of death from any cause or hospitalization for heart failure) did not differ significantly between the two groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the placebo group (12.6%) (HR, 1.38; P = 0.12). More increases in the creatinine concentration were reported as serious adverse events in the dronedarone group than in the placebo group. The authors concluded that in patients with severe heart failure and left ventricular systolic dysfunction, treatment with dronedarone was associated with increased early mortality related to the worsening of heart failure.

The results of the above two studies diverge from those of earlier studies, like the ATHENA trial,[4] but this does not offer any re-assurance on the use of dronedarone in patients with any risk factors. Dronedarone's use has thus been restricted to maintenance of sinus rhythm in patients with paroxysmal AF and no underlying heart disease. It is contraindicated in patients with permanent AF and patients with current or previous episodes of heart failure or left ventricular systolic dysfunction, as detrimental effects of dronedarone have been documented in these groups of patients. In the ATHENA trial, patients with persistent AF also received the drug without apparent harm, but the definition of persistent and permanent AF is not that clear, and thus, great caution should be exercised in the persistent AF group, as well. Whether there will be a return of dronedarone for a second chance after this recent potentially fatal blow or setback remains doubtful. All these drawbacks taken together with the harmful effects of the drug on the liver with reported cases of liver damage necessitating liver transplantation make everybody heavily pensive and hesitant in ever using this pharmaceutical agent.[5,6]

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Hypertension in the Elderly

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In our aging society, most of the elderly aged >65 years are affected by systolic hypertension (HTN) [blood pressure (BP) >140 mmHg], which constitutes a major risk factor for organ damage and cardiovascular (CV) events. Management of HTN in the elderly represents a therapeutic dilemma because HTN trials had upper age limits or did not present age-specific results. However, the HYVET trial documented that therapy is beneficial even in those >80 years. In the elderly, systolic BP and pulse pressure emerge as potent risk factors for CV events. In the past an empiric formula "100+age" was used to estimate appropriate systolic BP. Diastolic BP is more important in younger people <50 years.[1]

Hypertension in the elderly is due to increased stiffness and pulse wave velocity of the great arteries with earlier return of reflected waves, causing high systolic BP, low diastolic BP, increased myocardial oxygen demand with higher peripheral resistance and limited organ perfusion.[2] Furthermore, decreased renal function contributes to HTN through volume expansion, increased intracellular sodium, reduced Na-Ca exchange; K^+ excretion is limited and plasma aldosterone is low, so that the elderly are prone to drug-induced hyperkalemia. Autonomic dysfunction and venous insufficiency contribute to orthostatic hypotension, resulting in falls, syncope, CV events or orthostatic hypotension. Secondary HTN should also be considered, including renal artery stenosis, obstructive sleep apnea, primary aldosteronism, hyper- or hypo-thyroidism, tobacco, alcoholism, caffeine, use of no-steroidal anti-inflammatory drugs, glucocorticoids, sex hormones.[3]

Hypertension or poor BP control may affect different organs, leading to left ventricular hypertrophy, heart failure, arrhythmias, sudden death, coronary atherosclerosis, aortic aneurysm and/or dissection, peripheral vascular disease, ischemic stroke, cerebral hemorrhage, vascular dementia[4] and chronic kidney disease (CKD).[5] The diagnosis should be based on at least 3 different BP measurements, on >2 separate office visits, with the patient comfortable seated for at least 5 min. Measurements should be obtained in each arm and the arm with the highest BP should be used for future BP monitoring. A cuff with a bladder that encircles more than 80% of the upper arm circumference should be used. Elderly patients should also be evaluated for post-prandial and orthostatic hypotension.[1] Pseudo HTN, i.e. falsely increased BP from sclerotic arteries that do not collapse during inflation of the BP cuff, should be suspected in elderly patients with refractory HTN, no organ damage and/or symptoms of overmedication. Confirmation requires the Osler maneuver or direct intra-arterial BP measurement.[6,7] White-coat HTN is a persistently elevated office BP >140/90 mmHg, together with a normal daytime ambula-tory BP (<135/85 mmHg). Ambulatory BP monitoring is recommended in persistent office HTN but no organ damage, when HTN diagnosis or response to therapy is unclear from office visits, when syncope or hypotensive disorders are suspected and for evaluation of dizziness. Ambulatory systolic

BP independently predicts CV mortality.[8] Home BP readings evaluate excessive BP reductions. Electronic automatic devices are more convenient and easier to use, however they cannot measure BP in patients with arrhythmias, e.g. atrial fibrillation with rapid ventricular rate.

Evaluation of the elderly includes BP measurement, taking a good history that includes HTN duration, severity, causes of exacerbations, current and previous treatments, other CV risk factors or comorbidities; performing a complete physical examination, taking patient's weight and measuring waist circumference; performing blood testing that includes sodium, potassium, BUN and creatinine with estimated glomerular filtration rate, glucose, lipid profile, and glycosylated hemoglobin. Patients with HTN, diabetes, and/or CKD should be screened for albuminuria. Finally an ECG and an echocardiographic examination are deemed indispensable.[1]

TREATMENT

BP management should aim at maintaining it at <140/90 mmHg (JNC-7). This target for the elderly is based on expert opinion rather than on data from clinical trials. The decision to initiate anti-HTN therapy in the elderly should include consideration on potential impact on quality of life, because comorbid conditions and polypharmacy influence compliance and have economical impact for patients and families.

Non pharmacological treatment includes lifestyle modifications such as smoking cessation, weight and mental stress reduction, dietary Na restriction, Ca^{2+} - Mg^{-2} supplements, alcohol reduction (<2 drinks/day), and aerobic exercise, which may be the only treatment necessary for milder HTN forms. Risk stratification scores are useful; a team approach is necessary; telemedicine and text messaging are useful.

Drug therapy should be started at the lowest dose and gradually increased, depending on BP response. Target systolic BP is <140 mmHg if tolerated except for octogenarians or special populations. If the BP response is inadequate, a second drug from another class should be added. When BP remains >20/10 mmHg above the goal, therapy should be initiated with 2 anti- HTN drugs. The European Working Party on High BP in the Elderly (EWPHE) (1980) demonstrated that in patients >60 years with BP>160/90 mmHg, drug treatment reduced CV events. Other studies extended the beneficial effects to patients >70 years and to elderly with isolated systolic HTN (systolic BP>160 mmHg / diastolic BP<90-95 mmHg).[9,10] The *HYVET* trial modified previous recommendations for patients >80 years and systolic BP>160 mmHg. After 2 years, the trial was stopped prematurely because treatment decreased BP (144/78 mmHg vs 161/84 mmHg) and reduced adverse outcomes.[11] Despite several limitations of the trial, the extension phase of the HYVET reinforced the conclusion that treatment of HTN in octogenarians is beneficial, although BP control is difficult to achieve, given the low adherence to therapy.[12] Other reasons for inadequate BP response include volume overload, drug interactions, pseudo resistance, secondary hypertension, age-related physiological changes in drug absorption and distribution, declines in renal and/or hepatic function, contracted intravascular volumes and impaired baroreflexes. Furthermore, many physicians are less aggressive to treat the elderly believing that treating hypertensive octogenarians entails more risks than benefits.

Diuretics. The majority of hypertensive patients are controlled on diuretic monotherapy. *Thiazide diuretics* are most commonly used in clinical practice (*chlorothiazide*, *chrorthalidone*, i*ndapamide* and *metolazone*). They are secreted into the proximal convoluted tubule and act in the distal tubule by inhibiting the Na-Cl symport in the luminal membrane and also the water and electrolyte reabsorption. In severe CKD (creatinine clearance <30 ml/m), heart failure, and liver cirrhosis, thiazide diuretics are not effective. Side effects include dysglycemias, dyslipidemia, hypercalcemia, hyperuricemia, pancreatitis, photosensitivity and hypersensitivity to sulfonamides. Nevertheless, diuretics may reduce CV events in the elderly to a similar extent as other drug classes.

Loop diuretics (f*urosemide*, *bumetanide* and *torsemide*) are used in HTN associated with heart failure and/or CKD. They may increase blood sugar and cause headache, fever, anemia, and/or electrolyte disturbances. *Potassium sparing* diuretics (*amiloride*, *triamterene*, *spinonolactone*, *eplerenone*) are important in patient protection from hypokalemia and also treating secondary hyperaldosteronism.[13]

Beta-blockers are useful in combination therapy in arrhythmias**,** migraine headaches, senile tremor, coronary artery disease, and heart failure. Side effects include depression, sexual dysfunction, dyslipidemia, dysglycemia,[14,15] but newer agents, such as nebivolol, are better tolerated and have favorable outcomes (SENIORS trial).[16]

Alpha-blockers are not first line therapy in the elderly, although they are used for prostate hypertrophy. They are efficient but *doxazocin* showed an increase in CV events driven by an increase in heart failure and stroke (ALLHAT). Side effects include orthostatic hypotension and first dose syncope.[17]

Alpha-Beta-blockers are used in HTN urgencies or emergencies (*labetalol*), or in congestive heart failure (*carvedilol*).[18] However, their use in the elderly is not recommended due to the possibility of orthostatic HTN.

Calcium antagonists comprise phenylalkylamines (verapamil), benzothiazepines (diltiazem), or dihydropyridines (nifedipine, nicardipine, nimodipine, amlodipine, felodipine, isradipine, nitrendipine). They are appropriate for elderly patients with HTN and increased arterial stiffness, diastolic dysfunction, angina, or supraventricular arrhythmias. Adverse events include vasodilatation (ankle edema, headache, hypotension, dizziness, falls), and deterioration of underlying conduction defects. Diltiazem and verapamil may be useful in left ventricular diastolic dysfunction but may increase constipation and precipitate heart block. They should be avoided in systolic heart failure due to negative inotropy.

Angiotensin converting enzyme (ACE) inhibitors block conversion of angiotensin (AT)-I to AT-II in tissues and plasma, lowering peripheral vascular resistance and BP without reflex stimulation of heart rate.[19] They are the drugs of choice in patients with heart failure whereby they reduce morbidity and mortality, in diabetes and/or CKD where thay reduce progression of diabetic CKD and hypertensive

nephrosclerosis.[20] Furthermore, they reduce stroke-related dementia and/or stroke (PROGRESS trial). Adverse effects comprise hypotension, dry cough, rarely angioedema or rash; hyperkalemia in CKD or in those taking K^+ supplements or K^+ sparing diuretics; rarely neutropenia, agranulocytosis and renal failure in patients with renal artery srenosis.

Angiotensin receptor blockers (ARBs) are similar to other agents in BP reduction and well tolerated.[21] They protect the kidney in diabetes[22] and reduce mortality and morbidity in heart failure.[23] They are first line therapy in HTN and diabetes and second-line therapy in patients with HTN and heart failure who cannot tolerate ACE inhibitors.[24,25]

Renin inhibitor, aliskiren, is effective for BP management. Combined with thiazide or amlodipine may be more effective than ramipril.[26] However, evidence is lacking on combination of aliskiren with other agents;[27] rather, the premature discontinuation of the ALTITUDE study (19/12/2011), which showed no benefit from aliskiren added to an ACE inhibitor or ARB, while patients treated with it had more CV and renal problems, led to issuance of a warning advisory against its use.

Direct vasodilators (hydralazine, minoxidil) are potent vasodilators as fourth-line therapy. Hydralazine causes tachycardia, fluid accumulation, atrial arrhythmias. Nitrates have no role in chonic HTN because of tolerance.

Centrally acting agents (e.g. clonidine) are effective in reducing catecholamines but patients develop sedation and bradycardia, while abrupt discontinuation leads to a rebound phenomenon with excessive BP increase.

Combination therapy is more efficient, avoids adverse effects as drugs are administrated at lower doses, is convenient, leads to drug synergism and enhanced patient compliance and exploits drug pleiotropic effects.

RESISTANT HTN

Resistant or drug-refractory hypertension is defined as HTN not controlled with combination therapy that includes at least 3 different categories of medications, one of which is a diuretic. In these cases one should pay attention to uncover patient compliance, excessive salt intake or underlying causes of secondary hypertension. Recently, novel modalities have been introduced, with the most promising approach that of renal artery denervation, affected via radiofrequency ablation.

FUTURE CONSIDERATIONS

Prevention of HTN is always preferable to treatment and could be effected via lifestyle changes and with early blockade of the renin angiotensin aldosterone system in HTN-stage 1 in order to effectively limit hypertensive disease. Future research should be directed at the pathogenesis of increased vascular and left ventricular stiffness; defining appropriate thresholds and goals of therapy and comparing drug efficacy; and devising potential new therapeutic strategies.

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