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ORIGINAL ARTICLE

Diuretics for cardiovascular prevention in the elderly

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High blood pressure (BP) is a major risk factor for cardiovascular and cerebrovascular diseases in elderly subjects. Antihypertensive drugs have shown clinical benefit both in primary and secondary prevention of cardiovascular events. If BP lowering represents the major determinant of the effects conferred by the antihypertensive treatment for prevention, recent studies have suggested some differences between classes of antihypertensive drugs according to age. Based on the available clinical data, the recent medical guidelines have recommended thiazide-type diuretics as the preferred drug for the treatment of elderly hypertensive patients, followed by long-acting calcium antagonists. Indeed, diuretics constitute one of the most valuable classes of antihypertensive drugs, and in the elderly, diuretic-based treatment studies have been clearly shown to prevent major cardiovascular events, including stroke, heart failure and coronary heart disease.
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Introduction

The incidence of hypertension increases with age. Approximately 65% of elderly persons have been diagnosed as hypertensive. At ages 65–74 years, hypertension is present in 53% of non-Hispanic whites, 72% of non-Hispanic African Americans and 55% of Mexican Americans.[1] In geriatric patients aged 80 years and above, about 60% of men and 74% of women are hypertensives.[2] Hypertension represents one of the major risk factors for cardiovascular morbidity and mortality in the elderly. The risk related to hypertension has been demonstrated for stroke, left ventricular hypertrophy, congestive heart failure (CHF), coronary and peripheral artery diseases, end-stage renal disease, cognitive impairment and dementia. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are established risk factors, but with advancing age SBP becomes a better predictor than DBP. However, in this population of older subjects who are over 65 years, the lowest rates of blood pressure (BP) control is observed. All the recent recommendations of experts (JNC VII,[3] ESH-ESC,[4] WHO-ISH[5]) indicate that thiazide-type diuretics are to be favoured in elderly patients. This recommendation is based on evidence from long-term, controlled clinical trials, showing that these agents have excellent efficacy in lowering BP and reduce morbidity and mortality from cerebrovascular and cardiovascular disease. In this context, thiazide-type diuretics represent one of the principal antihypertensive agents to use for the treatment of hypertension in the elderly, because of their efficacy and good tolerance whether in monotherapy or in association with other drug families.

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Thiazide-type diuretics and BP lowering in elderly subjects

The effects of aging on the cardiovascular system induce an increase in arterial stiffness leading to an elevated SBP. Several studies have demonstrated the benefits of SBP lowering in elderly hypertensive patients, for cardiovascular prevention. In a meta-analysis[6] including 15 693 elderly patients with isolated systolic hypertension, antihypertensive treatment reduced the incidence of strokes by 30%. Total mortality was also decreased by 13%, cardiovascular mortality by 18%, all cardiovascular complications by 26% and coronary events by 23%. Treatment was more effective at preventing strokes than coronary events. The number of male patients needed to be treated for 5 years to prevent a cardiovascular event was only 18. However, in clinical practice, SBP lowering appears difficult to obtain particularly in elderly subjects. Several studies indicate that thiazide-type diuretics appear

to be more effective at lowering BP in the elderly. A randomised, crossover study[7] has compared the effect on BP lowering of placebo, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium antagonists and thiazide diuretics in elderly patients with previously untreated systolic hypertension. The results have shown that the diuretics and the calcium antagonists were significantly more effective at lowering SBP, whereas beta blockers were relatively ineffective and had more side effects. Decreases in SBP compared with placebo were 13 mmHg with diuretics and 15 mmHg with calcium antagonists, significantly higher than with ACE inhibitors (8 mmHg) and beta blockers (5 mmHg).

In the MRC trial,[8] and the STOP study,[9] diuretics appeared to be more effective than beta blockers at lowering BP. Indeed, in the STOP study, only 10 to 12% of subjects treated with beta blockers reached BP control compared with 30% with diuretics.[10] A systematic review by Messerli *et al*[11] has compared the effects of diuretics and beta blockers used as first-line agents in elderly hypertensive subjects. Among 4595 patients receiving a diuretic as a first drug, about 66% were well controlled on monotherapy and the remaining patients required an additional agent. Conversely, among 2040 patients who received beta blockers as a first drug, less than a third were controlled on monotherapy and about two-thirds required a diuretic as a supplement. The ALLHAT trial[12] evaluated 33 357 hypertensive patients (mean age = 67 years) including more than 5700 patients over the age of 75 years and more than 13 000 patients over the age of 65 years. The results after 5 years of follow-up indicate that the thiazide-type diuretic (chlorthalidone) was superior at lowering SBP compared with ACE inhibitor (2 mmHg, $P<0.001$ for all participants and 3 mmHg in those 65 years or older, $P<0.001$) and with calcium channel blocker (0.8 mmHg, $P=0.03$).

Overall, these studies emphasise that in elderly hypertensive subjects, only a small number (about 30%) could be well controlled with monotherapy. In this sense, more often combination therapy will be required to achieve the goal. According to the recent guidelines, many older hypertensive patients will need two or more antihypertensive drugs to control BP and so will necessarily need the addition of a thiazide-type diuretic.

Several hypotheses on the effectiveness of diuretics in the treatment of hypertension in the elderly have been suggested. Diuretics decrease the peripheral resistance by a direct effect or a secondary effect due to decreased plasma volume. Elderly hypertensive patients are generally more 'salt sensitive' than younger patients,[13] and therefore diuretics are preferred since they provide excretion of water and salt by the kidney. Moreover, elderly patients have a less active renin–angiotensin system relative to younger patients and diuretics appear particularly effective in low renin hypertension.[14]

Thiazide-type diuretics and cardiovascular prevention in elderly subjects

The principal randomised placebo-controlled trials of antihypertensive treatment in elderly hypertensive patients have used a diuretic or a beta blocker as first-line therapy. In the elderly, diuretics have clearly demonstrated BP-lowering efficacy and a proven ability to prevent strokes, myocardial infarction and CHF, when they are used as first-line therapy or added as a second-line therapy. The effects of thiazide-type diuretics in elderly hypertensive patients on cardiovascular prevention are summarised in Table 1 (used as first-line therapy) and in Table 2 (added as a second-line therapy). In all these studies, diuretics were superior to placebo and similar or superior to the other antihypertensive drugs for the prevention of cardiovascular events.

Effects of diuretics in elderly hypertensive patients used as first-line therapy for cardiovascular prevention

Randomised placebo-controlled trials

Since 1985, four large randomised placebo controlled trials have demonstrated the efficacy of thiazide-type diuretics in elderly hypertensive patients (Table 1). Data from the EWPHE,[15] the MRC,[8] the STOP[9] and the SHEP[16] studies have shown more than a 30% reduction in stroke and a reduction of 15 to 40% in all cardiovascular events when using a diuretic regimen compared with controls in elderly patients.

All these studies indicate similar and concordant results for cardiovascular prevention in subjects aged over 60 years. Mean age was 70 years in the MRC trial, 72 years in the EWPHE and the SHEP trials and 76 years in the SHEP study. In comparison with the placebo group, treatment with thiazide-type diuretics was associated with a significant reduction in strokes in systolodiastolic hypertension (47% in the STOP-hypertension trial, 32% in the EWPHE trial and 25% in the MRC trial) and in systolic isolated hypertension (36% in the SHEP trial). In the SHEP study, the number of patients needed to treat to prevent stroke was 83 between 60 and 69 years, 40 between 70 and 79 years and only 18 for 80 years and over. Moreover, a significant reduction in heart failure was observed in all studies (50% in the STOP trial, 63% in the EWPHE trial and 54% in the SHEP trial). Finally, a significant reduction in cardiovascular events was also demonstrated (40% in the STOP trial, 27% in the EWPHE trial, 17% in the MRC trial and 32% in the SHEP trial). The thiazide-type diuretics used were hydrochlorothiazide 25 mg + triamterene 50 mg in EWPHE, chlorthalidone 12.5 to 25 mg in SHEP, hydrochlorothiazide 25 mg + amiloride 2.5 mg in STOP and hydrochlorothiazide 25 to 50 mg + amiloride 2.5 to 5 mg in MRC.

Table 1 Effects of diuretics in elderly hypertensive patients used as first-line therapy for cardiovascular prevention

Studies	n	*Mean age*	*Diuretic*	*Dose of diuretics (mg/day)*	*Control group*	*Follow-up (years)*	*Stroke (%)*	*Coronary events (%)*	*Heart failure (%)*	*CV disease (%)*
Vs placebo										
EWPHE (1985)	840	72	HCTZ+triamterene	25–50	Placebo	4.6	−32	−38*	−63*	−27*
SHEP (1991)	4736	72	Chlorthalidone ± BB	12.5–25	Placebo	4.5	−36*	−27*	−54*	−32*
STOP (1991)	1627	76	HCTZ+amiloride or BB	25+2.5	Placebo	2.1	−47*	−13	−50*	−40*
MRC (1992)	4396	70	HCTZ+amiloride or BB	25–50+2.5–5	Placebo	5.8	−25*	−19		−17*
HYVET Pilot (2003)	1283	84	Bendroflumethiazide or ACEI	2.5	Placebo	1.1	−53*			
Vs CCB										
STOP 2 (1999)	4409	76	HCTZ+amiloride or BB	25+2.5	CCB	5	+12	−18	−6	+1
INSIGHT (2000)	6321	65	HCTZ+amiloride	25–50+2.5–5	DHP CCB	3.5	+13	−9	−120*	−11
NORDIL (2000)	10 881	60	Thiazide or BB	—	Non DHP CCB	4.5	+20*	−16	−16	−4
ALLHAT (2002)	24 303	67	Chlorthalidone	12.5–25	CCB	4.9	+7	−2	−38*	−4
CONVINCE (2003)	8241	66	HCTZ or BB	12.5–25	Non DHP CCB	3	−15	+18	−30*	−2
Vs ACEI										
STOP 2 (1999)	4418	76	HCTZ+amiloride or BB	25+2.5	ACEI	5	+10	+10	+17	+6
ALLHAT (2002)	24 309	67	Chlorthalidone	12.5–25	ACEI	4.9	−15*	+1	−20*	−10*
ANBP 2 (2003)	6083	72	HCTZ	—	ACEI	4.1	−2	+14	+15	+11*
Vs alpha blockers										
ALLHAT (2000)	24 335	67	Chlorthalidone	12.5–25	alpha blocker	3.3	−19*	−3	−104*	−25*

HCTZ = Hydrochlorothiazide, BB = beta blockers, ACEI = angiotensin-converting enzyme inhibitors, CCB = calcium channel blockers, DHP = dihydropyridine.
*$P<0.05$ diuretics *vs* control group.

Table 2 Effects of diuretics in elderly patients used in dual therapy for cardiovascular prevention

Studies	n	*Mean age*	*Combination*	*Dose of diuretic (mg/day)*	*Control group*	*Follow-up (years)*	*Stroke (%)*	*CV events (%)*
PROGRESS (2001)	6105	64	ACEI+indapamide	2.5	Placebo	4	−43*	−40*
LIFE (2002)	9193	67	ARB ± HCTZ	12.5–25	BB+HCTZ	4.8	−25*	−13*
LIFE (ISH) (2002)	1326	70	ARB ± HCTZ	12.5–25	BB+HCTZ	4.8	−40*	−25*
INVEST (2003)	22 576	66	BB+HCTZ	25	CCB+ACE	2	+11	+2
SCOPE (2003)	4964	76	ARB ± HCTZ	12.5	Placebo/other drugs/HCTZ	3.7	−24*	−11
VALUE (2004)	15 245	67	ARB ± HCTZ	12.5–25	CCB+HCTZ	4.2	+15	+4

ISH = isolated systolic hypertension, BB = beta blockers, CV = cardiovascular, CCB = calcium channel blockers, ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers.
*$P<0.05$ combination therapy using diuretics *vs* control group.

Randomised comparative antihypertensive drug trials

Since 2000, several studies have compared the effects of thiazide-type diuretics with other 'new classes' of antihypertensive agents, particularly calcium channel blockers or ACE inhibitors, in the populations of elderly hypertensives (mean age 60 to 76 years).

Thiazide-type diuretics *vs* calcium antagonists

Overall data of studies comparing thiazide-type diuretics with calcium channel blockers indicate similar results for cardiovascular prevention except for heart failure (Table 1). Indeed, the risk of heart failure was higher on calcium antagonists than on diuretics in the ALLHAT[12] (relative risk (RR) = 1.38, 95% confidence interval (CI) = 1.25–1.52), the INSIGHT[17] (odds ratio = 2.20, 95% CI = 1.07–4.49) and the CONVINCE[18] (hazard ratio = 1.30, 95% CI 1.00–1.69) trials.

The STOP Hypertension-2[19] showed no difference in long-term outcomes whether patients were randomised to a diuretic or a beta blocker or a calcium antagonist. The INSIGHT trial[17] indicated no difference for combined primary outcome (cardiovascular death, myocardial infarction, heart failure or stroke) between an initial dose of nifedipine and hydrochlorothiazide plus amiloride. However, the risk of nonfatal heart failure was significantly increased on nifedipine (odds ratio = 2.20, 95% CI = 1.07–4.49). The Nordic Diltiazem (NORDIL) Study[20] showed no difference between diltiazem and a diuretic (or a beta blocker) for the combined primary end point (stroke, myocardial infarction and cardiovascular death). However, a 3 mmHg difference in the reduction of BP in favour of diltiazem was associated with a significantly higher reduction of strokes with the calcium antagonist compared with the diuretic (RR 0.80, 95% CI = 0.65–0.99, $P = 0.04$).

Morbidity/mortality data were observed in the subgroup of ALLHAT[12] subjects aged 65 years and over. There were no statistically significant differences between drugs in terms of fatal and nonfatal myocardial infarctions, coronary heart disease and all-cause mortality, when chlorthalidone was compared with calcium antagonist or ACE inhibitor. However, a statistically significant difference in the occurrence of heart failure was observed in favour of the chlorthalidone regimen, which reduced heart failure incidence by 33% compared with the calcium antagonist. The CONVINCE trial[18] also indicated a similar efficacy of diuretic (or beta blocker) treatment in comparison with the calcium antagonist in reducing cardiovascular disease, but hospitalisation for heart failure was 30% higher (95% CI = 0–69%) with verapamil compared with hydrochlorothiazide or atenolol.

Thiazide-type diuretics *vs* ACE inhibitors

Data of studies comparing thiazide-type diuretics with ACE inhibitors indicate some conflicting results for cardiovascular and cerebrovascular prevention. Some studies demonstrate no difference between both drugs, others suggest a better prevention with diuretics whereas others still suggest better prevention with ACE inhibitors.

In the STOP Hypertension-2,[19] no difference for cardiovascular prevention was observed between the diuretics (or beta blockers) group compared with the ACE inhibitor group. In the large ALLHAT study, a statistically significant difference in the occurrence of strokes and heart failure was shown. The chlorthalidone-based regimen reduced heart failure incidence by 20% and strokes by 15% compared with the ACE inhibitor. Conversely, in the ANBP2 trial,[21] all cardiovascular events or death from any cause were less frequent in the ACE inhibitor group (hazard ratio = 0.89, 95% CI = 0.79–1.00) than in the diuretic group. However, strokes, heart failure and coronary events were similar in the ACE inhibitor groups and in the diuretic group. Finally, recent data of the HYVET pilot study[22] in a very elderly population (mean age 84 years) indicate a higher significant reduction of stroke events with diuretics (usually bendroflumethiazide), (69%, $P = 0.01$) compared with lisinopril (37%, $P = 0.21$).

Thiazide-type diuretics *vs* beta blockers

A systematic review, by Messerli *et al*,[11] has compared the effects of conventional drugs (diuretics

and beta blockers) used as first-line agents in 16 164 elderly hypertensive subjects (⩾60 years). The results indicate that beta blockers were less efficient than diuretics for cardiovascular prevention. Indeed, diuretic therapy was significantly superior to beta blockers in preventing cerebrovascular events (risk reduction = 39%, 95% CI = 28–49%), fatal stroke (risk reduction = 33%, 95% CI = 10–51%), coronary heart disease (risk reduction = 26%, 95% CI = 15–36%), cardiovascular mortality (risk reduction = 25%, 95% CI = 13–36%), and all-cause mortality (risk reduction = 14%, 95% CI = 4–23%). Conversely, beta blocker therapy only reduced the risk of cerebrovascular events (risk reduction = 25%, 95% CI = 2–43%) and was ineffective for prevention of coronary heart disease, cardiovascular mortality and all-cause mortality.

Thiazide-type diuretics *vs* alpha blockers

After a median follow-up of 3.3 years, data of ALLHAT[23] on 24 335 patients showed a higher risk of CHF (RR = 2.04, 95% CI = 1.79–2.32), strokes (RR = 1.19, 95% CI = 1.01–1.40) and combined cardiovascular disease (RR = 1.25, 95% CI = 1.17–1.33) in the alpha blocker group in comparison with chlorthalidone. These results are in favour of the use of diuretics compared with alpha blocker drugs.

Data of recent large meta-analysis concerning diuretics

The majority of recent therapeutic studies to evaluate antihypertensive drugs have been performed in elderly patients over 60 years. In 192 478 patients (including several elderly individuals) randomised to seven major treatments strategies, a recent network meta-analysis[24] from 42 clinical trials compared low dose of diuretics (equivalent of 12.5 to 25 mg per day of chlorthalidone or hydrochlorothiazide) with other active first-line therapies. The results indicate that low-dose diuretics were significantly associated with a lower incidence of cardiovascular disease events (RR = 0.89, 95% CI = 0.80–0.98) compared with beta blockers and with a lower risk of CHF (RR = 0.88, 95% CI = 0.80–0.96), stroke (RR = 0.86, 95% CI = 0.77–0.97) and cardiovascular disease (RR = 0.94, 95% CI = 0.89–1.00) in comparison with ACE inhibitors. Moreover, a significantly lower risk of CHF (RR = 0.74, 95% CI = 0.67–0.81) and cardiovascular diseases (RR = 0.94, 95% CI = 0.89–1.00) was observed with low-dose diuretics compared with calcium antagonists. The authors conclude that, based on extensive clinical trial evidence, low-dose diuretics appear as a first choice of treatment for patients with uncomplicated hypertension.

Effects of diuretics in elderly hypertensive patients used as second-line therapy for cardiovascular prevention

Most recent studies on elderly hypertensives have included diuretics as second-line therapy when the first therapy was not based on diuretics. All these trials demonstrated the benefit of two-drug combination therapies in terms of cardiovascular mortality/morbidity prevention. The following two-drug combinations, including thiazide-type diuretics, have been found to be effective and well tolerated in elderly hypertensive patients (Table 2):

Diuretics + beta blockers
Diuretics + ACE inhibitors
Diuretics + angiotensin receptor antagonists
Diuretics + calcium antagonists.

The results of PROGRESS[25] indicate that the effects of a diuretic + ACE inhibitor combination regimen in hypertensive and nonhypertensive patients with a history of stroke or transient ischaemic attack are beneficial for reducing stroke after 4 years of follow-up. In this study, the BP-lowering regimen reduced the risk of stroke by 28% (95% CI 17–38%). Combination therapy with perindopril and indapamide produced larger BP reductions by 12/5 mmHg and larger stroke reductions (by 43%, 95% CI = 30–54%) than single drug therapy with perindopril alone. Active treatment also reduced the risk of total major coronary events (26%, 95% CI = 6–42%) and combination therapy was also associated with fewer total major coronary events (35%, 95% CI = 12–52%). Moreover, a significant reduction of 34% (95% CI = 3–55%, $P = 0.03$) in dementia was observed with active treatment in patients with recurrent stroke.[26] The risk of dementia in the whole population was nonsignificantly reduced by 12% (95% CI = −8 to 28%) in the active treatment group. Interestingly, combination therapy was significantly more effective in reducing the risk of dementia (23%, 95% CI = 0–41%) than monotherapy (−8%, 95% CI = −48 to 21%). Furthermore, active treatment reduced the risk of cognitive decline by 19% in the whole population (95% CI = 4–32%, $P = 0.01$), and by 45% (95% CI = 21–61%, $P = 0.001$) in subjects with recurrent stroke. In the SYST-EUR study, the incidence of dementia (vascular or Alzheimer's types) was reduced by 50%, from 7.7 in the placebo group to 3.7 cases per 1000 patient-years in the active treatment group ($P = 0.05$). The active treatment was a calcium channel blocker (nitrendipine), possibly associated with the ACE inhibitor enalapril and/or the diuretic hydrochlorothiazide (taken in 15% of cases).

In the LIFE study,[27] the combination therapy with angiotensin receptor blockers (ARB) and hydrochlorothiazide in hypertensive patients with left ventricular hypertrophy, was more effective than the combination of beta blockers + hydrochlorothiazide, for the primary end point (death, myocardial infarction or stroke) (RR = 0.87, 95% CI = 0.77–0.98,

$P = 0.021$). In the subgroup of 1326 subjects with isolated systolic hypertension (mean age 70 years),[28] a higher reduction in strokes (RR = 0.60, 95% CI = 0.38–0.92, $P = 0.02$) and cardiovascular mortality (RR = 0.54, 95% CI = 0.34–0.87, $P = 0.01$) was observed in the ARB ± diuretics group. Similar data were observed in the SCOPE study[29] (mean age = 76 years), suggesting efficacy of the ARB + diuretics combination therapy in preventing strokes. In the recent INVEST study,[30] conducted in 22 576 hypertensive subjects, a similar efficacy of the calcium antagonist + ACE inhibitor and the beta blocker + diuretic (hydrochlorothiazide) strategies was demonstrated in hypertensives with coronary artery disease (mean age = 66 years, 33% of whom were over 70 years). The VALUE study[31] included 15 245 hypertensive patients with high cardiovascular risk, mean age 67 years, during 4.2 years of follow-up. The results indicate a similar occurrence of the primary outcome (composite of cardiac mortality and morbidity) between the ARB ± diuretic and the calcium antagonist ± diuretic strategies. For the secondary outcome, the incidence of myocardial infarction was significantly ($P = 0.02$) less frequent in the calcium antagonist group. The percentage of patients receiving diuretics as combination therapy was 29% in the valsartan group and 28% in the amlodipine group. BP lowering was more pronounced in the calcium antagonist group, especially during the monotherapy period.

In summary, in elderly hypertensives, dual therapy is needed for almost 60–70% of patients and the use of diuretics appears more often necessary to reach the BP goal.

Thiazide-type diuretics and cardiovascular prevention in very elderly subjects

With regard to the question about the benefit of antihypertensive treatment in the 'very elderly' subjects over 80 years, no answer of evidence-based medicine exists in the literature. Indeed, no randomised controlled study has specifically evaluated the effect of antihypertensive drugs in a population aged over 80 years. A meta-analysis[32] of data including 1670 participants aged 80 years and over in randomised controlled trials of antihypertensive drugs has been published. The results suggested that active treatment prevented 34% (95% CI = 8–52%) of strokes. Rates of major cardiovascular events and heart failure were also significantly decreased by 22 and 39%, respectively. However, no treatment benefit for cardiovascular mortality was observed. Moreover, a nonsignificant 6% (−5 to 18%) excess of deaths from all causes has been reported, as described in some epidemiological studies. Most of the studies from this analysis included trials using thiazide-type diuretics (EWPHE, SHEP, STOP).

Results of a large-scale specific trial are needed for a definite conclusion that antihypertensive treatment is beneficial in very elderly hypertensive patients. The specifically designed trial (the Hypertension in the Very Elderly Trial (HYVET)) is ongoing.[33] It is a double-blind study, with a follow-up of 5 years, enrolling hypertensive patients aged ⩾80 years randomised to receive either placebo or indapamide 1.5 mg sustained release, a thiazide-type diuretic, and addition of the ACE inhibitor perindopril if required. Data from the HYVET pilot study[22] have been recently published. This trial included 1283 patients older than 80 years (mean age = 84 years) with hypertension (160–129/90–109 mmHg) randomised in three groups (placebo, diuretics or ACE inhibitors) for a 13-month follow-up period. The results indicate a significant reduction in strokes in the active treatment group (53%, 95% CI 7–76%). They suggest that in very elderly hypertensive patients, treatment of 1000 patients for 1 year would prevent 19 strokes. Comparison between the two active drugs indicate a higher reduction in strokes with diuretics (69%, $P = 0.01$) rather than with ACE inhibitors (37%, $P = 0.21$). The diuretics were bendroflumethiazide (2.5 to 5 mg), chlorthalidone (25 to 50 mg) or hydrochlorothiazide (12.5 to 50 mg). No significant increase in total mortality was observed in the active treatment group (22%, $P = 0.42$) compared with placebo. These results suggesting a significant benefit of antihypertensive treatment on morbidity events (strokes) in subjects over 80 years, without an increase in total mortality, should be confirmed in the larger ongoing study (HYVET[33]).

Safety and tolerability of diuretic therapy in elderly hypertensive patients

Since elderly hypertensives constitute an especially frail population, fear of side effects could made physicians reluctant to pursue recommended drug therapies as diuretics. However, the safety and tolerability of diuretic treatment appears good in the different studies. No significant difference in noncardiovascular mortality was observed in patients treated with diuretics compared with those treated with placebo or other antihypertensive drugs in most trials conducted in elderly hypertensive subjects. The rate of withdrawal due to side effects did not differ for diuretics and other antihypertensive drugs (ALLHAT[12]) even in very old patients (HYVET pilot[22]) or was lower for diuretics than for beta blockers (MRC[8]) (Table 3). In the MRC study, some adverse events were more frequently reported in the diuretic group than in the placebo group: gout (4.4 *vs* 0.1/1000 patient-years, respectively); muscle cramp (5.2 *vs* 0.1); nausea (7.4 *vs* 1.1); dizziness (7.4 *vs* 1.2) and skin disorders (3.9 *vs* 1.1). In drug comparison trials such as ALLHAT,[12] chlorthalidone was better tolerated than ACE inhibitors (angioedema occurred 4 times more frequently with ACE inhibitors than with diuretics, 0.4 *vs* 0.1%,

Table 3 Treatment withdrawal for side effects

Studies	*Diuretic alone (%)*	*Diuretic+other drugs (%)*	*Placebo (%)*	*Other compared drugs (%)*
EWPHE	7.2		5.2	
SHEP		D+BB: 13	7	
STOP		D+BB: 7.1	5.7	
MRC	14.8		3.7	BB: 30.2
ALLHAT	15			CCB: 16.4, ACEI: 18.1
HYVET-pilot	3			ACEI: 4
PROGRESS		ACEI±D: 13.2	10.5	

D = diuretics, BB = beta blockers, CCB = calcium channel blockers, ACEI = angiotensin-converting enzyme inhibitors.

$P<0.001$). In other studies (STOP2,[19] NORDIL[20]), side effects were described in a group treated with a diuretic combined with a beta blocker compared to other drugs. Therefore, the higher frequency of dyspnoea, bradycardia, fatigue, and impotence may be due to the beta blocker compound rather than the diuretic. By the way, in STOP2 dry mouth was reported by 4.4% of patients in the diuretic + beta blocker group and by only 2.0% in the ACE inhibitor group and 2.7% in the calcium antagonist group. Age had no influence on tolerability of diuretic therapy. In a crossover study using bendrofluazide, bisoprolol and nifedipine, no statistically significant difference could be identified in the number of adverse events between younger (mean age 50.5) and older patients (mean age 72).[34]

Monitoring of kalaemia, natraemia and serum creatinine levels, uricaemia, glucose and cholesterol levels demonstrated a higher risk of metabolic disorders due to thiazide treatment than in the placebo group.[16] In ALLHAT,[12] the prevalence of hypokalaemia, new diabetes, and raised cholesterol levels was higher in the diabetic group than in the calcium antagonist or ACE inhibitor groups. However, these metabolic differences did not translate into more cardiovascular events in the diuretic group compared with the other two groups. Moreover, despite the effect on glucose levels and the potential of thiazides to induce insulin resistance, their efficacy was demonstrated in people with diabetes, who obtain a greater absolute benefit than people without diabetes. By the way, the metabolic disorders did not influence the rate of withdrawal and the cardiovascular morbidity or all-cause mortality. The thiazide-like diuretic indapamide 1.5 mg sustained release does not affect lipid or glucose levels but can also decrease kalaemia. In the NESTOR study,[35] indapamide 1.5 mg sustained release also showed a reduction in risk among elderly diabetic patients by a decrease in albuminuria.

In summary, safety and good tolerance of a diuretic based-regimen were demonstrated in clinical trials performed in elderly or very elderly hypertensive subjects. Since participants in those studies are highly selected (in SHEP only 1% of screened patients were randomised), this tolerability may not reflect the observations of daily practice particularly in very elderly subjects. Therefore, it is of major importance to monitor kalaemia, natraemia and creatinine levels in the elderly treated with diuretics. Particular attention should be given to older patients treated with concomitant drugs that can interact with diuretics in inducing metabolic disorders (nonsteroidal anti-inflammatory agents or serotonin-reuptake inhibitors, for example).

Conclusions

Antihypertensive drugs have shown clinical benefit in primary and secondary prevention in elderly hypertensive subjects. Most evidence-based medicine indicates that thiazide-type diuretics are considered as the preferred choice for the management of hypertension in this population for their efficacy and tolerance whether as monotherapy or in combination with other drug families. Indeed, for the majority of elderly patients with isolated systolic hypertension, two or three drugs will be required to achieve goal BPs, including necessarily a thiazide-type diuretic.

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