Circulatory therapeutics: use of antihypertensive agents and their effects on the vasculature

Ernesto L. Schiffrin *

Department of Medicine, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Québec, Canada
Hypertension and Vascular Research Unit, Lady Davis Institute for Medical Research, Montreal, Québec, Canada
Department of Medicine, McGill University, Montreal, Québec, Canada

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Abstract

This review addresses the use of the different antihypertensive agents currently available and some in development, and their effects on the vasculature. The different classes of agents used in the treatment of hypertension, and the results of recent large clinical trials, dosing protocols and adverse effects are first briefly summarized. The consequences on blood vessels of the use of antihypertensive drugs and the differential effects on the biology of large and small arteries resulting in modulation of vascular remodelling and dysfunction in hypertensive patients are then described. Large elastic conduit arteries exhibit outward hypertrophic remodelling and increased stiffness, which contributes to raise systolic blood pressure and afterload on the heart. Small resistance arteries undergo eutrophic or hypertrophic inward remodelling, and impair tissue perfusion. By these mechanisms both large and small arteries may contribute to trigger cardiovascular events. Some antihypertensive agents correct these changes, which could contribute to improved outcome. The mechanisms that at the level of the vascular wall lead to remodelling and can be beneficially affected by antihypertensive agents will also be addressed. These include vasoconstriction, growth and inflammation. The molecular pathways contributing to growth and inflammation will be summarily described. Further identification of these signalling pathways should allow identification of novel targets leading to development of new and improved medications for the treatment of hypertension and cardiovascular disease.

Keywords: antihypertensive drugs ● conduit arteries ● resistance small arteries ● endothelial function ● angiotensin converting enzyme inhibitors (ACEIs) ● angiotensin receptor blockers (ARBs) ● β-blockers ● calcium channel blockers ● oxidative stress ● inflammation ● nitric oxide

Antihypertensive agents

Antihypertensive agents are used as monotherapy only in a small number of hypertensive patients, since the majority of individuals with high blood pressure require two or more agents. Recommended combinations will be addressed after pointing out some of the salient features of the individual antihypertensive drugs (summarized in Table 1).

Diuretics

Diuretics, specifically thiazides and related drugs, are some of the most frequently employed antihypertensive agents. They are recommended by all guidelines, including WHO/ISH [1], JNC7 [2] in the USA, the British Hypertension Society Guidelines and the National Collaborating Center for Chronic Conditions recommendations [3], the Canadian Hypertension Education Program [4]

*Correspondence to: Ernesto L. SCHIFFRIN,
Department of Medicine, McGill University,
Montreal, Québec, Canada.

Tel.: 1-514-340-7538
Fax: 1-514-340-7539
E-mail: ernesto.schiffrin@mcgill.ca

Table 1 Antihypertensive agents and their mechanism of action and side effects

Agents	Mechanism of action
Diuretics	
Thiazides: hydrochlorothiazide, chlorthalidone, indapamide	Thiazides: mechanism unclear, related to natriuresis *via* the thiazide-sensitive chloride transporter (*SLC12A3*), leading to loss of sodium in tissues that reduces vasoconstriction. Side effects: hyponatremia, hypokalaemia, impotence, diabetes.
Loop diuretics: furosemide, bumetanide	Loop diuretics: similar to above, but not very effective except in renal failure with fluid overload. Effective in heart failure.
Potassium sparing diuretics: amiloride and triamtirene	Potassium sparing diuretics prevent K loss induced by thiazides, with which they are associated because they are not very potent.
Mineralocorticoid receptor blockers: spironolactone, eplerenone	Mineralocorticoid receptor blockers used alone not very potent, they retain potassium, very effective in hyperaldosteronism and in resistant hypertension (added in latter to other agents). Risk of hyperkalaemia, especially if GFR < 40 mL/min.
β-blockers	
Propranolol, timolol, nadolol, atenolol,metoprolol,bisoprolol, acebutolol, pindolol, carvedilol, labetalol.	Non-selective: propranolol, timolol, nadolol; β_1 selective: atenolol, metoprolol, bisoprolol; with intrinsic sympathomimetic activity: acebutolol, pindolol; combined α- and β-blockers: carvedilol, labetalol. Mechanism of action: reduced cardiac output, vasoconstriction except those that are α-blocking. Side effects: fatigue, Raynaud syndrome, weight gain, diabetes.
CCB	
Dihydropyridine: nifedipine, amlodipine, felodipine	
Non-dihydropyridine: diltiazem, verapamil	These agents act as vasodilators by blocking entry of calcium into the smooth muscle cells in the vascular wall. They may also have some anti-oxidant properties (nifedipine). CCBs induce oedema and flushing, sometimes headache and palpitations. There may be enhanced incidence of heart failure (in the INSIGHT study).
ACEI	
Captopril, enalapril, lisinopril, quinapril, cilazapril, perindopril, fosinopril, ramipril, benazepril, trandolapril	ACEIs inhibit ACE and generation of Ang II. Side effects include cough, rarely angioedema, and in renal failure they may induce hyperkalaemia. Occasionally they are associated with a transient worsening of renal function, although in long-term studies they protect kidney function, especially in diabetic nephropathy.
ARB	
Losartan, irbesartan, valsartan, candesartan, telmisartan, eprosartan, olmesartan	ARBs act by blocking AT_1 angiotensin receptors. Whether AT_2 receptor stimulation also participates has been suggested but remains controversial. They have very few side effects and are accordingly widely used as first line therapy in hypertension. They may also be used to replace ACEIs in patients who develop cough with the latter. They may occasionally also induce angioedema in patients who develop angioedema with ACEIs, so are not recommended in this situation. In renal failure they may induce hyperkalaemia. Occasionally they are associated with a transient worsening of renal function, although in long-term studies they protect kidney function, especially in diabetic nephropathy.
DRI	
Aliskiren	There is only one agent available currently. It acts by inhibiting activity of renin, therefore reducing formation of Ang I. It has few side effects, unless given at doses of 600 mg per day, at which it may induce diarrhoea through local effects.
α-adrenergic antagonists	
Phentolamine, phenoxybenzamine, prazosin, terazosin, doxazosin	These agents block α_1 adrenergic receptors in smooth muscle cells. Phentolamine is given i.v. and has been used as a test for pheochromocytoma, and phenoxybenzamine is used in preparation for surgery for the latter. The other three agents are fourth line treatments because they may cause heart failure (as shown in ALLHAT study [5]). They may produce severe hypotension on first administration.

Continued

Table 1 Continued

Agents	Mechanism of action
Centrally acting agents	
α-methyldopa, clonidine, reserpine, moxonidine	These agents act by generation of false neurotransmitters (α-methyldopa), as agonist of α₂ adrenergic receptors (clonidine), by depletion of central noradrenaline (reserpine) or centrally active imidazo-line receptor agonist (moxonidine). These agents may produce depression, somnolence, dry mouth (clonidine), blocked nose (reserpine), haemolytic anaemia (α-methyldopa).
Direct vasodilators	
Apresoline, minoxidil	Direct vasodilators act by opening potassium channels and as anti-oxidants. Minoxidil is particularly effective in chronic renal failure. Side effects include oedema, tachycardia, angina, headache, and in the case of minoxidil, hirsutism.
Endothelin antagonists	
ET$_A$ selective: darusentan, sitaxentan, ambrisentan, atrasentan, avosentan	These agents dilate small arteries and reduce inflammatory responses. They are approved for primary pulmonary hypertension. Darusentan has been used in a resistant hypertension trial. Avosentan has been used in proteinuric diabetic nephropathy. Side effects include headache, oedema, fluid overload and heart failure, and altered liver function.
ET$_{A/B}$: bosentan	

CCB = calcium channel blocker, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, DRI = direct renin inhibitor.

and other national guidelines. Their use is supported by numerous randomized clinical trials including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [5], the largest antihypertensive trial ever carried out. The antihypertensive mechanism of action of these agents is evidently related to their ability to increase sodium excretion as a result of binding to the thiazide receptor in the distal convoluted tubule in the kidney. Evidence for this is Gitelman's syndrome, in which inactivating mutations of *SLC12A3* that encodes for the thiazide-sensitive chloride transporter results in hypotension, hypokalaemia, metabolic alkalosis and hypocalciuria, and increased bone mineral density [6], all of which are effects seen when administering a thiazide diuretic. It is true, however, that the exact mechanisms whereby sodium loss which occurs usually only transiently, results in lower blood pressure, remains unclear, although it may be surmised that subtle reductions of intravascular volume, sodium content in the vascular wall, and other minute incremental changes that are not easily demonstrable and are hidden by compensatory mechanisms, result in reduced vascular tone and peripheral resistance.

Diuretics most frequently used include hydrochlorothiazide, indicated usually at doses of 6.25 to 25 mg per day, chlorthalidone (the diuretic used in Systolic Hypertension in the Elderly Program [7] and ALLHAT [5]) which is used at doses of 12.5 to 25 mg per day, and metolazone (zaroxolyn) given at doses of 2.5–5 mg per day. Indapamide is a closely related diuretic used at doses of 1.25–2.5 mg per day, which is supposed to induce less hypokalaemia and hyperuricaemia. Twenty-four hour duration of the effect of hydrochlorothiazide has been questioned. Concerns have been raised because of the ability of chlorthalidone to induce hypokalaemia more frequently than other agents. It should be noted that we often hear that low-dose thiazide diuretics are indi-cated, but the dose proven to reduce events in randomized controlled trials is chlorthalidone 25 mg per day, which is equivalent to hydrochlorothiazide 40 mg per day. Although hydrochlorothiazide may be given up to doses of 50 mg per day, it is unusual that doses higher than 25 mg per day are used. As mentioned above, hypokalaemia and hyperuricaemia are occasional to frequent with use of thiazide diuretics. However, overt gout is infrequent. In elderly patients who develop the syndrome of inappropriate secretion of antidiuretic hormone either as an effect of drugs, pneumonia, brain lesions or idiopathically, the development of hyponatremia may occur as a result of action of a thiazide diuretic, and may be very severe. Orthostatic hypotension is also a side effect that may occur, especially when associated with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). *De novo* diabetes is a more frequent occurrence with thiazide diuretics than with other antihypertensive agents. In the publications of the ALLHAT [5] study it was suggested that this effect was unimportant since despite this, patients had a lower incidence of events (secondary end-points) during the course of the study than with the comparators (calcium channel blockers [CCBs] and ACEIs). The importance of hyperglycaemia and *de novo* diabetes induced by thiazide diuretics remains controversial, but it is possible that this may be detrimental over the long-term, beyond the period of 3–5 years of a randomized clinical trial. An additional important side effect in male patients is impotence, which occurs more frequently with thiazide diuretics than other antihypertensives. Thiazide diuretics lose their effectiveness when patients exhibit renal failure with serum creatinine above 250 μM.

Loop diuretics such as bumetanide or furosemide are not effective antihypertensive agents except in advanced renal failure,

in which they work to reduce blood pressure through volume reduction, and may be substituted for thiazide diuretics when serum creatinine is above 250 μM.

The potassium sparing diuretics amiloride and triamtirene are usually used in combination with thiazide diuretics. Mineralocorticoid receptor blockers, both the older non-selective spironolactone, and the newer selective agent eplerenone, are increasingly being used in resistant hypertension in which they have been shown to be very effective. These agents may be associated with hyperkalaemia in some patients, particularly diabetic individuals with hyporeninemic hypoaldosteronism, or in stage 3 to 4 renal failure. In the case of spironolactone, gynecomastia and impotence, the result of androgen receptor blockade due to the non-selectivity of this agent, may be a disagreeable side effect. Blockade of the action of aldosterone through mineralocorticoid antagonism may induce beneficial anti-inflammatory and anti-fibrotic cardiovascular effects, but the actual occurrence of this and the consequence on hard end-points has not been tested in hypertension randomized clinical trials.

β-blockers

β-blockers have been used as antihypertensive drugs for more than 30 years. Of the different classes of β-blockers, atenolol is one of the most used around the world. These agents are recommended for treatment of hypertension in younger individuals, who may have hyperadrenergic or labile hypertension with a hyperdynamic circulation and increased cardiac output. Increasingly it has become apparent that in older individuals, β-blockers are not as effective as other antihypertensive agents, as already shown by the MRC in the Elderly trial [8] and more recently with Blood Pressure Lowering Treatment Trialists' Collaboration. Some guidelines such as the Canadian Hypertension Education Program [4] and National Collaborating Center for Chronic Conditions [3] have suggested that they should not be used in the elderly unless there are compelling indications such as coronary heart disease.

Among the β-blockers used as antihypertensive agents, some are selective β_1, such as atenolol (25–100 mg once daily), bisoprolol (2.5–10 mg daily) or metoprolol (25–100 mg twice daily), although selectivity is probably lost at the higher doses. Some β-blockers are non-selective, such as nadolol (40–120 mg daily), propranolol (20–80 mg two to four times daily) or timolol (20–40 mg daily). Some β-blockers have intrinsic sympathomimetic activity, such as acebutolol (100–400 mg twice daily) or pindolol (10–20 mg twice daily). Finally there are β-blockers with combined α- and β-blocking effects like carvedilol (12.5–25 mg twice daily) and labetalol (100–400 mg twice daily).

β-blockers, particularly the non-selective and β_1 selective, may induce bradycardia, and rarely, especially if interacting with other cardiovascular agents, they may cause atrioventricular block or arrhythmias, but weakness, fatigue and weight gain, feeling of heavy limbs, Raynaud's phenomenon and cold extremities are not infrequent. They may also adversely affect the lipid profile with decreased HDL-cholesterol and increased triglycerides in serum, and are associated with increased *de novo* diabetes.

The mechanism of action of β-blockers as antihypertensive agents may depend on reduction of cardiac output. Paradoxically, they may increase peripheral resistance rather than lower it, and central blood pressure may not decrease as much as with other agents despite decreased peripheral pressure as a result of vascular effects that are discussed below. β-blockers, particularly lipid-soluble ones like propranolol and atenolol may have central effects, which is beneficial in the case of migraines, as these agents have specific anti-migraine effects. As well, it has been proposed that they may block β-adrenergic receptors that increase the action of angiotensin to stimulate the release of norepinephrine by nerve endings, thus reducing norepinephrine release and accordingly blood pressure.

Calcium channel blockers

CCBs act as peripheral vasodilators, by blocking entry of calcium through voltage-dependent calcium channels. They include dihydropyridines such as amlodipine (2.5–10 mg daily), felodipine (extended release form 5–20 mg daily) and nifedipine (nifedipine GITS used at doses of 20–90 mg daily), and non-dihydropyridine CCBs, such as diltiazem (extended release form 120–480 mg daily) and verapamil (extended release form at 120–360 mg daily). Ankle oedema is the main side effect, headache, flushing and palpitations may occur with dihydropyridines, constipation with verapamil. These agents appear to be metabolically neutral, and are associated with hyperglycaemia or with *de novo* diabetes to a lower degree than diuretics. Heart failure incidence may be increased with CCBs compared to diuretics as shown in ALLHAT [5] and INSIGHT [9].

Concerns that were raised about CCBs regarding potential precipitation of myocardial infarction, bleeding and cancer induced by these agents has been demonstrated not to be justified, and the safety of CCBs has been confirmed quite definitively by ALLHAT [5] and ASCOT [10]. There is some evidence that non-dihydropyridine CCBs may be more nephroprotective than dihydropyridine CCBs [11]. However, in general there is agreement that beyond the beneficial renoprotective effects of renin–angiotensin inhibition [12–15], all other agents protect the kidney through their blood pressure lowering action.

Angiotensin converting enzyme inhibitors

The role of the renin–angiotensin system (RAAS) in true renovascular hypertension is clear, but how the RAAS is involved in essential hypertension remains elusive. Plasma renin activity or concentration may be low or normal, or even high, for sodium balance, and yet blockade of the RAAS is often effective in up to 60–70% of patients in lowering blood pressure. This is probably in large measure due to lowering concentrations of angiotensin II (Ang II) in the circulation and in tissues. The exact contribution of the

inhibition of kinase II by ACEIs, with increases in the concentration of bradykinin, which has been implicated in cardioprotective effects of ACEIs, remains to be determined. There are many ACEIs: benazepril (10–40 mg once daily), captopril (25–100 twice daily), cilazapril (2.5–5 mg daily), enalapril (5–40, one to two times daily), fosinopril (10–40 mg daily), lisinopril (10–40 mg daily), perindopril (4–8 mg daily), quinapril (10–80 mg daily), ramipril (2.5–20 mg daily), trandolapril (1–4 mg daily).

The blood pressure lowering action of these agents is often enhanced significantly by the addition of a thiazide diuretic. ACEIs have been shown to have significant cardiovascular protective actions, to be particularly effective in heart failure, and to be nephroprotective. They seem however to be less effective than CCBs in the primary prevention of stroke [16]. Nevertheless and paradoxically, particularly when associated to a diuretic, ACEIs have been shown to be effective in the secondary protection of stroke [17].

Side effects of ACEIs include cough which may be found in 5–30% of patients and could relate to increased bradykinin and tachykinins in the larynx, and rarely angioedema, which may require intubation and that can be fatal. Occurrence of angioedema is unpredictable currently, and may appear initially or many years after starting the use of ACEIs, and is more frequent and may be more severe in blacks.

Angiotensin receptor blockers

ARBs probably lower blood pressure by similar mechanisms as ACEIs, that is, inhibition of the RAAS. The blockade of AT_1 angiotensin receptors is probably the main mechanism whereby ARBs inhibit the effects of the RAAS, and exert most of their beneficial effects. The contribution of unblocked AT_2 receptors, that are stimulated by the reactive increased concentrations of Ang II, and which stimulate the production of nitric oxide in the heart, vasculature and kidney, remains unclear [18]. ARBs include candesartan (8–32 mg daily), eprosartan (600–800 mg, one to two times daily), irbesartan (150–300 mg daily), losartan (25–100 mg, one to two times daily), olmesartan (20–40 mg daily), telmisartan (20–80 mg daily) and valsartan (80–320 mg daily).

Side effects of ARBs are rare. They have been suggested to be ideal for replacement of ACEIs when these induce cough. In case of angioedema with ACEIs, there is evidence that if patients are switched to an ARB, the angioedema may recur, and accordingly this is not recommended.

The question of whether ACEIs and ARBs can or should be used in association as an interesting therapeutic avenue was addressed by the ONTARGET trial recently [19]. In ONTARGET, the association of ramipril and telmisartan induced lower blood pressures than either agent alone, but also increased adverse side effects including hypotension and more importantly hyperkalaemia or acute renal failure requiring dialysis in a small minority of patients. Accordingly the association of ACEIs and ARBs has been abandoned as a therapeutic approach except for patients with heart failure based on the CHARM (added) study [20] or in

proteinuric nephropathy, since patients with the latter were not included in enough numbers in the trial. Thus there is no evidence for or against the association in patients with proteinuric nephropathy.

ACEIs *versus* ARBs *versus* CCBs *versus* diuretics

Because ARBs are associated with few side effects, they have been recommended by many as ideal to initiate antihypertensive treatment. It should however be remembered that in the comparative heart failure trials such as CHARM (overall) [21], ARBs have not been shown to be superior to ACEIs with respect to cardiovascular protection. In renal protection (RENAAL [13] and IRMA [14] and IDNT [15]), ARBs have been shown to be highly effective, but there are no direct comparisons with ACEIs, which are also renoprotective as demonstrated by the HOPE study [12]. In ONTARGET in high cardiovascular risk patients, the ARB telmisartan was not inferior to the ACEI ramipril [20]. Whereas valsartan was in general equivalent to amlodipine in VALUE, it controlled BP less fast, which may have been the reason for the slight excess of myocardial infarctions in the valsartan-based group in this trial [22]. In ALLHAT [5], chlorthalidone was superior for some secondary endpoints over lisinopril or amlodipine, but similar for the primary end-point, despite the fact that control of blood pressure was better with chlorthalidone. This is probably due to the way the protocol was designed and the inappropriate combinations of drugs used which resulted in this lesser blood pressure control in the lisinopril and amlodipine groups. As a result, there was excess heart failure in both lisinopril and amlodipine groups, and excess stroke in the lisinopril group. The latter was dependent in part on the reduced blood pressure control in blacks and associated in that group with increased stroke, whereas the rest of the cohort did not exhibit enhanced strokes. There is evidence from the LIFE study that ARBs may be more protective from stroke than the β-blocker atenolol [23]. The Blood Pressure Lowering Treatment Trialists' Collaboration [24] suggests that all agents produce similar beneficial effects as long as blood pressure is well controlled.

Direct renin inhibitors

Aliskiren is a new antihypertensive that acts by inhibiting renin activity [25]. It therefore blocks the RAAS at the origin of the cascade, inhibiting the generation of angiotensin I, and therefore that of Ang II and stimulation of aldosterone secretion by the latter. Aliskiren has a very long duration of action, since it remains bound to tissues for a prolonged period of time after cessation of therapy. It is administered in doses of 150 or 300 mg per day, and is well tolerated with few side effects. When administered to patients with eGFR around 30 ml/min., it should be used with caution since it may cause hyperkalaemia. Aliskiren is being tested in many trials. These include the recent AVOID trial [26] in which aliskiren reduced proteinuria in patients with hypertension, type 2 diabetes and diabetic nephropathy. In the Aliskiren Left Ventricular

Assessment of Hypertrophy Trial [27], aliskiren in combination with losartan reduced left ventricular mass in overweight patients with hypertension as effectively as either drug alone. Ongoing trials include Aliskiren Trial in type 2 diabetes using cardio-renal end-points [28], a cardiovascular and renal morbidity and mortality study of ~8600 type 2 diabetic patients at high risk for cardiovascular or renal events.

α-adrenergic blockers

α-adrenergic blockade would appear to be one of the main approaches to treat hypertension, but their use has not proven as useful as expected. Agents include doxazosin (1–16 mg daily), prazosin (1–10 mg 1–2 daily) and terazosin (1–20 mg daily). Doxazosin was used in ALLHAT, and the doxazosin arm was discontinued prematurely because of an excess of events [29]. Heart failure was associated with the use of doxazosin in this trial. Other side effects include serious hypotensive episodes after the first dose of the agent, nightmares and impotence. α-adrenergic blockers have been relegated by most guidelines to third or fourth line therapy following ALLHAT.

Centrally acting agents

When control of blood pressure is ineffective with three or more agents it is often necessary to appeal to these older agents despite their undesirable CNS effects. Centrally acting agents include methyldopa (125–500 mg, two to three times daily), clonidine (0.05–0.3 mg three times daily) and reserpine (0.1–0.25 mg daily). Blood pressure lowering is effective, but patients often complain of somnolence and dry mouth. Methyldopa may produce a Coombs positive haemolytic anaemia and a lupus-like syndrome. Reserpine is an excellent antihypertensive but produces depression and nasal congestion. As a consequence of their side effect profile, these agents are reserved as a fourth or fifth line of therapy.

Direct vasodilators

Among older drugs used to treat hypertension there are the direct vasodilators such as hydralazine (25–100 twice daily) and minoxidil (2.5–40 twice daily). These agents produce dilatation of small arteries and arterioles, but the blood pressure lowering is associated to sympathetic activation and thus requires concomitant use of a β-blocker to avoid tachycardia and potentially myocardial ischemia that has been described in patients treated with hydralazine. Minoxidil is particularly effective in chronic renal failure. Side effects of minoxidil include hypertrichosis, which is a limitation for administration to female patients. The mechanism of action of the direct vasodilators is not well known but has been suggested to relate to potassium channel opening and to anti-oxidant action. Side effects of hydralazine include a lupus-like syndrome.

Mineralocorticoid receptor blockers

Spironolactone has been used for many years as a potassium-sparing diuretic, often in association with thiazide diuretics, but was not shown to be very potent as an antihypertensive agent. However, more recently, it has become apparent that in resistant hypertension, in which there is often a component of hyperaldosteronism, spironolactone will induce quite significant blood pressure lowering [30]. In the 4E Study (eplerenone, enalapril, and eplerenone/enalapril combination therapy in patients with left ventricular hypertrophy [LVH]) [31], comparison of treatment with eplerenone, a newer mineralocorticoid receptor blocker, to enalapril or eplerenone plus enalapril in patients with mild-to-moderate hypertension and echocardiographic evidence of LVH showed effective reduction of LVH by treatment with eplerenone similarly to enalapril, whereas the combination induced an even greater LVH reduction. Addition of spironolactone in the Randomized Aldactone Evaluation Study, reduced mortality by 30% in patients with New York Heart Association class 3 or 4 heart failure, who were already treated with an ACEI, diuretics, and digoxin [32]. In the Eplerenone Neurohormonal Efficacy and Survival Study trial, heart failure after myocardial infarction in patients already on therapy with ACEIs, ARBs, β-blockers, digoxin and diuretics, all cause and cardiovascular mortality were significantly improved by treatment with eplerenone [33].

Spironolactone is used in doses of 12.5 to 25 mg per day for hypertension and heart failure, and up to 100 to 400 mg per day in cases of primary hyperaldosteronism. Side effects include gynecomastia and impotence as a result of its anti-androgenic effect, and hyperkalaemia. The latter must be carefully monitored since many of the patients taking spironolactone are also on non-steroidal anti-inflammatory drugs, ACEIs or ARBs, compounding the hyperkalemic effect, or are diabetic and may have chronic kidney disease. In fact the use of these agents in patients with eGFR lower than 40 ml/min. is associated with hyperkalaemia, often difficult to control. Eplerenone is used in doses of 25–50 mg per day since it is less powerful a drug than spironolactone. It does not have anti-androgenic effects, and accordingly has less adverse side effects. However it is just as able to induce hyperkalaemia, which must be monitored, especially in those patients taking other RAS inhibitors or non-steroidal anti-inflammatory drugs, or who have lower eGFR. In fact, with the increased use of mineralocorticoid receptor blockade especially in heart failure, hyperkalaemia has become a more frequently observed undesirable and even dangerous side effect in cardiovascular therapy [34]. Eplerenone is metabolized primarily by CYP3A4. Therefore, inhibitors of CYP3A4 including grapefruit juice should be avoided in patients taking this drug.

Endothelin receptor antagonists

Blockers of endothelin receptors may bind with high affinity to type A endothelin receptors (ET$_A$R) and/or to type B endothelin

receptors (ET$_B$R) [35]. The endothelin system is activated in severe hypertension (stage 2), heart failure and primary pulmonary hypertension, and is associated with vascular remodelling, endothelial dysfunction, cardiovascular fibrosis and extended atherosclerosis. Endothelin antagonists may be dual ET$_A$R and ET$_B$R blockers such as bosentan (although binding with higher affinity to ET$_A$R), or predominant or highly selective ET$_A$R antagonists, such as darusentan, atrasentan, ambrisentan, avosentan, sitaxsentan. Bosentan and sixtasentan are approved for use in primary pulmonary hypertension. Bosentan, atrasentan and darusentan have been tested in hypertensive patients, and recently the DORADO trial has demonstrated that darusentan is effective in resistant hypertension [36]. Patients with systolic blood pressure of 140 mm Hg or more ($>$130 mm Hg if patient had diabetes or chronic kidney disease) on doses of at least full three antihypertensive drugs, including a diuretic, were treated for 14 weeks with placebo or darusentan 50, 100 or 300 mg once daily. Systolic and diastolic blood pressures were lowered 17/10 mm Hg with 50 mg, 18/10 mm Hg with 100 mg and 18/11 mm Hg with darusentan 300 mg ($P < 0.0001$). The main adverse effects were oedema or fluid retention in 27% of patients given darusentan. A total of five patients on darusentan had serious cardiac adverse events. The authors concluded that darusentan provides additional reduction of blood pressure in patients with resistant hypertension, but as with other vasodilatory drugs, diuretic therapy might be needed for management of fluid retention [36].

Effects of antihypertensive treatment on blood vessels

Antihypertensive therapy and large artery stiffness

Antihypertensive agents affect the vascular wall both directly and indirectly, the latter as a result of the effect that blood pressure has acting on the wall of blood vessels. Blood pressure lowering produces a shift to the more compliant segment of a compliance–pressure curve, so that more elastin and less collagen are determining vascular stiffness. The linking of collagen to smooth muscle cells and the degree of tensing of the collagen jacket may play an important role in the effects of antihypertensive agents on the vascular wall. The contribution of collagen to stiffness of the vessel wall occurs in the latter portion of the pressure curve, since collagen fibres may be coiled and not under tension until the smooth muscle cells in series and the elastin in parallel have been stretched. In the remodelled artery, with rearranged cellular and fibrillar components due to changes in the interaction of these structures, the collagen fibres may be recruited at higher distending pressures in some vessels which exhibit decreased stiffness, or collagen fibres may be increased in density in other vessels which exhibit increased stiffness such as the aorta.

However, antihypertensive therapy may also have direct effects on the vascular wall. CCBs, ACEIs, ARBs, mineralocorticoid receptor blockers and nitrates may alter the mechanical properties of conduit arteries. The changes which occur may depend on the agent and dose used, the degree to which blood pressure is lowered, and the vascular bed examined. Whereas nitrates may increase compliance by vasodilation, ACEIs and CCBs may decrease stiffness (elastic modulus) without affecting arterial diameter [37]. ARBs [38] and mineralocorticoid receptor blockers [39] also exert direct effects on conduit blood vessels resulting in decreased stiffness. Some of these effects are related to the ability of ACEIs, ARBs, CCBs and mineralocorticoid receptor blockers to exert anti-fibrotic actions, usually as a result of downregulation of expression of transforming growth factor-β (TGF-β). This leads to decreased activation of SMADs that are transcription factors that mediate the action of TGF-β on collagen synthesis, and consequently reduced vascular stiffness as less collagen is deposited in the media of large vessels. At the same time, similar changes in small arteries that reduce impedance and wave reflection, contribute to delay the latter and reduce augmentation of pulse pressure in the proximal aorta. With decreased augmentation and reduction of central pressure, aortic systolic blood pressure is lowered, decreasing afterload on the heart. β-blockers on the other hand, appear not to result in changes in compliance or distensibility of large vessels.

Antihypertensive therapy and small artery structure

We and others have proposed the idea that to improve clinical outcome in hypertensive patients therapy must induce regression of vascular remodelling [40]. The failure to produce regression of vessel wall changes may explain the limited success in preventing hypertension-related coronary events when blood pressure-lowering is the sole therapeutic aim.

Several studies have examined the beneficial effects of antihypertensive agents on small artery structure. Angiotensin-converting enzyme inhibition with cilazapril [41, 42] or perindopril [43] normalized structure of gluteal subcutaneous small arteries from essential hypertension patients. Similar results have more recently been demonstrated with other renin–angiotensin blockers, particularly the ARBs, which have corrected both small artery structure and endothelial function in patients with essential hypertension [44, 45]. Calcium channel blockade may also normalize small artery structure [46, 47]. In contrast, antagonism of β-adrenoceptors with atenolol appears ineffective in improving small artery structural abnormalities [39–45].

Whether the reversal of structural abnormalities demonstrated in gluteal subcutaneous arteries will result in improved clinical outcome remains to be determined [37]. However, regression of structural and functional abnormalities of gluteal subcutaneous arteries from hypertensive patients may be associated with improved structure and function of other more critical vascular beds such as the coronary circulation, as shown by indirect measurements [48–50]. The prognostic importance of small artery
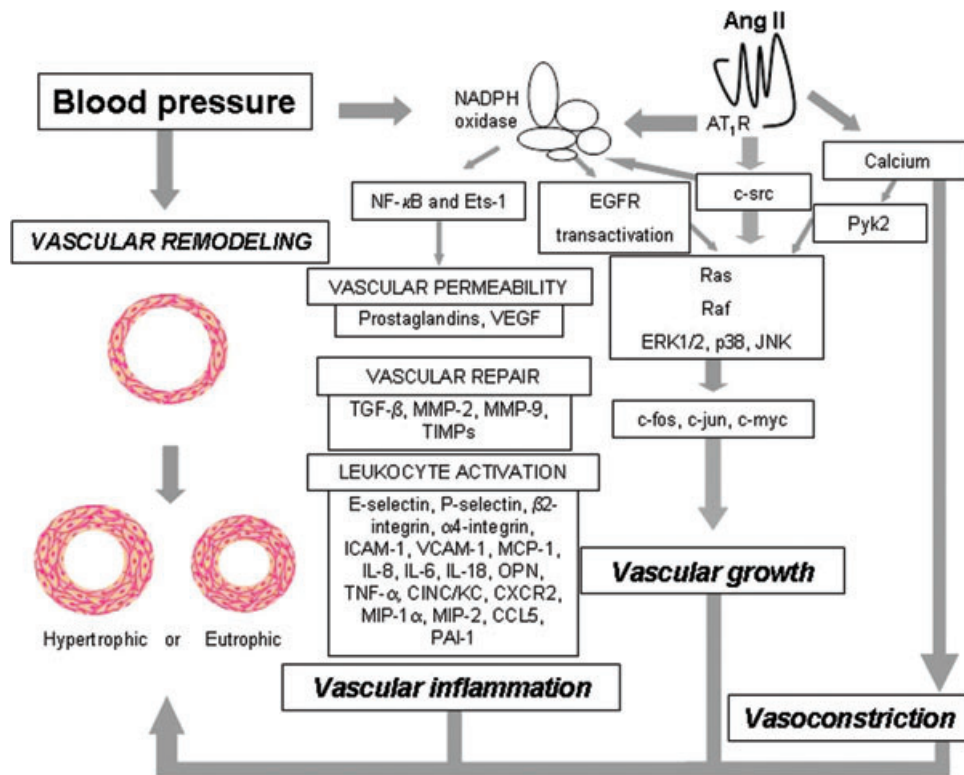
Fig. 1 Small artery remodelling may be eutrophic when media-to-lumen ratio is enhanced but media cross-sectional area is not, or hypertrophic, when both are increased. In both forms, when media lumen is reduced the remodelling is called inward remodelling. Blood pressure elevation directly affects remodelling of blood vessels by increasing media stress and stimulation of mechanoreceptors. It may also stimulate oxidative stress in the vascular wall by enhancing reduced NADPH oxidase. Remodelling of the wall is importantly affected by Ang II, stimulates calcium release leading to vasoconstriction, which may become embedded as deposition of extracellular matrix occurs, also under the influence of Ang II. Growth, inflammation and repair processes interact with vasoconstriction to contribute to remodelling. Ang II enhances all the stages of the inflammatory response: vascular permeability through prostaglandins and vascular endothelial growth factor, leucocyte recruitment and activation through selectins, integrins, adhesion molecules, cytokines and chemokines, and vascular repair processes through mediators of cell growth and fibrosis. Ang II-induced vascular inflammation is mediated through differentially countervailing modulation of vascular wall effectors by its AT_1R and AT_2R, the former being mainly pro-growth and pro-inflammatory and the latter anti-growth and anti-inflammatory. CCL5, CC chemokine ligand 5; CINC/KC, cytokine-inducible neutrophil chemoattractant/keratinocyte-derived chemokine; CXCR2, CXC chemokine receptor 2; EGFR, epidermal growth factor receptor; ERK, extracellular regulated kinase; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; IGF, insulin growth factor; JNK, c-Jun N-terminal kinase; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; MMP, matrix metalloprotease; OPN, osteopontin; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of MMP; TNF-α, tumor necrosis factor-α. VCAM-1, vascular cell adhesion molecule-1.

remodelling has been demonstrated by a study that showed that greater remodelling (media to lumen ratio) of small arteries was associated to more frequent cardiovascular events in a cohort of hypertensive patients [51]. Interestingly, the beneficial effects of blockade of the RAAS on structural remodelling of small arteries of hypertensive patients are also found on vessels from high risk patients with type 2 diabetes mellitus [52, 53].

Aldosterone is recognized as an agent that induces collagen deposition and remodelling in pathophysiological conditions [54]. Accordingly, it is not surprising that treatment of hypertensive patients with eplerenone, a selective mineralocorticoid receptor blocker, resulted in reduced stiffness of both large arteries [55] and small arteries [56]. Interestingly, in the latter study, neither remodelling of small arteries nor endothelial function was improved by treatment with eplerenone, although blood pressure was normalized. However, collagen deposition and the collagen-to-elastin ratio were reduced [56].

Although blockade of the renin -angiotensin system would be expected to result in improved vascular structure through inhibition of the growth-promoting, pro-oxidative and pro-inflammatory action of Ang II [57], it has been argued that correction of small artery remodelling occurs mainly as a result of vasodilatation [58]. Arguments in favour are the fact that vasoconstriction contributes to the mechanism of small artery remodelling [59], and that changes in flow associated with different states of vasodilation modulate vascular remodelling [60]. This may explain the absence of correction of vascular remodelling found with agents such as atenolol [41–47] which induces peripheral vasoconstriction [61].

As shown in Fig. 1, it is likely that the inhibition of AT_1 receptor stimulation by either reduction of angiotensin levels in plasma by ACEIs or blockade of the receptor by ARBs will result in reduction of intracellular calcium and diminished activation of calcium-dependent kinases like Pyk-2, a member of focal adhesion kinase family. It will also lead to reduced nicotinamide

adenine dinucleotide (NADPH) oxidase activation, with a decrease in the generation of reactive oxygen species, decreased PDGF and EGF receptor transactivation and subsequently, diminished activity of the MAP kinase pathway, including ERK1/2, p38MAPK and c-Jun N-terminal kinase, as well as the JAK/STAT pathway [62]. These different pathways will then through diminished effects of proto-oncogenes such as c-fos, c-jun and c-myc and other transcription factors, lead to reduced growth of smooth muscle and remodelling. As well, a reduced inflammatory response will be found when NF-κB activation is decreased, leading to diminished adhesion molecule expression and less attraction of leucocytes into the vascular wall. Together with reduced TGF-β stimulation, and reduced fibrosis, the blunting of oxidative stress and inflammation in the vascular wall by these agents will result in regression of remodelling of the vasculature (Fig. 1).

Antihypertensive therapy and small artery function

As with small artery structure, numerous studies have investigated the effects of antihypertensive therapy on small artery function. ACE inhibition restores endothelial function variably, as measured by acetylcholine-induced relaxation. Following 2-year treatment with the ACEI cilazapril, abnormal endothelium-dependent relaxation of small human arteries *in vitro* was normalized [63]. However, short-term treatment with enalapril or cilazapril failed to regress endothelial dysfunction measured *in vivo* [64, 65]. Treatment with ARBs corrected endothelial dysfunction [44, 45, 66]. Chronic calcium channel blockade also normalized endothelial function in one study [46] but not in another [47]. Interestingly, as with structural abnormalities, β-adrenoceptor blockade with atenolol did not improve endothelial function [40, 42, 44, 63]. These studies collectively show that in essential hypertension, normalization of endothelial function may depend specifically on the antihypertensive agent, rather than on the blood pressure-lowering effect of the drug. Similarly, in early type 2 diabetes, ARBs normalized endothelial function [67]. However, in patients with advanced type 2 diabetes and hypertension addition of an ARB on top of previous antihypertensive therapy that included ACEIs and CCBs did not improve endothelial function even though structure of small arteries was partially corrected [52]. Thus, it would appear that regression of remodelling of blood vessels is divorced from the improvement in endothelial function. This could mean that either the mechanisms operating are different in the media and the endothelium, or that one is more resistant to improved blood pressure and molecular effects of antihypertensive agents. One explanation for this may be the role of different subunits of NADPH oxidase (nox1, nox2 and nox4) in smooth muscle and endothelium [68]. The generation of vasodilator hydrogen peroxide in endothelium is another difference between endothelial reactive oxygen species and smooth muscle cell-generated free radicals. As well, endothelial heme-oxygenase-1 generates carbon monoxide, which is also a vasodilator. The relationship between endothelium and the remainder of the wall is

currently being investigated among others using co-culture of endothelial and smooth muscle cells.

Effect of antihypertensive treatment on arterioles

Arterioles with lumen diameters smaller than 100 μm are also an important site of vascular resistance [69]. As with small arteries, some arterioles undergo eutrophic remodelling in hypertension; for example, pial arterioles in stroke-prone spontaneously hypertensive rats, in which in fact this phenomenon was first described [70]. Regression of structural remodelling towards normal, similar to that found in small arteries, has been reported to occur in arterioles of the brain in stroke-prone spontaneously hypertensive rats under antihypertensive therapy with ACEIs [71]. Similarly to their effects on structure, ACEIs may be more effective than β-blockers in improving the impaired cerebral vasodilatation of chronic hypertension [72].

The contribution of very small arterioles to increased resistance may occur *via* an alternate mechanism which has been called rarefaction, characterized by a reduction in the number of vessels per unit surface [73]. Rarefaction may be functional and reversible, or represent a permanent (anatomical) reduction of arteriolar and capillary density. It has been reported in several vascular beds of rat models of hypertension, including one kidney-one clip and spontaneously hypertensive rats, and in human beings with hypertension. The extent to which rarefaction augments peripheral resistance has been estimated to represent between 15% and 20% of total peripheral resistance in some experimental models, but its definitive impact on blood pressure elevation remains to be established. The effect of antihypertensive therapy on rarefaction has not been demonstrated in human beings. There is some evidence that in experimental animals, rarefaction may be improved by ACEIs [74].

Conclusions and future perspectives

Changes in vascular structure and function play important roles in the pathophysiology of hypertension, and together with atherosclerosis, in the complications of hypertension. The limited improvement in cardiac-related clinical outcome in randomized multicenter clinical trials by therapy aimed only at lowering blood pressure suggests that the goals of antihypertensive treatment should be broadened to include correction of the structural and function abnormalities in blood vessels of essential hypertensive patients, since these changes could play a role in the pathogenesis of complications of high blood pressure. This hypothesis, although reasonable, requires proof in large randomized multicenter clinical trials demonstrating improvement of hard end-points associated with correction of the surrogate vascular end-points discussed in this chapter. Up to the present, although some studies like HOPE [12] and LIFE [23] have suggested blood

pressure-independent effects that could imply a vascular protective action of some antihypertensive agents, current evidence from other large prospective studies [5] and meta-analyses [24, 75] indicates that effects found are not blood pressure independent but rather the result of blood pressure lowering, which seems to exert the greatest cardiovascular protective action in hypertension.

What awaits us in the next few years in this field? There is no doubt that the evidence with the renin inhibitor aliskiren will continue to accrue, and that other renin inhibitors may be added to the therapeutic arsenal. Trials will indicate whether these agents provide the same or better cardiovascular protection to hypertensive patients. New data with these and other agents will demonstrate whether blood vessels, large and small, are equally or better protected and whether regression of vascular remodelling and improved vascular function is achieved with these agents at the level of large and small vessels, and whether this is associated with better outcome for patients with respect to cardiovascular and all cause morbidity and mortality. Studies of vessels from rodents and human beings will allow identification of new molecular targets and development of new agents that may target the remodelled vessel and allow return to a more normal vascular structure and function which may result in improved outcome. Co-culture experiments using endothelial cells and smooth muscle cells are already elucidating some of the different molecular mechanisms operating in both types of cells contained in the vascular media. Crosses of rodents with deletion of genes involved in vas-

cular remodelling and atherosclerosis are already revealing some of the signalling pathways that cross-talk and need to be targeted therapeutically in the near future. I believe that the future is bright in this field, and that progress will be made in future years, particularly with development of new approaches to less invasively image at the molecular level the vasculature of human beings with hypertension and other cardiovascular diseases.

Acknowledgements

Conflict of interest

In the past 2 years the author has served in advisory boards of Bristol Myers-Squibb, Daiichi-Sankyo, Novartis, Pfizer and has received research awards from Cardiovascular Pfizer Award and Canadian Institutes of Health Research.

References

1. **Whitworth JA, Chalmers J.** World Health Organisation-International Society of Hypertension (WHO/ISH) hypertension guidelines. *Clin Exp Hypert.* 2004; 26: 747–52.
2. **Chobanian AV, Bakris GL, Black HR, et al.** Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JNC 7-complete version. *Hypertension.* 2003; 42: 1206–52.
3. **The National Collaborating Center for Chronic Conditions.** Hypertension: management in adults in primary care: pharmacological update. London: Royal College of Physicians, 2006.
4. **Khan NA, Hemmelgarn BR, Herman RJ.** The 2009 Canadian Hypertension Education Program (CHEP) recommendations for the management of hypertension: part 2- therapy. *Can J Cardiol.* 2009; 25: 287–98.
5. **The ALLHAT Officers and Coordinators.** Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Am Med Assoc.* 2002; 288: 2981–97.
6. **Ecelbarger CA, Tiwari S.** Sodium transporters in the distal nephron and disease implications. *Curr Hypertens Rep.* 2006; 8: 158–65.
7. **SHEP Cooperative Research Group.** Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *J Am Med Assoc.* 1991; 265: 3255–64.
8. **Medical Research Council Working Party.** Medical Research Council trial of treatment of hypertension in older adults: principal results. *Brit Med J.* 1992; 304: 405–12.
9. **Brown MJ, Palmer CR, Castaigne A, et al.** Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet.* 2000; 356: 366–72.
10. **Poulter NR, Wedel H, Dahlöf B, et al.** Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-blood pressure lowering arm (ASCOT-BPLA). *Lancet.* 2005; 366: 907–13.
11. **Bakris GL, Copley JB, Vicknair N, et al.** Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int.* 1996; 50: 1641–50.
12. **Heart Outcomes Prevention Evaluation Study Investigators.** Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet.* 2000; 355: 253–9.
13. **Brenner BM, Cooper ME, de Zeeuw D, et al.** Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001; 345: 861–9.

14. **Parving H-H, Lehnert H, Brochner-Mortensen J**, *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001; 345: 870–8.

15. **Lewis EJ, Hunsicker LG, Clarke WR**, *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001; 345: 851–60.

16. **Hansson L, Lindholm LH, Niskanen L**, *et al.* Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 1999; 353: 611–6.

17. **PROGRESS Collaborative Group**. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001; 358: 1033–41.

18. **Carey RM**. Cardiovascular and renal regulation by the angiotensin type 2 receptor: the AT_2 receptor comes of age. *Hypertension*. 2005; 45: 840–4.

19. **The ONTARGET Investigators**. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008; 358: 1547–59.

20. **McMurray JJV, Östergren J, Swedberg K**, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003; 362: 767–71.

21. **Pfeffer MA, Swedberg K, Granger CB**, *et al.* Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-overall programme. *Lancet*. 2003; 362: 759–66.

22. **Julius S, Kjeldsen SE, Weber M**, *et al.* Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. *Lancet*. 2004; 363: 2022–31.

23. **Dahlöf B, Devereux RB, Kjeldsen SE**, *et al.* Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002; 359: 995–1003.

24. **Turnbull F, and the Blood Pressure Lowering Treatment Trialists' Collaboration**. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003; 362: 1527–35.

25. **Brown MJ**. Aliskiren. *Circulation*. 2008; 118: 773–84.

26. **Parving H-H, Persson F, Lewis JB**, *et al.* Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med*. 2008; 358: 2433–46.

27. **Solomon SC, Appelbaum E, Manning WJ**, *et al.* Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation*. 2009; 119: 530–7.

28. **Parving HH, Brenner BM, McMurray JJ**, *et al.* Aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE): rationale and study design. *Nephrol Dial Transplant*. 2009; 24: 1663–71.

29. **The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group**. Major cardiovascular events in hypertensive patients randomized to doxazosin vs. chlorthalidone – The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Am Med Assoc*. 2000; 283: 1967–75.

30. **Calhoun DA, Jones D, Textor S**, *et al.* Resistant hypertension: diagnosis, evaluation, and treatment: A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension*. 2008; 51: 1403–19.

31. **Pitt B, Reichek N, Willenbrock R**, *et al.* Eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: The 4E–Left Ventricular Hypertrophy Study. *Circulation*. 2003; 108: 1831–8.

32. **Pitt B, Zannad F, Remme WJ**, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999; 341: 709–17.

33. **Pitt B, Remme W, Zannad F**, *et al.* Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003; 348: 1309–21.

34. **Juurlink DN, Mamdani MM, Lee DS**, *et al.* Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004; 351: 543–51.

35. **Schiffrin EL**. Vascular endothelin in hypertension. *Vasc Pharmacol*. 2005; 43: 19–29.

36. **Weber MA, Black H, Bakris G**, *et al.* A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009; 374: 1423–31.

37. **Van Vortel LM, Kool MJ, Struijker-Boudier HA**. Effects of antihypertensive agents on local arterial distensibility and compliance. *Hypertension*. 1995; 26: 531–4.

38. **Benetos A, Gautier S, Laflèche A**, *et al.* Blockade of angiotensin II type 1 receptors: Effect on carotid and radial artery structure and function in hypertensive humans. *J Vasc Res*. 2000; 37: 8–15.

39. **Davies J, Gavin A, Band M**, *et al.* Spironolactone reduces brachial pulse wave velocity and PIIINP levels in hypertensive diabetic patients. *Brit J Clin Pharmacol*. 2005; 59: 520–3.

40. **Schiffrin EL**. Effects of antihypertensive drugs on vascular remodeling: do they predict outcome in response to antihypertensive therapy? *Curr Opin Nephrol Hypertens*. 2001; 10: 617–24.

41. **Schiffrin EL, Deng LY, Larochelle P**. Effects of a β-blocker or a converting enzyme inhibitor on resistance arteries in essential hypertension. *Hypertension*. 1994; 23: 83–91.

42. **Schiffrin EL, Deng LY, Larochelle P**. Progressive improvement in the structure of resistance arteries of hypertensive patients after 2 years of treatment with an angiotensin converting enzyme inhibitor. Comparison with effects of a beta blocker. *Am J Hypertens*. 1995; 8: 229–36.

43. **Thybo NK, Stephens N, Cooper A**, *et al.* Effect of antihypertensive treatment on small arteries of patients with previously untreated essential hypertension. *Hypertension*. 1995; 25: 474–81.

44. **Schiffrin EL, Park J-B, Intengan HD**, *et al.* Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan. *Circulation*. 2000; 101: 1653–9.

45. **Schiffrin EL, Park JB, Pu Q**. Effect of crossing over hypertensive patients from a beta-blocker to an angiotensin receptor antagonist on resistance artery structure and on endothelial function. *J Hypertens*. 2002; 20: 71–8.

46. **Schiffrin EL, Deng LY**. Structure and function of resistance arteries of hypertensive patients treated with a β-blocker or a calcium channel antagonist. *J Hypertens*. 1996; 14: 1247–55.

47. **Schiffrin EL, Pu Q, Park JB**. Effect of amlodipine compared to atenolol on small

arteries of previously untreated essential hypertensive patients. *Am J Hypertens*. 2002; 15: 105–10.

48. **Motz W, Strauer BE**. Improvement of coronary flow reserve after long-term therapy with enalapril. *Hypertension*. 1996; 27: 1031–8.

49. **Schwartzkopff B, Brehm M, Mundhenke M, et al.** Repair of coronary arterioles after treatment with perindopril in hypertensive heart disease. *Hypertension*. 2000; 36: 220–5.

50. **Rizzoni D, Palombo C, Porteri E, et al.** Relationships between coronary flow vasodilator capacity and small artery remodelling in hypertensive patients. *J Hypertens*. 2003; 21: 625–31.

51. **Rizzoni D, Porteri E, Boari GEM, et al.** Prognostic significance of small-artery structure in hypertension. *Circulation*. 2003; 108: 2230–5.

52. **Rizzoni D, Porteri E, De Ciuceis C, et al.** Effect of treatment with candesartan or enalapril on subcutaneous small artery structure in hypertensive patients with noninsulin-dependent diabetes mellitus. *Hypertension*. 2005; 45: 659–65.

53. **Savoia C, Touyz RM, Endemann D, et al.** Angiotensin receptor blocker added to previous antihypertensive agents on arteries of diabetic hypertensive patients. *Hypertension*. 2006; 48: 271–7.

54. **Schiffrin EL**. Effects of aldosterone on the vasculature. *Hypertension*. 2006; 47: 312–8.

55. **Epstein M, Safar ME**. Aldosterone and large artery vessels. *Hypertension*. 2006; 47: e24.

56. **Savoia C, Touyz RM, Amiri F, et al.** The selective mineralocorticoid receptor blocker eplerenone reduces resistance artery stiffness in hypertensive patients. *Hypertension*. 2008; 51: 432–9.

57. **Touyz RM, Schiffrin EL**. Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. *Pharmacol Rev*. 2000; 52: 639–72.

58. **Christensen KL, Mulvany MJ**. Vasodilatation, not hypotension, improves resistance vessel design during treatment of essential hypertension: a literature survey. *J Hypertens*. 2001; 19: 1001–6.

59. **Bakker ENTP, van der Meulen ET, van den Berg BM, et al.** Inward remodeling follows chronic vasoconstriction in isolated resistance arteries. *J Vasc Res*. 2002; 39: 12–20.

60. **Pourageaud F, De Mey JG**. Structural properties of rat mesenteric small arteries after 4-week exposure to elevated or reduced blood flow. *Am J Physiol*. 1997; 273: H1699-706.

61. **Lund-Johannes P, Omvik P**. Acute and chronic effects of drugs with different actions on adrenergic receptors: a comparison between alpha blockers and different types of beta blockers with and without vasodilating effect. *Cardiovasc Drug Ther*. 1991; 5: 605–15.

62. **Marchesi C, Paradis P, Schiffrin EL**. Role of the renin-angiotensin system in vascular inflammation. *Trends Pharmacol Sci (TIPS)*. 2008; 29: 367–74.

63. **Schiffrin EL, Deng LY**. Comparison of effects of angiotensin converting enzyme inhibition and beta blockade on function of small arteries from hypertensive patients. *Hypertension*. 1995; 25: 699–703.

64. **Creager MA, Roddy M-A**. Effect of captopril and enalapril on endothelial function in hypertensive patients. *Hypertension*. 1994; 24: 499–505.

65. **Kiowski W, Linder L, Nuesch R, et al.** Effects of cilazapril on vascular structure and function in essential hypertension. *Hypertension*. 1996; 27: 371–6.

66. **Ghiadoni L, Virdis A, Magagna A, et al.** Effect of the angiotensin II type 1 receptor blocker candesartan on endothelial function in patients with essential hypertension. *Hypertension*. 2000; 35: 501–6.

67. **Malik RA, Schofield IJ, Izzard A, et al.** Effects of angiotensin type-1 receptor antagonism on small artery function in patients with type 2 diabetes mellitus. *Hypertension*. 2005; 45: 264–9.

68. **Touyz RM, Schiffrin EL**. Reactive oxygen species in vascular biology: implications in hypertension. *Histochem Cell Biol*. 2004; 122: 339–52.

69. **Bohlen HG**. Localization of vascular resistance changes during hypertension. *Hypertension*. 1986; 8: 181–3.

70. **Baumbach GL, Heistad DD**. Remodeling of cerebral arterioles in chronic hypertension. *Hypertension*. 1989; 13: 968–72.

71. **Chillon J-M, Baumbach GL**. Effects of an angiotensin-converting enzyme inhibitor and a fl-blocker on cerebral arterioles in rats. *Hypertension*. 1999; 33: 856–61.

72. **Chillon J-M, Baumbach GL**. Effects of an angiotensin-converting enzyme inhibitor and a fl-blocker on cerebral arteriolar dilatation in hypertensive rats. *Hypertension*. 2001; 37: 1388–93.

73. **Prasad A, Dunnill GS, Mortimer PS, et al.** Capillary rarefaction in the forearm skin in essential hypertension. *J Hypertens*. 1995; 13: 265–8.

74. **Unger T, Mattfeldt T, Lamberty V, et al.** Effects of early-onset angiotensin converting enzyme inhibition on myocardial capillaries. *Hypertension*. 1992; 20: 478–82.

75. **Staessen JA, Wang YG, Thijs L**. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet*. 2001; 358: 1305–15.