The Role of Aldosterone Blockade in Patients with Hypertensive Heart and Cardiovascular Disease

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Abstract: Aldosterone blockade has been shown to be effective in reducing total mortality in patients with severe heart failure due to systolic left ventricular dysfunction and in patients with heart failure post myocardial infarction. Increasing evidence suggests that aldosterone blockade alone and or in conjunction with an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) with or without a thiazide diuretic may also prevent target organ damage (TOD) in patients with hypertensive heart disease (HHD) independent of its effects on blood pressure. Aldosterone blockade may be of especial value in patients with resistant hypertension, visceral obesity, and sleep apnea. Aldosterone blockade prevents myocardial fibrosis and improves echocardiographic indices of diastolic function in patients with heart failure and a normal left ventricular ejection fraction (HFNEF). Its effects on cardiovascular mortality and hospitalization for heart failure in HFNEF are currently under investigation. Aldosterone blockade has also been shown to be beneficial in preventing experimental atherosclerosis and in limiting experimental stroke, although not as yet in man. Although aldosterone may cause serious hyperkalemia this is unlikely in patients with normal renal function. Nevertheless careful selection of patients and serial monitoring of serum potassium, especially in patients with chronic kidney disease, is essential if one is to obtain benefit from this strategy. The risk/benefit of aldosterone blockade alone and or in combination with an ACE-I or ARB with or without a thiazide diuretic in patients with HHD will however require further large scale prospective randomized study.

Keywords: aldosterone blockade, hypertensive heart disease, HHD
Introduction

It is estimated that approximately 7.6 million patient deaths per year in the world can be attributed to high blood pressure. About 54% of strokes and 47% of myocardial infarctions are also attributable to high blood pressure.¹ Hypertensive heart disease (HHD) defined as the consequence of uncontrolled hypertension on the heart including myocardial fibrosis and hypertrophy with consequent diastolic dysfunction, heart failure (HF), and sudden cardiac death (SCD) is therefore of importance. However since the heart is often affected in conjunction with other target organs for the purpose of this discussion HHD will be broadly defined as the effect of uncontrolled hypertension on the cardiovascular system including the heart, kidney, brain and vessels. Target organ damage (TOD) including left ventricular fibrosis and hypertrophy, renal vascular fibrosis and hypertrophy, as well as cerebral vasculature hypertrophy and atherosclerosis with resultant heart failure, stroke, myocardial infarction, renal failure, and SCD are the consequences of uncontrolled hypertension and HHD, or more correctly hypertensive cardiovascular disease. It has been assumed that all antihypertensive agents are equally effective in reducing TOD and the consequences of HHD. Recently however the results of the Avoiding Cardiovascular events through COMbination therapy in patients with Systolic Hypertension (ACCOMPLISH)² comparing an angiotensin converting enzyme inhibitor (ACE-I)/amlodipine combination to an ACE-I/hydrochlorothiazide combination has suggested that at essentially equal blood pressure reduction (confirmed by ambulatory blood pressure monitoring in a subset)³ there is a significant difference in a composite end point of cardiovascular (CV) events including: CV death, myocardial infarction, stroke, hospitalization for unstable angina pectoris, and need for coronary revascularization favoring the ACE-I/amlodipine combination. While confirmation of the concept that antihypertensive strategies at equal blood pressure reductions can result in different CV outcomes requires further investigation this finding opens the possibility that other antihypertensive agents and/or combination of agents may have a beneficial effect on TOD and the consequences of HHD independent of their effect on blood pressure. Of the currently available antihypertensive agents aldosterone blockers, other than the combination of an ACE-I and amlodipine, have the most convincing evidence for a blood pressure independent effect on TOD. Thus, this review will focus on the role of aldosterone and the potential effect of aldosterone blockade in patients with HHD.

The Role of Aldosterone and Aldosterone Blockade in Patients with Hypertensive Heart Disease

Aldosterone blockade has been shown to be effective in reducing total mortality in patients with chronic severe heart failure due to systolic left ventricular dysfunction⁴ and in patients with heart failure and systolic left ventricular dysfunction early post myocardial infarction.⁵ One of the most important effects of aldosterone blockade in patients with HF post myocardial infarction is an early reduction in SCD as well as a latter reduction in death due to progressive HF. In EPHESUS eplerenone significantly reduced all cause mortality within 30 days of randomization (mean time to randomization post myocardial infarction 7 days) mainly due to a reduction in SCD.⁶ A clue to the potential role of aldosterone blockade in patients with HHD can be seen from the results of EPHESUS⁷ in which all of the mortality benefits of the aldosterone blocker eplerenone could be attributed to the subset of patients with a prior history of hypertension, although they were not hypertensive at the time of randomization after their myocardial infarction. An aldosterone blocker is also indicated for the treatment of essential hypertension. Although the aldosterone blocker spironolactone has been available and used in patients with essential hypertension alone and or in conjunction with a thiazide diuretic for several decades its use over the last decade has been limited in part due to the associated side effects of spironolactone including breast pain and gynecomastia in males and menstrual irregularities in premenstrual females; in part due to the fear of inducing serious hyperkalemia and therefore the need for serial monitoring of serum potassium; and in part due to the introduction of newer drugs such as angiotensin converting enzyme inhibitors (ACE-Is), angiotensin receptor blocking agents (ARBs), calcium channel blocking agents (CCBs), and direct renin inhibitors (DRIs).
with their attendant intense marketing to clinicians. The availability of the selective aldosterone blocker eplerenone, which is essentially devoid of the sexually related side effects associated with spironolactone along with new insights into the risks of hyperkalemia with aldosterone blockade and new approaches to inhibiting aldosterone and blocking the MR prompts a brief review of the potential role of aldosterone blockade in patients with HHD. The critical question however, is not whether aldosterone blockers are effective in lowering blood pressure but rather do they confer benefit on target organs and prevent TOD and its consequences independent of their effect on lowering blood pressure.

A clue to the blood pressure independent effect of aldosterone in the pathophysiology of hypertension and thus the potential role of a blood pressure independent role of AB in its treatment can be found in the comparison of patients with primary aldosteronism to those with essential hypertension at similar blood pressures. Patients with primary aldosteronism have been shown to have a significant excess in the incidence of left ventricular hypertrophy, heart failure, stroke, myocardial infarction, atrial fibrillation, urinary albuminuria, the metabolic syndrome, and SCD. The role of aldosterone blockade in patients with HHD. Nevertheless given the relatively high sodium content of the western diet aldosterone is likely to play an important role in the pathophysiology of HHD and its consequences in a large percentage of individuals on a “normal” sodium diet. MRs have been identified not only in the renal tubule but in the vascular wall, myocardium, brain, kidney, colon, adipocyte, retina, and skin. In the renal tubule the MR is protected from activation by cortisol, which has a greater affinity for the MR than aldosterone, by the enzyme Beta HSD 2. This enzyme may however be down regulated in patients with essential hypertension such that cortisol may also play a role in MR activation in the renal tubule. In the myocardium this enzyme is less abundant and it is thought that cortisol occupies the MR and under circumstances of increased oxidative stress cortisol may activate the MR with all of its deleterious consequences.

Angiotensin II (AT II) is an important stimulus for the adrenal production of aldosterone. However, there are other important stimuli that control aldosterone production. For example in the angiotensinogen knock out mouse in which there is no angiotensin II an alteration in serum electrolytes is associated with an increase in aldosterone secretion. In the RESOLVD trial of an ACE-I alone and in conjunction with an ARB in patients with HF due to systolic left ventricular dysfunction the combination of an ACE-I and an ARB was able to transiently suppress plasma aldosterone levels. However after several months plasma aldosterone levels were found to have increased above baseline values. Thus, regardless of the dose of an ACE-I and or ARB aldosterone production can not be suppressed and as mentioned above aldosterone is more important and MRs have a wider distribution than originally thought. It should also be emphasized that while angiotensin II is an important stimulus for the adrenal production of aldosterone, aldosterone can up regulate ACE and AT1 receptor expression, thus creating a vicious cycle that may be difficult to terminate once initiated. An increase in aldosterone and or activation of the MR is associated
with an increase in reactive oxygen species (ROS), a decrease in nitric oxide availability and endothelial dysfunction.35 The decrease in nitric oxide availability is also associated with an increase in aldosterone release from the adrenal gland and with an increase in the release of norepinephrine from sympathetic nerve terminals suggesting that once AT II and the MR are activated a cascade of neurohumoral mechanisms come into play that can initiate and perpetuate HHD unless AT II and the MR are blocked. Increasing data suggests that blockade and or inhibition of both angiotensin II and aldosterone provides benefits which are greater than either alone.36 Thus, while ACE-I s and ARBs have been shown to play an important role in the therapy of HHD it appears likely that the combination of an ACE-I or ARB and an aldosterone blocker with or without a thiazide diuretic will in the future be even more effective.

The Role of Aldosterone Blockade on Vascular Function

Aldosterone decreases antioxidant reserves, in part by decreasing the expression of the enzyme G-6PD and in part by increasing vascular NADPH oxidase in the vascular wall thereby increasing oxidative stress and endothelial dysfunction.37 Aldosterone blockade restores antioxidant reserves, reduces oxidative stress, restores endothelial function. Aldosterone blockade also prevents activation of NF kappa B and AP-1 signaling, vascular inflammation, vascular fibrosis, and a decrease in vascular compliance.38 The potential importance of aldosterone blockade in the therapy of patients with HHD can be seen in a study of patients with stage I hypertension in which the beta adrenergic blocking agent atenolol was compared to the AB eplerenone.39 Patients randomized to atenolol had an increase in vascular stiffness and resistance whereas those randomized to eplerenone had a decrease in vascular stiffness, a decreased ratio of collagen/elastin, and a reduction in circulating inflammatory cytokines at a blood pressure reduction similar to atenolol.

The Role of Aldosterone Blockade on Ventricular Hypertrophy

Patients with primary aldosteronism have a significant increase in the incidence of left ventricular hypertrophy compared to patients with essential hypertension at similar blood pressures,1 suggesting again a blood pressure independent of effect of aldosterone. There is a good correlation between aldosterone levels and left ventricular mass40 while AB has been shown to reduce ventricular mass.41 In the 4E trial42 patients with echocardiographic evidence of left ventricular hypertrophy underwent evaluation by magnetic resonance imaging and were then randomized to the aldosterone blocker eplerenone, the ACE-I enalapril, or their combination. The aldosterone blocker was as effective as the ACE-I in reducing blood pressure, left ventricular mass, and urinary albuminuria while the combination was more effective than either alone. It is of interest to note that the plasma levels of aldosterone in this study were within normal limits despite significant effects of eplerenone on blood pressure, left ventricular mass, and urinary albuminuria suggesting a potential role of cortisol in activating the MR under these circumstances. While the reduction in diastolic pressure was similar with the aldosterone blocker and its combination systolic pressure was not, in that those patients on the combination of eplerenone and enalapril had a small but significantly greater reduction in systolic blood pressure than either one alone. It was not therefore possible with certainty to exclude an effect of blood pressure on the beneficial effects of the combination on left ventricular mass and urinary albuminuria. In a study by Epstein et al42 in patients with diabetic nephropathy the combination of eplerenone and enalapril was however more effective in reducing urinary albuminuria than either one alone at a similar blood pressure reduction, suggesting a blood pressure independent effect of eplerenone.

The Role of Aldosterone Blockade in Patients with Essential Hypertension

Approximately 10%–15% of patients with hypertension have an increased aldosterone to renin ratio suggesting inappropriate aldosterone secretion.43–45 A recent study46 correlating birth weight to aldosterone levels in patients 67–78 years of age has shown that low birth weight, which has been associated with an increase in cortisol levels and subsequent hypertension is also associated with an increase in ACTH stimulated and dexamethasone suppression of aldosterone secretion. This and other data suggests that aldosterone is an important target for blood pressure control. Aldosterone blocking agents have been known to lower blood pressure alone and in conjunction with
other antihypertensive agents for several decades. In contrast to ACE-Is and ARBs however, ABs appear to be equally effective in lowering blood pressure in African Americans and blacks as in Caucasians. A recent study showing that African Americans with hypertension have high aldosterone, low renin levels, and high salivary cortisol levels suggests that AB may be of particular value in African Americans. The effectiveness of AB in lowering blood pressure in a wide spectrum of patients with hypertension, while as mentioned above aldosterone/renin levels are increased in only 10%–15% of patients, suggests that MR activation by cortisol under conditions of increased oxidative stress in the myocardium and vascular wall and or by a decrease in the expression of the enzyme 11 beta HSD 2 in the kidney may play a more important role in the pathophysiology of essential hypertension than has previously been thought.

There may be subsets of patients with essential hypertension in whom an aldosterone blocker might be of particular benefit such as those with low birth weight; those with evidence of visceral obesity and or the metabolic syndrome, in view of the fact that the adipocyte produces aldosterone; as well as in patients with salt sensitive hypertension such as those with mild renal impairment, post menopausal woman, blacks, and the aged. When considering an aldosterone blocking agent in a patient with HHD one might also consider the use of a concomitant thiazide diuretic to reduce the risk of hyperkalemia. At the moment however there are no large scale trials that have compared an aldosterone blocking strategy alone or in conjunction with an ACE-I or ARB with or without a diuretic to other antihypertensive strategies at a similar reduction in blood pressure in any of these subsets.

The Role of Aldosterone Blockade in Patients with Resistant Hypertension

The prevalence of resistant hypertension (defined as: A blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes. Ideally one of the three agents should be a diuretic and all agents should be prescribed at optimal doses) is increasing in part due to the aging of the population and the increased incidence of visceral obesity. The role of aldosterone blockade in patients with resistant hypertension has recently been reviewed by Calhoun who has suggested that the incidence of primary aldosteronism in patients with resistant hypertension is approximately 20%, far greater than in patients with essential hypertension. Patients with resistant hypertension have been shown to have increased plasma volume and inappropriate plasma aldosterone levels, possibly in part related to the occurrence of visceral obesity in a large percentage of these patients. Calhoun et al have shown that relatively small doses of spironolactone were effective in lowering blood pressure in patients with resistant hypertension regardless of the presence or absence of evidence of primary aldosteronism. A retrospective analysis of ASCOT has also suggested that spironolactone is effective in treating patients with resistant hypertension. One explanation for the effectiveness of AB in patients with resistant hypertension relates to the fact that both patients with visceral obesity and sleep apnea have increased levels of plasma aldosterone and that both of these conditions are commonly associated with resistant hypertension. The finding that aldosterone levels may not always predict the response to AB in patients with resistant hypertension may relate to the suggestion referred to above that cortisol may occupy and activate the MR. Aldosterone blocking agents block the MR regardless of whether it is stimulated by aldosterone or cortisol. Thus, agents such as spironolactone and eplerenone should properly be designated as MR antagonists rather than aldosterone blocking agents.

The Potential Role of Aldosterone Blockade in the Transition from HHD to Heart Failure and the Treatment of Heart Failure with a Normal Left Ventricular Ejection Fraction

The effect of MR activation on the vasculature and the myocardium reviewed above suggests an important role of aldosterone blockade in the transition from HHD to heart failure with a normal left ventricular ejection fraction (HFNEF) as well as in the treatment of HFNEF. Myocardial fibrosis precedes the development of hypertrophy in patients with hypertension and is associated with a decrease in diastolic function, and a decrease in vascular compliance predisposing the patient with HHD to HFNEF. Studies comparing patients with HHD and left ventricular hypertrophy to those with HFNEF have suggested
that the most important factor differentiating those with HFNEF is a further increase in myocardial fibrosis. The resultant diastolic dysfunction with a decrease in ventricular compliance sets the stage for the development of manifest HF. Relatively small changes in dietary sodium intake and an increase in plasma volume lead to a rapid and steep rise in left ventricular end diastolic pressure and thus pulmonary congestion and peripheral edema. Aldosterone levels are elevated in atrial fibrillation and aldosterone blockade has been suggested to be of value in the prevention of atrial fibrillation, at least in experimental models, which is an important trigger for the development of HF in a patient with diastolic dysfunction. In patients with HFNEF spironolactone has been shown to improve all of the echocardiographic indices of diastolic function. The effect of spironolactone on the composite endpoint of CV death and hospitalization for HF in patients with HFNEF is currently under investigation in the NHLBI TOPCAT trial in which patients with a serum potassium </= 5.0 meq/l and an estimated glomerular filtration rate (eGFR) > 30 ml/min/1.73 m² are being randomized to spironolactone beginning at a dose of 15 mg/day or placebo with up titration to 45 mg/day if the serum potassium remains </= 5.0 meq/l. Prior to randomization an attempt is made to control blood pressure by standard antihypertensive drugs and patients are excluded from entry if their blood pressure is not controlled and they are on >3 antihypertensive drugs. The primary endpoint is the combination of cardiovascular mortality and hospitalization for heart failure. In view of the failure of the IPRESERVE trial with the ARB irbesartan to reduce CV events in patients with HFNEF one should be cautious in predicting the results of TOPCAT. Nevertheless, the known effects of aldosterone blockade on vascular compliance, myocardial fibrosis and hypertrophy, as well as sudden cardiac death, should predict a beneficial outcome. The treatment of patients with HFNEF has important health care and health cost implications given the fact that hospitalization for HF is the most frequent and expensive cause of hospitalization in patients over the age of 65 years. The increasing age of the population and the increase in the incidence of visceral obesity suggests that efforts to prevent the transition from HHD to HFNEF may be even more important than the treatment of HFNEF in the future.

Control of blood pressure in the US and in most parts of the world is less than optimal. Increased efforts to control blood pressure are therefore of utmost importance. As pointed out above however the means of achieving blood pressure control may also be important in that aldosterone blockade appears to have important blood pressure independent effects. Thus high risk patients with hypertension should be considered for an aldosterone blocking agent as part of their antihypertensive regimen if there are no contraindications due to severe renal dysfunction.

Potential Role of Aldosterone Blockade in Stroke

A recent retrospective study of patients with hypertension has shown that an increase in aldosterone levels within the normal range predicts the risk of stroke and transient ischemic attacks (TIAs) independent of blood pressure or other standard risk factors. A link between aldosterone and stroke independent of systemic blood pressure is also supported by the finding of an increased incidence of stroke in patients with primary aldosteronism compared to those with essential hypertension at similar blood pressures. Thus there may be an opportunity to prevent the development of stroke independent of an effect on blood pressure by using an aldosterone blocker alone or in conjunction with other antihypertensive agents such as an ACE-I, ARB, or diuretic.

While the prevention of stroke independent of the effects of aldosterone blockade on systemic blood pressure will require further prospective evaluation there is also evidence that aldosterone blockade might be of benefit in the therapy of acute stroke. MR are normally expressed in the hippocampus and cerebral cortex of the brain but not the striatum. However, during the acute and sub acute phases of stroke after experimental middle cerebral artery occlusion in a mouse model MR expression in the striatum was increased. The majority of cells expressing MRs in the ischemic area occur in astrocytes. Astrocytes while supporting tissue repair may also produce cytotoxic and inflammatory modulators such as nitric oxide, TNF alpha, and IL-6. Aldosterone blockade in this experimental model blocks the expression of MRs in astrocytes and results in a reduction in cerebral infarct size. This reduction in cerebral infarct size by aldosterone blockade has been attributed to a reduction in reactive oxygen species (ROS) and
an induction of bFGF and VEGF expression by astrocytes with prevention of neuronal apoptosis and an enhancement of angiogenesis.

Aldosterone blockade has also been shown to be effective in preventing hemorrhagic stroke independent of a reduction in blood pressure in SHRS rats fed a high salt diet. Epidermal growth factor (EGF) has been suggested to play an important role in the cerebral vasculature effects of aldosterone. It should however be pointed out activation of the MR in the brain may have beneficial effects by inhibiting cell death so that the timing of aldosterone blockade in the therapy of acute stroke may be critical with potential detrimental and beneficial effects which as yet have not been fully elucidated. Nevertheless there is ample evidence to suggest that this may be a fruitful area of clinical investigation.

The Potential Role of Aldosterone Blockade in Atherosclerosis

Hypertension is accompanied by accelerated atherosclerosis. Thus agents with a beneficial effect on both blood pressure and the progression of atherosclerosis independent of blood pressure lowering may be of particular benefit. Evidence for an effect of aldosterone blockade on the development and progression of atherosclerosis is evolving, at least in experimental animal models. The first clue to the benefit of aldosterone blockade on atherosclerosis independent of its effects on blood pressure and or heart failure came from studies by Rajagopalan et al in normal rabbits fed a high lipid diet. These animals developed endothelial dysfunction associated with the lipid induced increase in oxygen free radicals. Aldosterone blockade with eplerenone significantly improved endothelial function suggesting an improvement in nitric oxide availability. Endothelial dysfunction has been shown to correlate with the extent of standard atherosclerotic risk factors such as smoking, hypertension, hypercholesterolemia, and diabetes mellitus and to be a precursor of atherosclerosis. Further evidence for the role of aldosterone in atherosclerosis comes from studies in the Apo E lipoprotein knock out mouse in which angiotensin II has been shown to induce endothelial dysfunction and atherosclerosis. Atherosclerosis in this model can be blocked by an ARB, adrenalectomy, and by an aldosterone blocker, suggesting that the detrimental effects of angiotensin II in this model are mediated by the MR. Aldosterone increases macrophage oxidized low density lipoprotein—cholesterol (LDL-C) and atherosclerotic plaques in the Apo E lipoprotein knock out mouse. The combination of an AB and an ACE-I was more effective than either alone in reducing atherosclerosis in the apo E knock out mouse. Aldosterone has also been shown to increase the expression of the enzyme LOX-1 which is responsible for the oxidation of LDL-C. Aldosterone also increases vascular inflammation and the expression of MMP 2 and 9 suggesting a possible role of ABs in atherosclerotic plaque rupture. Aldosterone blockade also been shown to reduce the progression of atherosclerosis in a primate model, although not as yet in man.

The HOPE and EUROPA trials have suggested a benefit of ACE-Is in reducing CV events in high risk patients with vascular disease independent of the presence of HF or an effect on blood pressure. Thus, there is reason to postulate that an AB alone or in conjunction with an ACE-I might prevent the progression of atherosclerosis in patients with HHD both by lowering blood pressure and by blood pressure independent effects thus potentially reducing cardiovascular events even more than in HOPE and EUROPA.

The Risks of Aldosterone Blockade

The risks of hyperkalemia (serum potassium > 5.5 meq/l) in patients receiving an aldosterone blocking agent alone and or in conjunction with an ACE-I or ARB with or without a diuretic are well known. Experience in the EPHEUS trial suggests however that in patients with an estimated glomerular filtration fraction (eGFR) > 60 ml/min 1.73 m2 there is no increase in the incidence of hyperkalemia in that the normal kidney can maintain serum potassium within the normal range of 4–5.5 meq/l. However in patients with chronic renal disease (CKD) and an eGFR <= 60 ml/min/1.73 m2 the renal excretion of potassium is impaired and it is essential to serially monitor serum potassium and to adjust the dose of the aldosterone blocker accordingly. An aldosterone blocker should not be administered if the serum potassium is >5.0 meq/l (or under special circumstances >5.5 meq/l) or the eGFR is <= 30 ml/min/1.73 m2 and if at any time the serum potassium increases to >5.5 meq/l the dose of the aldosterone blocker should be halved and a
careful review of the patients medications undertaken to eliminate if possible any that might contribute to hyperkalemia such as a non steroidal anti-inflammatory agent, cox-2 inhibitor, or potassium supplement. If despite a reduction in the dose of the aldosterone blocker the serum potassium remains > 5.5 meq/l it should be discontinued. If at any time the serum potassium is > = 6.0 meq/l on a non hemolyzed sample an electrocardiogram should be obtained to look for evidence of hyperkalemia and the AB should be discontinued and not reinstituted unless the serum potassium is < 5.0 meq/l. The frequency of potassium monitoring will in large part depend upon the degree of renal dysfunction but in general potassium should be measured at baseline before instituting an aldosterone blocker, within the first week after administration or increasing the dose, at 1 month, and then every 3–6 months thereafter. Using this strategy in several thousand patients with chronic HF and or HF post myocardial infarction there has been a single death attributable to hyperkalemia and as mentioned above a reduction in total mortality. The risk of hyperkalemia in a patient on an aldosterone blocking agent can potentially be reduced by adding a diuretic. However, in patients with CKD one should nevertheless be cautious, monitor serum potassium, and adjust the dose of the aldosterone blocking agent as outlined above.

Preston et al have recently shown that the degree of hyperkalemia in a patient with CKD on an ACE-I + an aldosterone blocker can be predicted by an oral potassium load prior to initiating therapy with these agents. Thus in a patient with HHD and normal renal function there is little need for close monitoring of serum potassium unless there is a change in renal function or serum electrolyte status such as vomiting or diarrhea at which time serum potassium should be monitored and the dose of the aldosterone blocker reevaluated. In patients with HHD and CKD the degree of potassium increase with an ACE-I and or an aldosterone blocker can be predicted as described by Preston et al, the dose of the aldosterone blocking agent adjusted accordingly and serial monitoring of serum potassium as described above undertaken. While serial monitoring of serum potassium may be a burden it can be postulated that the blood pressure independent benefits of aldosterone blockade reviewed above will more than compensate for this effort. This hypotheses will however require further proof from large scale prospective randomized trials in patients with HHD demonstrating the safety and efficacy of an aldosterone blocker alone or in combination with an ACE-I or ARB with or without a diuretic in comparison to blood pressure lowering by an ACE-I and amlodipine which has proven benefits on cardiovascular outcomes in high risk patients with hypertension.

Conclusion
Control of blood pressure in patients with HHD or hypertensive cardiovascular disease remains essential. There may however be important blood pressure independent effects of certain antihypertensive agents such as the aldosterone blockers alone or in combination with an ACE-I or ARB and or a diuretic which would favor their use in selected patients with HHD. This hypotheses will however require further confirmation from large scale prospective randomized trials evaluating the effectiveness and safety of this strategy on major cardiovascular events in comparison to other antihypertensive agents at equal blood pressure reduction. The results of ONTARGET in which the combination of an ACE-I and an ARB failed to provide additional benefit but had an increased risk of adverse events in comparison to an ACE-I alone suggests the need for careful study before adopting any new strategy for the treatment of HHD, including an aldosterone blocking agent. Regardless, there is an opportunity over the next decade for further basic and clinical investigation exploring the potential blood pressure independent effects of aldosterone blockade in patients with HHD. The recent introduction of new aldosterone synthase inhibitors and new more selective aldosterone blocking agents holds promise for further investigation of this hypotheses and a further reduction in the morbidity and mortality of patients with HHD and thus an improvement in their quality of life and a reduction in health care costs associated with the epidemic of hypertension and HHD in the western world. The role of aldosterone blockade and or synthase inhibition alone and or in conjunction with an ACE-I or ARB with or without a diuretic for patients with HHD will however need to be compared in regard to efficacy and safety to the results of an ACE-I and a dihydropyridine CCB as demonstrated in the ACCOMPLISH trial and recently emphasized in hypertensive patients with type 2 diabetes mellitus by Reboldi et al.
Disclosures

References


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