of vasa vasorum with ensuing aortic stiffness	Drugs promoting NO bioavailability, such as ACE inhibitors and nebivolol
Antidepressants MAOIs Tricyclics Selective serotonin Re-uptake inhibitors (SSRI)	MAOI increase the half-life of monoamines as norepinephrine, thus enhancing their action at sympathetic nerve endings	Whenever withdrawal is unfeasible, use α-blockers with β-blockers
HDL-raising agents Torcetrapib	Increased aldosterone secretion	MR antagonists

Evidence-based trials were available for no drugs. For each drug, level of evidence was C, that is, recommendation based on expert opinion, case studies, or standards of care [6], and class of recommendation was IIa, that is, weight of evidence/opinion is in favour of usefulness/efficacy [6]. ACE, angiotensin-converting enzyme; AME, apparent mineralocorticoid excess; ET-1, endothelin-1; HDL, high-density lipoprotein; MAOI, monoamine oxidase inhibitor; MR, mineralocorticoid receptor; NE, norepinephrine; NO, nitric oxide; RAS, renin–angiotensin system; RTKI, receptor tyrosine kinase inhibitor; PGE_2, prostaglandin E; PGI_2, prostacyclin; SSRI, selective serotonin reuptake inhibitors.

specific forms. This approach was based on knowledge of the underlying pathophysiological mechanism(s), which differs for the diverse classes of drugs. The caveat has to be stated that it represents a class IIB recommendation [6].

Pressor effects of NSAIDs and analgesics

Prostaglandins play a central role in BP regulation by exerting vasodilatatory and natriuretic effects. The NSAIDs inhibit cyclo-oxygenase (COX) and blunt the synthesis of prostaglandin E and prostacyclin (PGI_2). Therefore, they cause renal vasoconstriction with sodium and water retention, weight gain, blood volume expansion, and ultimately high BP. However, as prostaglandins mediate the release of renin and aldosterone by decreasing prostaglandin levels, NSAIDs can lower BP when the renin–angiotensin system (RAS) is activated as, for example, in renovascular hypertension and heart failure [8]. Hence, depending on the prevailing degree of activation of the RAS, of prostaglandin synthesis, and on individual susceptibility, the BP changes induced by NSAIDs can vary widely across individuals.

In normotensive individuals receiving NSAIDs, the BP changes are usually negligible, but studies were small and short in duration [9,10]. In a small randomized, parallel-group study in volunteers receiving 75-mg diclofenac twice daily, 200-mg celecoxib twice daily, or 25-mg rofecoxib once daily for 8 days, diclofenac elicited the most pronounced BP elevation (10-mmHg SBP and 2.6-mmHg DBP) which was attributed to the more marked COX-2 inhibition induced by this agent compared with the two COX-2 inhibitors (COXIBs) [11]. The risk of developing hypertension was examined for a longer (8 years) period in two large subcohorts of the Nurses' Health Study I (NHS I and NHS II) composed of older (51–77 years) and younger (34–53 years) normotensive women, respectively (Table 2) [12,13]. Compared with women who did not use acetaminophen, those who took the drug showed an increased multivariable-adjusted relative risk (RR) (1.93 and 1.99 among older and younger women, respectively) of incident hypertension. In the same cohorts, the RR was less increased with NSAIDs, but not with aspirin, in older and younger women (1.78 and 1.60, respectively) (Table 2) [12].

According to meta-analyses, the older NSAIDs (such as ibuprofen, indomethacin, and naproxen) increase mean BP in hypertensive patients by an average of 5–6 mmHg [9,10,14]. However, these changes can be more substantial in hypertensive patients who are older and/or have impaired glomerular filtration rate [14,15]. In an observational study involving a very elderly population, new onset hypertension developed in 21% of patients receiving celecoxib, in 23% of those receiving nonselective NSAIDs, and in 27% of those given rofecoxib. These rates were similar to that (22%) observed among individuals not receiving NSAIDs in this very elderly population [16]. Of note, the risk of hypertension was higher if patients had a history of congestive heart failure, kidney, or liver disease.

Table 2 Relative risk of developing hypertension for acetaminophen, NSAIDs, and cyclooxygenase 2 inhibitors vs. placebo

Drug (study sample size)	RR (95% CI)	Reference
Acetaminophen ($n=1903$)	1.93 (1.30–2.88)	[12]
Acetaminophen ($n=3220$)	1.99 (1.39–2.85)	[12]
NSAIDs ($n=1903$)	1.78 (1.21–2.61)	[12]
NSAIDs ($n=3220$)	1.60 (1.10–2.32)	[12]
Rofecoxib ($n=16512$)	1.87 (1.63–2.14)	[13]
Celecoxib ($n=20987$)	1.24 (0.80–1.93)	[13]
Etoricoxib ($n=15728$)	1.1 (0.7–1.75)	[13]
Valdecoxib ($n=2553$)	4.13 (0.75–22.8)	[13]
Lumiracoxib ($n=11930$)	1.12 (0.64–1.95)	[13]

Relative risk (RR) for acetaminophen and NSAIDs was calculated in two subcohorts of the Nurses' Health Study I (NHS I) and NHS II, consisting of 1903 older (51–77 years) and younger (34–53 years) normotensive women, respectively, with no history of hypertension at baseline. RR for cyclooxygenase 2 inhibitors was obtained from a meta-analysis including 51 randomized controlled studies with a total of 130 541 participants in which BP values were available. RR was calculated in each cohort using as reference the subcohort not exposed to each agent. CI, confidence interval.

As regards the COX-2-specific inhibitors, a meta-analysis showed that the risk of developing hypertension in normotensive individuals at baseline was marked for rofecoxib and etoricoxib and negligible for the other COXIBs (Table 2) [13]. However, according to another meta-analysis of randomized controlled trials [17], atherothrombosis and overall cardiovascular risk might be increased with COXIBs. It was proposed that this could be because COXIBs blunt PGI_2 production in endothelial cells without inhibiting thromboxane in platelets [17]. A further meta-analysis of 114 randomized double-blind clinical trials that included 116 094 participants showed that compared with controls, rofecoxib, which has a higher COX-2 selectivity than the other COXIBs [18], was associated with increased risk of renal events [RR 1.53, 95% confidence interval (CI) 1.33–1.76], hypertension (RR 1.55, 95% CI 1.29–1.85), and renal dysfunction (RR 2.31, 95% CI 1.05–5.07). In contrast, celecoxib was associated with lower risk of both renal dysfunction (RR 0.61, 95% CI 0.40–0.94) and hypertension (RR 0.83, 95% CI 0.71–0.97) compared with controls. As the other agents (valdecoxib with parecoxib, etoricoxib, and lumiracoxib) were not significantly associated with risk, the authors concluded that rofecoxib uniquely increased risks of renal (peripheral oedema, renal dysfunction, hypertension) and arrhythmic events [19,20]. Thus, the increases in BP and cardiovascular risk vary among selective and nonselective NSAIDs. Moreover, differences among COXIBs may be related to COX-2 selectivity, potency, and also to dose and duration of treatment.

Finally, there have been few large observational studies on the cardiovascular effect of acetaminophen in hypertensive patients. Results, although being diverse, suggested that regular administration of this agent (e.g., 22 days/month) has the same effects as that of NSAIDs on incident hypertension. Moreover, a case–control study showed that acetaminophen administration was associated with a significant increase in the risk for chronic renal failure [21].

Hence, overall available data suggest that long-term administration of moderate-to-high doses of acetaminophen are not safer than NSAIDs as regards the risk of developing high BP or kidney dysfunction.

Effects of NSAIDs on action of antihypertensive drugs

Prostaglandins mediate renal vasodilation and the antihypertensive action of some antihypertensive agents, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, β-blockers, and diuretics. The BP-lowering effect of these agents can, therefore, be blunted by NSAIDs. Risk factors for NSAID-related destabilization of BP and renal dysfunction include advanced age, a history of heart and/or kidney disease, and/or treated hypertension (especially with

RAS-blocking agents and diuretics). Differences in the rates of induced cardio-renal dysfunction and hypertension do exist within the NSAIDs as a class. These differences, which may be related to pharmacodynamics, drug disposition and metabolites, and molecular effects, remain incompletely understood. Fortunately, BP destabilization and renal dysfunction are easy to identify and occur within days or weeks of administration. Furthermore, most of the cardio-renal effects of NSAIDs are reversible. Hence, physicians must be vigilant and monitor their patients taking NSAIDS.

In a careful multicentre study using ambulatory BP monitoring to assess the effect of indomethacin on the antihypertensive effects of losartan and captopril, Conlin *et al.* [15] found that this drug attenuated the 24-h DBP decrease induced by either angiotensin II receptor, type 1 receptor antagonist. Notably, NSAIDs do not affect the BP-lowering action of other agents as, for instance, the calcium channel blockers [22,23], indicating that these latter agents do not crucially depend on vascular PGI_2 for their mechanism of action [24–26]. Table 3 [27] shows the average raise of BP observed in normotensive and hypertensive patients with some widely used NSAIDs and the changes in BP observed with COXIBs, including rofecoxib (that was withdrawn in 2004 for an increased cardiovascular event rate that could be partially due to its pressor effect) [28]. The BP increase found in patients assuming COXIBs was quite variable, depending on the COXIB and the concomitant history of hypertension.

Of note, celecoxib is held to have little, if any, effect on BP, as shown by the Successive Celecoxib Efficacy and Safety Study (SUCCESS VII) [28,29], studies with ambulatory BP recording [30], and also by a retrospective analysis of over 17 000 individuals aged at lest 65 years in whom use of this drug was not associated with development of hypertension [16]. The newer COXIB etoricoxib showed an even shallower dose-related increase in the incidence of hypertension. Collectively available findings suggest that COXIBs differ in their ability to inhibit prostaglandins and prostaglandin-related BP-lowering effects of some antihypertensive agents and particularly of the diuretics.

Table 3 Changes in blood pressure in hypertensive patients and in normotensive individuals with different anti-inflammatory drugs

	Hypertensive patients (mmHg)	Normotensive individuals (mmHg)
NSAIDs (pooled)	3.6–5.4	1.0–1.1
Indomethacin	4.8–6.0	1.0
Naproxen	3.1–6.1	ND
Piroxicam	2.9–6.2	ND
Sulindac	−1.6 to 2.2	−1.6
Aspirin	−1.8 to 1.0	0.6
COXIBs		
Rofecoxib	2.6–4.7	3.4
Celecoxib	−0.4	4.3

COXIBs, cyclooxygenase-2 inhibitors. Adapted from [27].

Hence, all NSAIDs should be prescribed for the period for which it is strictly necessary and by instructing the hypertensive patients, particularly those with nephropathy, to watch their BP carefully. Treatment of NSAID-related hypertension and RHT is based on tapering or withdrawing these drugs [29], or, when possible, replacing them with agents that have less effect on BP [31,32]. As there seems to be no interference of NSAIDs with calcium channel blockers or central adrenergic agonists, these agents could be, at least theoretically, the first-line drugs, whenever withdrawal of the NSAIDs is not possible.

Oestro-progestinic treatment

Hypertension occurs in about 5% of women taking high-dose oestro-progestinic oral (50 μg of oestrogen and 1–4 mg of progestin) contraceptive formulations and is usually mild, although severe RHT can also occur [4]; small BP increases were associated also with low doses [33]. A family history of hypertension, cigarette smoking, pre-existing gestational hypertension, renal disease, obesity, diabetes mellitus, and age more than 35 years predict the risk of developing hypertension during oestro-progestinic treatment [33]. The main mechanisms involve an increased synthesis of angiotensinogen in the liver, with ensuing enhanced angiotensin II synthesis, increased aldosterone secretion, plasma volume, and exchangeable sodium [34]. Progesterone antagonizes the effects of aldosterone at the mineralocorticoid receptor, but it is uncertain whether this action can counterbalance the pressor effect of the oestrogenic component.

In fertile women on contraceptive pill, BP normalization occurs usually within 3 months after interrupting treatment; hence, the persistence of hypertension should alert the possibility of primary or secondary hypertension.

In postmenopausal women with well controlled hypertension, BP does not generally increase significantly with HRT; moreover, HRT can have a beneficial effect on endothelial function by restoring the NO bioactivity [35], and HRT was even shown to lower BP, as assessed by 24-h ambulatory BP measurements [36]. However, the Women's Health Initiative, a large study on postmenopausal women, was stopped prematurely based on an excess risk of cardiovascular events, which exceeded benefits, over an average follow-up of 5.2 years (coronary heart disease: hazard ratio 1.29, 95% CI 1.02–1.63; stroke: hazard ratio 1.41, 95% CI 1.07–1.85) [37]. A post-hoc analysis of the same study showed that the lack of benefit or the increased cardiovascular risk occurred mainly in the older women who started therapy many years after onset of menopause [38]. Although the hazard ratio for coronary heart disease was 0.76 (95% CI 0.50–1.16) in women with less than 10 years since menopause began, in those with 10–19 years of menopause the hazard ratio was 1.10 (95% CI 0.84–1.45) and increased to 1.28

(95% CI 1.03–1.58) when menopause lasted 20 or more years (P for trend = 0.02) [38]. Hormone therapy also increased the risk of stroke (hazard ratio 1.32, 95% CI 1.12–1.56), but this risk did not vary significantly by age or time since menopause [38]. Thus, the usefulness of HRT should be carefully assessed on an individual basis.

Men receiving oestrogens for the treatment of prostate cancer and women receiving the semisynthetic androgen danazol for endometriosis and hereditary angioedema have also been reported to exhibit an increase in BP, likely through similar mechanisms [39].

If withdrawal of hormonal treatment is unfeasible, antihypertensive treatment should be tailored to woman's age and status. Although it remains controversial as to which therapy should be used in the hypertensive women of childbearing potential [40], long-acting calcium channel blockers, α_1-blockers, and methyldopa could be valuable choices. However, RAS inhibitors can also be prescribed during effective contraception; they can be effectively combined with diuretics. In postmenopausal women, there is no limitation to the use of RAS inhibitors. Considering, however, that these women can have a prominent increase in pulse pressure, calcium channel blockers, diuretics, and aliskiren can be an option because of their effectiveness in lowering SBP [41].

Carbenoxolone, liquorice, and glycyrrhizinic acid

Before the advent of H_2-antagonists and proton pump inhibitors, carbenoloxone, a synthetic derivative of glycyrrhizinic acid, was a popular remedy for peptic disease. It is still licensed in some countries for oesophageal ulceration and inflammation, and treatment of oral and perioral lesions. Similarly to glycyrrhizinic acid, carbenoloxone acts as a potent inhibitor of 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2), an enzyme associated with the mineralocorticoid receptor that converts cortisol to cortisone. Under normal circumstances, cortisol, despite circulating in blood at concentrations from a 100–1000-fold higher than those of aldosterone and despite having an affinity for the mineralocorticoid receptor similar to that of aldosterone, does not activate mineralocorticoid receptor in aldosterone target tissues because it is rapidly inactivated by HSD11B2. At high doses, or even at small doses in susceptible individuals carrying loss-of-function allelic variants of the gene, liquorice and carbenoloxone, by inhibiting HSD11B2, may induce apparent mineralocorticoid excess (AME), a syndrome mimicking aldosteronism in that it shows hypertension, hypokalemia, and increased exchangeable Na^+. Under these conditions, enhanced blood volume causes low renin release, despite no aldosterone excess.

Steroids

Hypertension occurs in at least 20% of patients treated with synthetic corticosteroids in a dose-dependent fashion. The pressor effect is prominent with the α-F-derived steroids due to their mineralocorticoid receptor-activating properties, causing a form of hypertension resembling AME. Less known, and often neglected when taking history, is the fact that long-term topic application of preparations of these steroids, as nasal drops or skin ointments, can also induce hypertension or RHT. Withdrawal of these agents usually normalizes BP and serum K^+ in these cases.

Oral corticosteroids are also well known to increase BP in a dose-dependent fashion, more often in patients who are elderly and/or have a history of primary (essential) hypertension. The pressor mechanisms of steroids are complex and involve interplay of effects, including increased angiotensinogen synthesis, activation of the sympathetic nervous system (Table 1) [42], and moreover saturation of the inactivating capabilities of HSD11B2 with consequences similar to those just described for AME. According to Funder's hypothesis [43] oxidative stress, which may concur with many cardiovascular risk factors, as hypertension, diabetes mellitus, and hypercholesterolemia and is a feature of the chronic inflammatory diseases that require steroids, can blunt HSD11B2 activity by impairing NADH. This would allow endogenous cortisol and exogenous steroids, as dexamethasone or corticosterone, to activate the mineralocorticoid receptor as in AME [43]. Hypokalemia, suppressed renin, and normal or low aldosterone levels are biochemical clues to this form of steroids-induced RHT that, besides being correctable with tapering of the steroids, respond well to mineralocorticoid receptor antagonists.

As a general rule, attempts should be made to use the minimal needed dose of steroids. When steroid withdrawal is unfeasible, the tailoring of an antihypertensive regimen aimed at blocking the RAS and the mineralocorticoid receptor, along with adequate doses of diuretics to counteract sodium and water retention, are rational and useful therapeutic strategies. Although supported by a level of evidence C, the association with a RAS blocker is justified because steroids increase angiotensinogen synthesis. Close monitoring of serum K^+ levels is also advised because diuretics can worsen the steroid-induced hypokalemia, particularly in patients on a high salt intake.

Immunosuppressive agents

Hypertension or RHT occurs in 36–80% of organ transplant recipients or patients requiring chronic immunesuppression with cyclosporine A, tacrolimus, sirolimus, and steroids which can all exert strong pressor effects [44–46]. An acute and transient hypertension can occur after the first large dose of cyclosporine A. It is due to sympathetic activation resulting from inhibition of dephosphorylation of synapsin and does not usually require long-term therapy [19]. After weeks or months,

chronic hypertension develops, and antihypertensive therapy is needed in more than 80% of patients in kidney transplant recipients [46]. Even with medical intervention, hypertension can be difficult to control in these patients [46]. This may cause worsening of renal function [47], increasing cardiovascular risk disease [48], and diminishing graft survival [49,50].

As compared with cyclosporine-based therapy, a lower incidence of hypertension was observed in patients treated with sirolimus (29 vs. 47%, $P < 0.02$) or tacrolimus (67 vs. 80%, $P < 0.001$) [51]. Patients receiving tacrolimus after cardiac or lung transplantation also showed a smaller incidence of hypertension and required a smaller number of antihypertensive agents as compared with those assuming cyclosporine [52–55]. Development of hypertension is also common in liver transplant recipients, with incidence (26–54%) depending on the immunosuppressant regimen therapy [56,57]. However, a lower incidence with tacrolimus as compared with cyclosporine was not invariably found [56,57].

A transient BP raise, but not chronic hypertension, was seen after 12 months of low-dose cyclosporine (mean final dose: 2.89 ± 0.69 mg/kg per day, range 1.70–3.75) in patients suffering from rheumatoid arthritis [58], whereas higher dose regimen (3.3 mg/kg per day, range 1–6) caused discontinuation of cyclosporine in 3% of the patients because of uncontrolled hypertension [59]. A dose-dependency of side-effects was also found in patients assuming cyclosporine for psoriasis in which a significant BP rise was evident only with 5 mg/kg per day or higher doses after 16 weeks of treatment [60].

The potential mechanisms by which cyclosporine A can raise BP (summarized in Fig. 2) include inhibition of dephosphorylation of calcineurin substrates, vasoconstriction via increased angiotensin II type 1 receptor expression [45], sympathetic activation, and water and salt retention. At the endothelial level, cyclosporine A enhances endothelin-1 (ET-1) release and increases reactive oxygen species generation with ensuing NO inactivation. Cyclosporine A also displaces ET-1 from the endothelin receptor type B receptors that are predominantly located on endothelial cells and mediate the clearance of the peptide and the release of vasodilators as NO, adrenomedullin, and PGI_2. Hence, impaired ET-1 clearance, enhanced ET_A receptor-mediated effects and blunted endothelium-dependent vasodilatation can account for the pressor effect of cyclosporine A. Similar mechanisms can be involved in the pressor effect of tacrolimus, even though hypertension seems to develop less commonly with this agent than with cyclosporine A [61]; studies on the pressor mechanisms of this agent are, however, far more limited.

Rapamicin (sirolimus), another immunosuppressant used in drug-eluting stents, acts without inhibiting calcineurin and, thus, might have less pressor and nephrotoxic effects if taken alone. Association of rapamicin with cyclosporine A can augment the risk of developing hypertension because of their synergistic nephrotoxic actions. Therefore, lowering the dose of cyclosporine A can be considered under this condition.

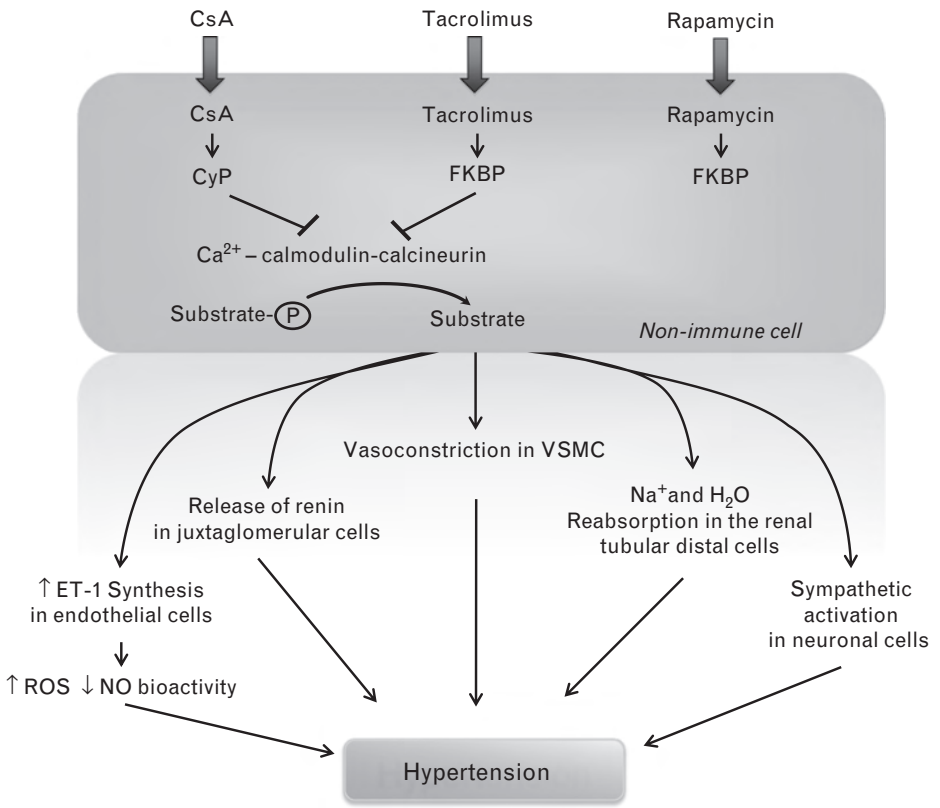
Antihypertensive treatment is mandatory in the patients who develop hypertension on chronic immunosuppression, because withdrawal of corticosteroids and/or conversion from cyclosporine A to a tacrolimus-based immunosuppression or replacement of calcineurin inhibitors with mycophenolate mofetil is often unfeasible. [45,62] Calcium channel blockers and RAS inhibitors are well tolerated in transplant recipients, the choice of either drugs depending on the presence of proteinuria, which is more effectively controlled by the latter agents. However, most patients require both drugs, and sometimes in combination with an α1-blocker, such as doxazosin [45,63–66].

Erythropoietin

About one-third of the patients on chronic treatment with erythropoietin (Epo) and the newer continuous Epo receptor activators develop hypertension [67], which can occur as early as 2 weeks after the initiation of treatment or later, even 4 or 5 months after starting the Epo. Withdrawal of Epo can resolve hypertension in few months, usually later than the fall of haematocrit, suggesting that the pressor effect of Epo involves mechanisms more complex than the increase in haematocrit, blood volume, and viscosity [68]. These mechanisms include a rise in cytosolic Ca^{2+} content in vascular smooth muscle cells [7], activation of the local RAS system [69], increased ET-1 production [70], decreased NO synthesis via a truncated Epo receptor [71], and increased vasoconstriction to catecholamines [72,73].

In chronic kidney disease patients, the strongest pressor effect is seen in those on chronic haemodialysis, rather than in predialysis or in chronic ambulatory peritoneal dialysis [74]. The increase in SBP (ranging from 4 to 13%) and DBP (ranging from 6 to 8%) [75,76] required withdrawal of Epo in 15% of the patients for uncontrolled hypertension [76]. Withdrawal of Epo, and the associated worsening of anaemia, can adversely affect quality of life and prognosis of these patients. Therefore, practical recommendations are to avoid allowing the haemoglobin to go above 120 g/l; evaluate whether a reduction of Epo is possible, the risk of RHT being minimized if hematocrit gradually gets better; optimize dialysis therapy by carefully balancing fluid and volume regulation; and start or modify the on-going antihypertensive treatment. Hypertension related to Epo therapy is usually well controlled with a wide fluid removal during dialysis and use of antihypertensive agent(s) of any class.

Fig. 2



Mechanisms underlying immunosuppressant-induced hypertension. Although structurally unrelated, tacrolimus and cyclosporine (CsA) inhibit the synthesis of interleukin-2 and numerous other cytokines that are important mediators in graft rejection and other autoimmune diseases. To exert their effects, these agents bind to different immunophilins: tacrolimus complexes with FK506 binding protein-12 (FKBP) and cyclosporine complexes with cyclophilin (CyP), and then the drug-immunophilin complex inhibits the activity of the enzyme calcineurin consisting in the dephosphorylation of its substrates. Persistent phosphorylation of calcineurin takes place not only in T cells, but also in the kidney, the nervous system, the endothelial and vascular smooth muscle cells, thereby causing, besides suppression of interleukin-2 gene transcription, activation of endothelin-1 (ET-1) synthesis, which in turn induces vasoconstriction, sympathetic activation and water and salt retention. When there is endothelial dysfunction ET-1, by reducing nitric oxide (NO) bioavailability and activating generation of reactive oxygen species (ROS), potentiates vasoconstriction and other deleterious effects. Similar mechanisms are deemed to be involved in the development of hypertension after administration of tacrolimus and sirolimus. P: phosphate moiety; Na^+: sodium ion; Ca^{2+}: calcium ion; CyP and FKBP: immunophilins binding calcineurin and generating the two immunophilin-immunosuppressant complexes: CyP-calcineurin and FKBP-calcineurin.

Cocaine and amphetamines

The illicit use of these substances is unfortunately steadily increasing in a manner that is inversely proportional to the knowledge of their nefarious cardiovascular effects among consumers. Cocaine, like amphetamines, inhibits the peripheral re-uptake of norepinephrine, thus enhancing its sympathomimetic effects on the cardiovascular system. Hence, the BP changes induced by cocaine mimic a pheochromocytoma crisis. According to one study, if taken intranasally, cocaine would inhibit also baroreceptor function, thus causing sympathetic activation [77]. The hypertensive crises induced by these substances can be severe and life threatening, as they can be complicated by stroke, acute coronary syndromes, and sudden death.

The route of administration is relevant: despite reaching similar plasma concentrations, intrabrachial infusion and intranasal administration of cocaine can induce different effects on mean BP, for example, unappreciable changes in the first case and prominent increases (+11%) in the latter [77]. Therefore, the importance of strongly tackling illicit use of cocaine, amphetamines, and other substances cannot be neglected, particularly in patients with hypertension and/or cardiovascular diseases. Inadvertent users should be warned against the possibility of disastrous adverse cardiovascular and cerebrovascular events, which can mark the rest of their life.

Derivatives of amphetamines are currently prescribed for attention deficit hyperactivity disorder in both adults and adolescents. A significant increase in BP was found with methylphenidate in some studies in both children (SBP +4%, DBP +2–5%) [78,79] and adults (SBP +3.5 mmHg, DBP+2.4 mmHg) [80–82], but not in others [83]. The more recent lisdexamfetamine

dimesylate, which is a long-acting oral prodrug converted to active D-amphetamine, showed minimal pressor effect, with no change after 4 weeks in adults [84] and 1 year in children [85]. However, even though the data from these studies are promising, longer studies are needed.

The use of amphetamine-derivatives for behaviour modifications has been increased in recent years in the paediatric age, as evidenced by a two-fold to three-fold rise in prescriptions in preschool-aged children [86]. Concomitantly, concerns have been raised regarding the safety of these psychotropic medications, the appropriate selection of patients for therapy, and the indications for cardiovascular monitoring. Hence, in 2008 the American Heart Association (AHA) spread a scientific statement [87] in which recommended cardiovascular monitoring, including control of BP values (class I, level of evidence C) in children assuming methylphenidate and dextroamphetamine for attention deficit hyperactivity disorder. As randomized placebo-controlled studies are lacking, AHA indicated a registry collecting children and adolescents with and without heart disease as a useful tool to gather data on a larger, organized scale and to assess the true cardiovascular risk of psycostimulants [87].

Alcohol

Excess alcohol intake is a well known cause of hypertension [88–90]. Ambulatory BP monitoring has evidenced biphasic effects of alcohol on BP: a large intake of alcohol (>30 g) lowers BP in the first 4 h after ingestion, but BP increases approximately 10–15 h later [91]. This might account for the discrepancies existing in the literature about alcohol-induced BP effects [92]. Chronic consumption of three standard drinks (8–10 g of alcohol per drink) or more per day usually implies a raise in BP, whereas below this threshold the data are less consistent [90]. However, according to a recent systematic review of 12-cohort longitudinal studies, the risk of hypertension increases linearly with alcohol consumption in both men and women [93]. Perhaps less known is that heavy alcohol intake renders BP much more difficult to control and can be a cause of RHT [91,92,94,95].

The mechanisms by which alcohol increases BP remain unclear. Potential explanations include stimulation of the sympathetic nervous system, activation of the renin–angiotensin–aldosterone system, and abnormal calcium-mediated vasoconstriction [96]. The susceptibility to alcohol-induced hypertension could be under genetic control: a cohort study showed that the met-met genotype of cathecol-O-methyl transferase was associated with a greater reduction in BP with reducing alcohol intake or abstinence following prolonged heavy drinking [97]. If confirmed, these findings could contribute to explaining the marked variation in susceptibility to alcohol-induced BP elevation.

Given the unclear pathophysiologic mechanisms, the choice of the antihypertensive drug remains mostly empiric, with the ACE inhibitors and calcium channel blockers being the most frequently used agents.

Caffeine

Data from cross-sectional studies provide a little support for a BP-raising effect of caffeine, with the possible exception for BP measured shortly after coffee intake. They rather suggest an inverse linear or a U-shaped relation between coffee intake and BP in habitual coffee drinkers [98–105], although this relationship may be absent at the young age [106]. Prospective epidemiological studies also do not provide a clear picture, with a few studies showing a lower risk of hypertension in abstainers and in individuals with a relatively high coffee intake [107,108] and others showing an association between coffee consumption and BP [109,110]. Moreover, sex might influence the relation of coffee with BP, as women would have a lower risk of hypertension even at higher intakes (>4–6 cups/day) (see [111]).

The mechanisms by which caffeine can affect BP include sympathetic over-activation, antagonism of adenosine receptors, increased norepinephrine release, renal effects, and activation of the renin–angiotensin system [112–114]. However, caffeine can also induce endothelium-dependent vasodilatation [115], which can explain why it lowers BP in some individuals. In experimental studies, caffeine administration acutely raised BP, but tolerance to this effect developed rapidly and heavy coffee drinkers are less likely to show a BP response after caffeine intake [112,113,116].

Coffee is a rich source of polyphenols, including chlorogenic acid and isoflavonoids [117–119], which suggests that these substances can outweigh the pressor effects of caffeine. The results of the prospective study in US Nurses [108], which showed that caffeinated cola, being poor in polyphenols, increased the risk of hypertension, whereas coffee did not support this hypothesis.

Clozapine

Clozapine, a drug used to treat schizophrenic symptoms in patients refractory to classical antipsychotics, may raise BP by sympathetic activation, thus causing a syndrome known as 'pseudopheochromocytoma' [120]. Sympathetic over-activity and BP usually normalize upon treatment discontinuation, but it remains controversial whether long-term use of clozapine may induce hypertension [121,122].

Modafinil

The Food and Drug Administration approved this psychostimulant agent in 1998 for the treatment of daytime sleepiness in narcolepsy. Because it is more potent than caffeine and apparently does not have the addiction potential of amphetamines, its use has rapidly expanded for the treatment of many other conditions such as fatigue, depression, deficiency of attention in hyperactive disorders, or sleepiness caused by other drugs. As modafinil causes sustained adrenomedullary activation, it may raise heart rate and BP (SBP +7.3 mmHg, DBP +1.9–5.3 mmHg) [123,124], which needs increase in the number of antihypertensive medications [125]. Hence, use of modafinil should be restricted to approved indications and BP monitored during therapy.

Sympathomimetic amines

Sympathomimetics are widely used over-the-counter nasal decongestionants, and cold and flu remedies [126]. Owing to illicit conversion to methamphetamine, restriction has been imposed on the sale of pseudoephedrine; therefore, this drug has been replaced by phenylephrine. Like amphetamines, sympathomimetics cause vasoconstriction and raise BP via α1-adrenergic receptor stimulation. As the nasal blood vessels are about five times more sensitive to adrenaline than the heart vessels, sympathomimetic amines used at low doses in over-the-counter preparations usually exert minimal cardiac effects. However, the overuse of phenylephrine can cause severe hypertension in some patients, particularly in those taking monoamineoxidase inhibitors (MAOIs) [127].

Angiogenesis and kinase inhibitors

Angiogenesis is critical for the development, growth, and spread of cancer. Crucial for this process is the vascular endothelial growth factor (VEGF) acting via vascular endothelial growth factor receptor (VEGFR)-1 and VEGFR-2 receptors. Therefore, blockade of the VEGFR-2 signalling pathway represents an effective strategy for many solid tumours [128].

Three inhibitors of VEGF signalling have been approved by the US Food Drug Administration: the humanized monoclonal antibody bevacizumab that binds VEGF; sorafenib; and sunitinib which inhibit the receptor tyrosine kinase (RTK) involved in the downstream signalling of VEGF [129]. They are collectively referred as VEGF signalling pathway inhibitors (VSPI). The yet unapproved RTK inhibitors (RTKIs) aflibercept, axitinib, cediranib, motesanib, and vandetanib, and the VEGF-Trap, also belong to this class, but information on their pressor effects lacks [130]. Inhibition of angiogenesis was originally expected to produce minimal side-effects, but experience with VSPIs thereafter showed that hypertension is common [131]. It was seen in 20–30% of the patients receiving bevacizumab, and in 15–60% of patients treated with other RTKIs [132]. According to a meta-analysis of randomized controlled trials, the RR of developing hypertension with bevacizumab would be dose-related, with an incidence of hypertension ranging between 2.7 and 32% with a low dose (3–7.5 mg/kg) and between 17.6 and 36% with a high dose (10–15 mg/kg) [133]. The severity of hypertension was variable, with rare reports of malignant hypertension complicated by stroke with bevacizumab and also with sunitinib [134,135].

Hypertension occurs early and disappears slowly with withdrawal of VSPI therapy. This temporal association would suggest that hypertension is directly related to the on target therapeutic effect of VSPIs. Nonetheless, the mechanisms of VSPI-induced hypertension are poorly understood. According to the prevailing view, as VEGF modulates vascular contractility and upregulates endothelial nitric oxide synthase (eNOS) *in vitro*, the major pressor mechanism of VSPIs would be inhibition of the release of vasodilating factors, such as NO [136], and a post-translational activation of eNOS with ensuing enhanced NO production [137–139]. The mechanisms by which the VEGF pathway affects BP seem, however, to be far more complex, as they also involve ET-1 and PGI_2 release, endothelial cell apoptosis, structural of functional capillary rarefaction, and impaired angiogenesis of vasa vasorum in large elastic arteries with ensuing aortic stiffness [139–143].

On the basis of the aforementioned on theoretical ground (level of evidence C), drugs promoting NO bioavailability, such as ACE-I and nebivolol, could be preferred [144,145]. Likewise, as angiotensin II induces expression of VEGF and VEGFRs via angiotensin II receptor, type 1 and angiotensin II receptor, type 2 receptors, respectively, there is a rationale to support the use of ACE-I or angiotensin II receptor blockers as first-line antihypertensive agents in patients receiving VSPIs, albeit conclusive evidences lack.

Finally, it must be mentioned that the clinically approved RTKIs are metabolized in the liver by the same CYP3A4 system that inactivate some antihypertensive agents such as verapamil and diltiazem [146]; therefore, the plasma concentrations may be reciprocally affected which can require dose adjustment of either agents [132].

Antidepressants

MAOI can cause severe hypertension in patients eating tyramine-containing foods or taking amphetamines by increasing the action of monoamines as norepinephrine at sympathetic nerve endings [147,148]. Treatment with oral MAOI should, therefore, be confined to patients with major depressive disorders which are resistant to other antidepressants.

Tricyclic antidepressants also increase the risk of hypertension [149]. A cohort study of 2981 individuals showed

that patients taking tricyclic antidepressants were more likely to have hypertension stage 1 (odds ratio 1.90, 95% CI 0.94–3.84, $P < 0.05$) and stage 2 (odds ratio 3.19, 95% CI 1.35–7.59, $P < 0.01$) [149]. Moreover, these agents can trigger hypertensive crises in patients with an unrecognized pheochromocytoma [150,151]. The selective inhibitors of serotonin re-uptake or of serotonin/norepinephrine dosedependently increased BP in a small proportion of the patients (about 1 and 5% of patients chronically assuming fluoxetine and venlafaxine, respectively) [147,152]; however, rapid normalization of BP occurred after discontinuation of treatment [153].

High-density lipoprotein-raising agents

Raising high-density lipoprotein (HDL)–cholesterol has been a dream in cardiovascular prevention for decades [154]. Torcetrapib, a cholesteryl ester transfer protein inhibitor that increases HDL–cholesterol, neither delayed the progression of coronary atherosclerosis nor did it lower but rather increased mortality and morbidity in two large trials: the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation and the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events study [155,156]. Torcetrapib is no longer being developed; however, in both studies, it raised BP (+4.6 and +5.4 mmHg, respectively, in SBP), possibly by increasing aldosterone secretion and Na^+ reabsorption [156,157]. It seems that these pressor effects are unique to torcetrapib and not common to other HDL-raising agents. Nonetheless, the lack of consideration to BP effect even in the more recent largely advertised Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis trial (ARBITER 6-HALTS) [158] indicates the need to pay more attention to the pressor effect of novel therapeutic strategies that are being proposed in cardiovascular prevention.

Anti-HIV treatment

Some reports retrospectively documented a high prevalence of hypertension in patients assuming the recent HAART [159,160]. A cohort study examining 5578 patients found that the risk of developing systolic hypertension was related to the duration of the treatment (2–5 years of treatment: OR 1.51, 95% CI 1.25–1.82; more than 5 years: OR 1.70, 95% CI 1.34–2.16) [159,160]. Another four studies reported an increase in SBP [161–164], which was attributed to enhanced arterial stiffness [165]. Not unexpectedly, this pressor effect was more marked in elderly patients and in those with higher baseline SBP [162,163]. However, this observation was not confirmed by two prospective studies that reported no association of this treatment with hypertension [166,167]. At present, given the poor knowledge of the underlying mechanisms, treatment of this form of hypertension remains empirical and recommendations cannot be given [161–165].

Conclusion

Drug-related RHT is common and can be diagnosed with a thorough history. The latter will avoid the undertaking of a complex and sometime invasive diagnostic work-up as well as unnecessary changes of the therapeutic regimen. Identification of the offending drug(s) and knowledge of the underlying pressor mechanisms are crucial steps for the success of treatment.

The immunosuppressant agents and the angiogenesis inhibitors (VSPI) have had a beneficial impact on the prognosis of patients with autoimmune disorders and cancer, respectively, at the cost of inducing hypertension in many. VSPI have increased the survival of these patients, who mostly comprise middle-aged or elderly patients and likely have concomitant conditions, such as hypertension and atherosclerosis, which increase their long-term risk of developing adverse effects. As many new VSPI molecules are in preclinical development and early phase clinical trials, a better understanding of the mechanisms by which they induce hypertension is urgent and represents one of the challenges for the next decade.

Acknowledgement

Conflict of interest

There are no conflicts of interest.

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