Management of hypertension in elderly diabetic patients

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SUMMARY
Hypertension is a major vascular risk factor in the elderly diabetic. The benefit of proper management is well recognized, even if treatment has no influence on overall mortality or might even tend to increase it in very elderly subjects. Globally, the efficacy of the major classes of antihypertensive drugs, diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, or angiotensin II receptor antagonists appears to be equivalent so that the therapeutic choice depends on the type of hypertension, systolic or systolic-diastolic, and the rapidity of the desired effect, co-morbid conditions, particularly coronary or renal disease, or drug tolerance. Blood pressure goals are similar to those in middle-aged persons, except in very old, frail or sick subjects.

Key-words: Diabetes · Elderly subject · Hypertension · Anti-hypertensive drugs.

RéSUMÉ
Prise en charge de l'hypertension artérielle du diabétique âgé
L'hypertension artérielle (HTA) représente un facteur de risque vasculaire majeur chez le diabétique âgé. Les bénéfices liés à sa prise en charge ne sont plus discutés, même si le traitement est sans influence sur la mortalité totale, voire tend à l’augmenter légèrement chez les sujets très âgés. Globalement, l’efficacité des principales classes d’antihypertenseurs, diurétiques, β-bloquants, inhibiteurs calciques, inhibiteurs de l’enzyme de conversion ou antagonistes des récepteurs de l’angiotensine 2 apparaît identique, le choix thérapeutique s’exerçant en fonction du type d’HTA, systolique isolée ou systolodiastolique, de la rapidité de l’effet recherché, des pathologies associées, en particulier coronariennes ou rénales, ou du profil de tolérance des médicaments. Les objectifs tensionnels rejoignent ceux des diabétiques d’âge moyen, sauf peut-être chez les sujets très âgés, les patients fragiles ou en mauvaise santé.

Mots-clés : Diabète · Sujet âgé · Hypertension artérielle · Anti-hypertenseurs.
In the general population, systolic blood pressure increases with increasing age, reaching a peak in the 66-69 year range, then declining in older subjects. High blood pressure is associated with higher risk of cardiovascular events (strokes, coronary artery disease) [1].

High blood pressure is more prevalent in the elderly diabetic population than in the general population. It is associated with the metabolic syndrome or the development of diabetic nephropathy and is generally expressed as systolic-diastolic hypertension. Isolated systolic hypertension can also be observed with increased pulse pressure which is a factor more predictive of cardiovascular events than systolic-diastolic hypertension. This increased pulse pressure is related to arterial rigidity. In one study from Japan, pulse pressure was correlated with the presence of diabetes and low HDL cholesterol (HDL-C) in hypertensive patients aged over 50 years [2].

While studies specifically designed to demonstrate the effects of management of hypertension in elderly diabetics or evaluate blood pressure objectives desirable in this very heterogeneous population are lacking, there are several recent large-scale studies which identify relatively large groups of elderly and diabetic patients, limiting the zone of uncertainty concerning proper care.

Beneficial effect of treating hypertension in the elderly subjects

- A meta-analysis [3] of drug intervention trials in hypertensive subjects aged over 60 years concluded that the results are remarkably similar in terms of cardiovascular morbidity-mortality. In particular, it was observed that treatment has a significant effect on mortality due to coronary artery disease, stroke or all causes as well as on the incidence of non-fatal vascular events (Table I).

<table>
<thead>
<tr>
<th>Relative risk reduction (%) [95% CI]</th>
<th>Number of prevented events (n) [% 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>16 [6-25]</td>
</tr>
<tr>
<td>Coronary mortality</td>
<td>26 [14-36]</td>
</tr>
<tr>
<td>Coronary events</td>
<td>20 [10-13]</td>
</tr>
<tr>
<td>Cerebro-vascular mortality</td>
<td>40 [21-54]</td>
</tr>
<tr>
<td>Cerebro-vascular events</td>
<td>37 [28-45]</td>
</tr>
<tr>
<td>Cardio-vascular mortality</td>
<td>30 [19-39]</td>
</tr>
<tr>
<td>Cardio-vascular events</td>
<td>33 [25-41]</td>
</tr>
</tbody>
</table>

*NEA: number of events prevented by treating 1,000 patients during 5 years.

Data in the elderly diabetic population

Beneficial effect of controlling blood pressure level

In general, the benefit expected from a therapeutic intervention depends on multiple factors, including the baseline risk of events. In subjects with multiple risk factors (for example diabetes, familial history of early cardiovascular morbidity-mortality, left ventricular hypertrophy) the benefit of treating hypertension would be expected to be greater.

Beyond the results of the UKPDS (United Kingdom Diabetes Prospective Study) which did not include elderly subjects, the results obtained in groups of diabetics enrolled in large-scale studies confirm the usefulness of treatment for isolated systolic or systolic-diastolic hypertension.

- SHEP (Systolic Hypertension in the Elderly Programme) compared chlorthalidone, a thiazidic diuretic, with placebo in a population of 4,736 subjects (583 diabetics) aged over 60 years who presented isolated systolic hypertension and demonstrated that treatment-induced reduction in blood pressure and treatment benefits were equivalent in diabetics and non-diabetics. Compared with placebo, the risk of major cardiovascular events at five years was 34% in both populations (95% CI 6-54% in diabetics and 21-45% in non-diabetics). The risk of stroke was reduced by 36%. The reduction in the risk of coronary events with treatment was greater in diabetics than non-diabetics. Because of the higher risk in diabetics, the absolute reduction in the risk of major cardiovascular events was two-fold greater in diabetics than non-diabetics. That treatment of hypertension reduced the risk of stroke and treatment benefits were equivalent in diabetics and non-diabetics. Compared with placebo, the risk of major cardiovascular events at five years was 34% in both populations (95% CI 6-54% in diabetics and 21-45% in non-diabetics). The risk of stroke was reduced by 36%. The reduction in the risk of coronary events with treatment was greater in diabetics than non-diabetics. Because of the higher risk in diabetics, the absolute reduction in the risk of major cardiovascular events was two-fold greater in diabetics than non-diabetics. (101‰ vs 51‰). An effect on all-causes mortality was however not demonstrated [5].

Very recently, the long-term results of this study were published and the presence or not of diabetes was specifically mentioned [6]. After a median follow-up of 14.3 years, cardiovascular mortality was 66% higher in diabetics (95% CI 41-95%) than non-diabetics as was all-causes mortality (51%, 95% CI 35-69%). In diabetics, the effect of treatment with chlorthalidone (compared with placebo) on cardiovascular mortality (–31.2%, 95% CI –15.2 to –47.4%) and on all-causes mortality (–19.5%, 95% CI –4.8 to –32%) was greater than observed in non-diabetics. Interestingly, onset of diabetes...
during the course of the study (169 cases in the placebo group and 218 in the chlorthalidone group) was associated with higher cardiovascular mortality (+56%, 95% CI 12-118%) and all-causes mortality (+35%, 95% CI 5-73%) in the placebo group, but did not have a significant effect (relative risk RR 1.043 and 1.151 respectively) in the group treated with chlorthalidone.

– **SYST-Eur** (Systolic hypertension in Europe) compared the effect of nitrendipine versus placebo in a population of 4,695 subjects aged over 60 years with isolated systolic hypertension, including 492 diabetics. In the diabetic subgroup, the benefit of treatment at two years was greater than in the non-diabetic subgroup, with in particular a trend towards reduced all-causes mortality (−41%, 95% CI −69 to −9%, NS) and a significant reduction in cardiovascular mortality (−70%, 95% CI −19 to −89%) while mortality was not affected by treatment in non-diabetics. Major cardiovascular events (−62%, 95% CI −19 to −80%, vs −5%, 95% CI −5 to −41%) and stroke (−69%, 95% CI −14 to −89% vs −36%, 95% CI −5 to −57%) showed greater reduction in diabetics than non-diabetics [7].

Continuing after the randomized trial, the study was extended to an open trial in 3,517 patients for four years. All were given nitrendipine (10-40 mg/d), associated in some patients with enalapril and/or hydrochlorothiazide. The beneficial effect persisted in patients initially randomized to the nitrendipine group. Early therapeutic intervention reduced the risk of stroke by 28% and the risk of cardiovascular complications 15% compared with later treatment and avoided 17 strokes and 25 major cardiovascular events per 1,000 patients treated for six years [8].

– **HYVET-Pilot** (Hypertension in the Very Elderly Trial) was conducted in 1,283 hypertensive patients aged over 80 years with systolic-diastolic hypertension (160-219/90-109 mmHg) either treated with a diuretic or an angiotensin converting enzyme inhibitor (ACEI) (mainly lisinopril) or not treated. With active treatment, the risk of stroke was reduced by 53% (95% CI −7 to −76%) and the risk of stroke mortality by 43% (NS). There was a discrete non-significant trend to greater all-causes mortality (+23%, 95% CI −25 to 101%). In this study, diabetic subjects were unfortunately not individualized [9].

– In **SCOPE** (Study on Cognition and Prognosis in the Elderly), 4,964 patients aged 70-89 years (12% diabetics) with moderate hypertension (160-179/90-99 mmHg) and a Mini-Mental Score (MMS) > 24 were given candesartan or placebo, which could be combined with other anti-hypertensive drugs in both groups. Blood pressure was reduced by 21.7/10.8 mmHg in the candesartan group versus 18.5/9.2 mmHg in the placebo group. There was no significant reduction in the incidence of major cardiovascular events or stroke, but the risk of non-fatal stroke was reduced by 27.8% (95% CI −1.3 to −47.2%) with candesartan. Cognitive decline during the observation period and the proportion of subjects progressing to dementia were comparable in both groups. The results of the subgroup of diabetic patients were not mentioned [10].

– Finally, in a population of 9,297 patients with high vascular risk aged over 55 years, including 3,577 diabetics with or without hypertension, the **HOPE** (Heart Outcomes Prevention Evaluation) study compared ramipril with placebo given for 4.5 years and also demonstrated a 25% lower risk of major cardiovascular events (95% CI −12 to 36%) in the ramipril treated diabetics versus placebo. The risk reduction was greater in diabetics compared with non-diabetics. The risk was 22% lower for myocardial infarction (95% CI −6 to −36%), 37% lower for stroke (95% CI −21 to −51%), 24% lower for all-causes mortality (95% CI −8 to −37%), 37% lower for cardiovascular mortality (95% CI −21 to −51%), 17% lower for revascularization (95% CI −2 to −30%) and 24% lower for overt nephropathy (95% CI −3 to −40%) [11]. The reduction in risk of major cardiovascular events was greater in patients aged over 65 years compared with those aged less than 65 years [12].

Globally, these trials show that in the elderly subject hypertension increases diabetes-related risks and that the benefit of antihypertensive treatment is comparable or even superior in diabetic patients than in the general population.

**Studies designed to determine desirable blood pressure goals in the elderly diabetic**

– The **HOT** (Hypertension Optimal Treatment) study was designed to evaluate the benefit of lowering diastolic pressure below three target levels: 90, 85 and 80 mmHg in patients with systolic-diastolic hypertension with diastolic pressures in the 100-115 mmHg range. In all, 18,790 patients aged 50-80 years (mean 61.5 years) including 8% diabetics were included in this trial using felodipine as the first-line treatment. In diabetic patients, the risk of a major cardiovascular event was lowered by 51% and the risk of stroke about 30% among those whose diastolic pressure goal was ≤ 80 mmHg compared with the ≤ 90 mmHg group. Cardiovascular mortality was also lower in this treatment group.

In the overall population, analysis of events by blood pressure level effectively reached suggests that the risk of a major cardiovascular event, and particularly coronary mortality is greater when diastolic pressure is < 75 mmHg (J-shaped curve). Results were not stratified by age in this study, but the overall subgroup of diabetic patients also benefited more from aggressive therapeutic intervention than the overall study population [13].

– The **VALISH** (Valsartan in elderly Isolated Systolic Hypertension) study was designed to compare two therapeutic goals for systolic pressure (≤ 140 and ≤ 150 mmHg) in 3,000 patients aged 70-85 years with isolated systolic hypertension with systolic pressure in the 160-200 mmHg range and diastolic pressure < 90 mmHg. The results will become available in 2006-2007 [14].

**Studies comparing therapeutic strategies**

– The purpose of **MIDAS** (Multicenter Isradipine Diuretic Atherosclerosis Study) was to compare the effect of isradipine
and hydrochlorothiazide on carotid intima-media thickness in 883 hypertensive patients treated for three years. Only 8% of patients in this study were older than 70 years and the presence of diabetes was not mentioned. No significant difference was observed in the main endpoint but non-major cardiovascular events were more frequent in the isradipine group [15].

– INSIGHT (International Nifedipine GIT Study) compared prolonged-release nifedipine with the combination hydrochlorothiazide plus amiloride in 6,321 hypertensive patients aged 55-80 years (28% over 70 years) including 20% diabetics. In the diabetic patients, the incidence of major cardiovascular events was the same in the two treatment arms (8.3% and 8.4% at three years respectively) and was greater than in non-diabetics [16]. At the end of the study, the decline in glomerular filtration rate was statistically greater among patients taking the diuretic than those on nifedipine GITS (−2 ml/min vs –5 ml/min, p <0.05) and kidney failure developed in 5% of the patients on diuretics versus 2% of the patients on calcium channel blocker. The increased cardiovascular risk in subjects with elevated serum creatinine (R = 2.89, 95% CI 1.92-4.36) or creatinine clearance below 60 ml/min (R = 1.51, 95% CI 1.22-1.88) was confirmed in this study [17].

– CONVIENT (Controlled onset Verapamil Investigation of Cardiovascular Endpoints) was a large-scale trial comparing the effect of verapamil versus conventional treatment using atenolol or hydrochlorothiazide (8,179 hypertensive patients with an additional risk factor [including 1,616 diabetics and 1,097 subjects aged over 75 years]) in the verapamil group and 8,297 hypertensive patients (1,623 diabetics and 1,097 subjects aged over 75 years) were included in the atenolol or hydrochlorothiazide group. The effect of both therapeutic strategies was similar for the main endpoint (major cardiovascular event). However, the RR of heart failure (1.30, 95% CI 1.00-1.69) and hospitalization for non-cerebral hemorrhage (1.54, 95% CI 1.15-2.04) was significantly higher in the verapamil group than in the conventional group. Age or diabetes did not have any impact on therapeutic effect as assessed by the main endpoint [18].

– NORDIL (Nordic Diltiazem study) was a large-scale trial which included 10,881 patients aged 50-74 years (5,516 >60 years and 727 diabetics) with systolic-diastolic hypertension. Diltiazem had an effect equivalent to diuretic plus beta-blocker (R = 1) on cardiovascular morbidity-mortality. The RR of stoke was however lower with diltiazem (R = 0.8, 95% CI 0.65-0.99) while the risk of myocardial infarction was non-significantly greater. The lower RR of stroke with diltiazem was more pronounced and statistically significant in the subgroups with systolic pressure > 170 mmHg, diastolic pressure ≥ 105 mmHg and pulse pressure ≥ 66 mmHg. The increase in the RR of myocardial infarction was significant in the subgroup of patients with heart rate < 74 bpm [19].

– IN STOP-Hypertension-2 (Swedish Trial in Old Patients with Hypertension), 6,614 hypertensive patients aged 70-84 years (including 10.9% diabetics) were randomized into three treatment arms: conventional (diuretic ± beta-blocker), calcium channel blocker, or angiotensin converting enzyme inhibitors. Blood pressure lowering and effect on the main endpoint were the same in the three arms. There were however fewer myocardial infarctions in the angiotensin converting enzyme inhibitor group than in the calcium channel blocker group (R = 0.51, 95% CI –0.28 to –0.92) and a non-significant trend in favour of an increased risk of stroke in the angiotensin converting enzyme inhibitor group (R = 1.16, 95% CI –0.71 to –1.91) [20].

– ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) is the largest trial evaluating anti-hypertensive strategies. 33,357 patients aged over 55 years with grade 1 or 2 hypertension and at least one other risk factor (57% age > 65 years and 36% diabetes) were randomized into four treatment arms as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Study Duration</th>
<th>N (Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>12.5 to 25 mg</td>
<td>n = 15,255</td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>2.5 to 10 mg</td>
<td>n = 9,048</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10 to 40 mg</td>
<td>n = 9,054</td>
<td></td>
</tr>
<tr>
<td>Doxazosine</td>
<td>2 to 8 mg</td>
<td>n = 9,061</td>
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</tr>
</tbody>
</table>

The doxazosine arm was discontinued prematurely due to a significant rise in the risk of major cardiovascular events (+25%) and heart failure (+104%) compared with the diuretic group.

The other patients were followed for a mean 4.9 years. Amlodipine was found equivalent to chlorthalidone for the main endpoint (fatal coronary artery disease and non-fatal myocardial infarction) and the secondary endpoints, excepting heart failure where the risk was 38% higher (95% CI 25-52%).

The effect of lisinopril on the main endpoint was equivalent to that of diuretic but the risk of stroke (+ 15% IC95 % 2-30%), cardiovascular disease (+10%; 95% CI 5-16%) and heart failure (+ 20%, 95% CI 9-34%) were significantly greater.

In the subgroup of patients aged over 65 years, the thiazidic was superior to angiotensin converting enzyme inhibitors for risk of coronary artery disease, cardiovascular disease, and heart failure and greater than the calcium channel blocker for risk of heart failure. The same findings were reported for the subpopulation of diabetic patients, with the exception of an equivalence of lisinopril and chlorthalidone for coronary risk [21].

– In the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study [22], losartan was compared with atenolol; a subgroup of 1,195 diabetics was examined in a separate analysis [23]. Mean age of patients who presented hypertension and left ventricular hypertrophy was 67.4 years. In the diabetic group, losartan was superior to atenolol for cardiovascular morbidity-mortality (R = 0.76, 95% CI 0.58-0.98), the main endpoint, and for cardiovascular mortality (R = 0.63, 95% CI 0.42-0.95) and all-causes mortality (R = 0.61, 95% CI 0.45-0.84). In the subgroup of 960 patients of the LIFE study who had an ultrasound study, treatment with losartan plus hydrochlorothiazide was associated with greater regression of left ventricular hypertrophy compared with the atenolol group [24].
– The ABCD (Appropriate Blood pressure Control in Diabetes) study compared nisoldipine and enalapril in 470 patients with type 2 diabetes aged 40-74 years. There was a lower incidence of fatal and non-fatal myocardial infarction (secondary endpoints) in the enalapril group. A separate analysis was not performed for older patients [25].

– FACET (Fosinopril vs Amlodipine Cardiovascular Events Trial) was performed in 380 type 2 diabetic patients with systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg. After a 2.5 to 3.5 year treatment, fosinopril was found superior to amlodipine for reducing the risk of major cardiovascular events (R = 0.49, 95% CI 0.26-0.95). This difference was observed in both genders but stratification by age showed that the advantage for fosinopril for major cardiovascular events was only observed in subjects aged over 65 years (R = 0.24, 95% CI 0.09-0.65). This was however a secondary endpoint, and the study, designed to analyze the impact of treatments on lipid and glycaemic parameters was not powered for a clinical endpoint analysis [26].

– VALUE (Valsartan anti-hypertensive Long-term Use Evaluation) was designed to examine the hypothesis that valsartan has a more beneficial effect than amlodipine for equivalent blood pressure control in hypertensive patients with a high vascular risk [27]. 15,245 patients aged 67.2 ± 8.2 years were followed for 4.2 years. The subgroup of diabetic patients was not individualized. This study was unable to confirm the initial hypothesis. The frequency of major cardiovascular events was the same in the two groups, or even slightly lower during the first six months due to more rapid reduction in blood pressure in the amlodipine group. Like the other studies, the occurrence of new cases of diabetes was less frequent with the angiotensin II receptor inhibitor valsartan than with amlodipine (R = 0.77, p < 0.001).

Beneficial effect of antihypertensive treatment in particular situations

Prevention in coronary patients

– EUROPA (European trial on reduction of cardiac events with Perindopril in stable coronary artery disease) compared the effect of perindopril (8 mg) versus placebo for a mean duration of 3.7 years in 12,218 patients with coronary artery disease with or without hypertension (31% aged more than 65 yrs and 12.2% diabetics). There was a significant 20% reduction in the risk of major cardiovascular events (95% CI –9 to –29%) (main endpoint) and 22% reduction in non-fatal myocardial infarction (95% CI –10 to –33%) in the perindopril group where the systolic pressures were 5 mmHg lower and the diastolic pressures 2 mmHg lower than in the placebo group. Analysis of subgroups showed a statistically significant benefit of treatment in patients aged over 65 years. In diabetics, the difference did not reach statistical significance due to the small sample size (1,502 patients), but the mean reduction in coronary risk was comparable to that in the total study population [28].

– INVEST (International Verapamil-Trandolapril Study) compared a strategy using a calcium channel blocker (prolonged-release verapamil) versus other antihypertensive agents (first line atenolol) in 22,579 hypertensive coronary patients (33% aged over 70 years, 28.4% diabetics). The therapeutic goal was 140/90 mmHg in the general population and 130/85 mmHg in diabetics. Blood pressure control, all-cause mortality, and risk of major cardiovascular events, myocardial infarction, and stroke were equivalent in the two arms. There was a non-significant trend towards increased risk of major cardiovascular events in patients with heart failure taking calcium channel blockers. The subgroup of diabetic patients aged 70 years and older appeared to respond more favorably to the angiotensin converting enzyme inhibitor, while patients aged less than 70 years appeared to have been slightly better results for major cardiovascular events with the other strategies (NS). Diabetic patients were not different from the general population [29].

Secondary prevention of stroke

– PROGRESS (Perindopril protection against recurrent stroke study) included 6,105 stroke or transient ischemic attack victims aged 26-91 years (mean 64 ± 10), with or without hypertension. These patients, including 13% diabetics, were given perindopril ± indapamide or placebo for four years. Lower blood pressure (9/4 mmHg), 28% (95% CI –17 to –38%) fewer strokes (main endpoint), and 26% (95% CI –16 to –34%) fewer cardiovascular events were observed in the perindopril group. The reduction in the risk of stroke was observed for both hemorrhagic and ischemic events. It was also found in patients with normal blood pressure levels but was greater in patients given indapamide in addition to perindopril. All-cause mortality was however not affected by treatment [30].

Patients with microalbuminuria

– In the MICRO-HOPE (Microalbuminuria cardiovascular and renal outcomes in subjects with diabetes) study, ramipril enabled a 24% reduction (95% CI 3-40%) in the development of renal failure in diabetics with or without microalbuminuria at enrolment. Conversely, the risk of developing microalbuminuria was not affected among patients free of this condition at inclusion [11]. The risk of undergoing dialysis was reduced 16%. In microalbuminuric patients on ramipril, there was also a reduction in the risk of ocular microangiopathic events, of myocardial infarction (~22%) and of stroke (~33%).

– CALM (Candesartan and Lisinopril Microalbuminuria Study) compared the short-term (three months) effect of candesartan, lisinopril, and their combination in 199 type 2 diabetic patients with microalbuminuria aged less than 75 years. Blood pressure curves and albumin/creatinine ratios were equivalent in the three arms [31].

– RENAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) [32], IRMA 2 (Irbesar-
The differences between ambulatory measurements, self-monitoring, and ambulatory monitoring appear to increase with age [37]. The “white coat effect” might concern 25% of older patients who have a diagnosis of systolic hypertension, particularly female patients [38].

The SHEAF study estimated that masked hypertension could concern 10% of elderly patients. It can be detected with a relatively limited number of self-monitoring measurements in the patient’s home or measurements at medical consultation [39].

Similarly, blood pressure self-monitoring enables the detection of a significant number of type 2 diabetes patients whose pressure goals are not achieved despite apparently correct levels at measurements made in the medical office [40].

Self-monitoring and ambulatory monitoring require the definition of new thresholds. In the 2005 guidelines, the AFSSAPS proposes the following levels to be equivalent: medical office measurements: 140/90 mmHg; self-monitoring or ambulatory monitoring at awakening 135/85 mmHg; ambulatory monitoring asleep: 120/70 mmHg [36].

Arterial rigidity due to medialcalciosis is another source of error, particularly in the elderly diabetic. This phenomenon can prevent correct detection of peripheral arteriopathy of the lower limbs and increases abnormally the ankle/arm pressure gradient [41]. It also concerns the humeral artery and can lead to an overestimation of blood pressure [42].

**Institution of antihypertensive treatment**

Institution of antihypertensive treatment in the elderly diabetic is advocated by the American Geriatrics Society (AGS) [43], the National Institute for Clinical Excellence (NICE) in Great Britain, and in the European guidelines [1] for patients whose blood pressure is above 140/80 or 140/85 mmHg.

Guidelines published by the WHO, the JNC VII and the AFSSAPS [36] do not modulate thresholds for intervention as a function of age and set a cutoff level of 130/80 mmHg for diabetic patients.

**Pressure goals in the elderly diabetic**

Current guidelines do not however rule out attempting to reach levels below 140/80 mmHg if the patient tolerates treatment well [43].

Analysis of the HOT results do not however suggest any benefit from lowering blood pressure below 125/75 mmHg and emphasizes the coronary risk associated with diastolic pressure below 75 mmHg [11].

The therapeutic goal of 130/80 mmHg should be modulated as a function of the baseline levels observed. If the baseline pressure is higher than 180 mmHg, it would be reasonable to start with a goal of lowering blood pressure 20 to 30 mmHg [36, 43] then to adjust treatment according to tolerance. The urgency of treatment depends on the severity of the hypertension. The delay should not be greater than one month if the
patient’s pressure is measured above 160/100 mmHg, but could be delayed up to three months for more moderate levels [43].

**Choice of the antihypertensive drug**

Available data do not provide evidence clearly demonstrating the superiority of any one therapeutic class over another. The beneficial effect appears to be essentially related to the reduction in the blood pressure level. Small differences in capacity to prevent certain specific complications may however be observed between different drug classes depending on the specific clinical situation.

**Diuretics**

Diuretic drugs, essentially thiazidics, often associated with a potassium sparer, have clearly demonstrated efficacy in the elderly subject with hypertension and diabetes (SHEP, HYVET-Pilot) [5, 6, 9]. In comparative trials with other more recent therapeutic classes such as angiotensin converting enzyme inhibitors or calcium channel blockers, diuretics have demonstrated equivalent, or slightly better, efficacy, particularly for the risk of heart failure (ALLHAT, MIDAS) [15, 21].

Despite these favorable results, calcium channel blockers, or angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists are often preferred for first-intention treatment because of the lesser metabolic effects and the lower risk of perturbing potassium balance. In the elderly subject, worry about dehydration and hyperosmolar coma as well as the risk of orthostatic hypotension also explain why physicians sometimes hesitate to prescribe diuretics despite the fact that these complications have not been specifically demonstrated in randomized studies.

**β-blockers**

Beta-blockers, frequently combined with diuretics (CONVICE, NORDIL, Stop-Hypertension) [18-20], also have proven efficacy in the elderly diabetic with hypertension, but in the LIFE trial, treatment with losartan produced significantly better results than atenolol [23]. Resistance to use in the elderly subject is related to the risk of heart failure, unrecognized hypoglycaemia in patients on insulin or sulfonylurea, and less often to deleterious metabolic effects. This class of drugs remains nevertheless a valid therapeutic option, particularly in patients with coronary artery disease.

**Calcium channel blockers**

Calcium channel blockers constitute a heterogeneous class of drugs (dihydropyridines, α-phenylalkylamines, benzothiazepines) with different pharmacokinetic and pharmacodynamic properties leading to different therapeutic spectra. For the treatment of hypertension, long-acting or prolonged-release formulations would be preferable. In comparison with other drug classes (diuretics, angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists) calcium channel blockers enables more rapid reduction in blood pressure level and thus a certain advantage in the early phase (VALUE) [27] and perhaps even in long-term treatment (extension of the Syst-Eur trial) [8]. Their efficacy in reducing the risk of stroke has been established in the Syst-Eur trial [7] and is perhaps superior to that of other classes (NORDIL, Stop-Hypertension) [19, 20]. Conversely, the risk of heart failure could be greater than with diuretics (CONVICE, ALLHAT, MIDAS) [15, 18, 20] and the risk of myocardial infarction may be slightly greater compared with diuretics (NORDIL) [19] or angiotensin converting enzyme inhibitors (Stop-Hypertension, ABCD) [20, 25]. The CONVICE study also reported a risk of bleeding [18].

This class is widely used as first-line treatment in elderly diabetics because of its weak metabolic impact, its efficacy in lowering blood pressure without excessive risk of orthostatic hypotension, and its demonstrated efficacy in preventing stroke, particularly in patients with isolated systolic hypertension.

**Angiotensin converting enzyme inhibitors**

The efficacy of this class of drugs has also been well demonstrated as has its usefulness for cardio-vascular prevention in patients with high vascular risk, even without hypertension (HOPE) [11]. The superiority of angiotensin converting enzyme inhibitors over older drug classes is however not demonstrated. Diuretics might be more effective in preventing heart failure, stroke or coronary events in elderly and diabetic patients (ALLHAT) [21]. It is difficult to attribute the reduction of cardiovascular and myocardial infarction risk observed in the EUROPA study to a specific effect of perindopril since the pressure levels in the active treatment arm were lower than those in the placebo arm [28]. Conversely, the nephroprotective effect observed with these drugs in young diabetics has been confirmed in type 2 diabetics by the micro-HOPE study [11]. Cough is a frequent undesirable effect and can limit their use. The risk of renal failure in patients with renal artery stenosis or hyperkalaemia in certain patients is well known and requires surveillance. Excepting these adverse effects, angiotensin converting enzyme inhibitors are widely used as first-intention treatment in elderly subjects, particularly in those with systolic-diastolic hypertension, because of the low risk of hypotension and the drug’s metabolic neutrality.

**Angiotensin II receptor antagonists**

This therapeutic class has well documented efficacy. Of particular interest is its nephroprotective effect in middle-aged subjects with type 2 diabetes. The hypothesis of a particular beneficial effect for the prevention of stroke or cognitive decline (SCOPE) [10] has not been confirmed, nor its superiority over amlodipine for the reduction of risk of major cardiovascular events (VALUE) [27]. While waiting for the results of the VALISH study [14], which should provide information on systolic blood pressure goals in the elderly subject, this class of drugs suffers from a lack of clinical trials.

**Other antihypertensive drugs**

Other antihypertensive drugs, specifically alpha-blockers and central antihypertensive drugs cannot be proposed for first-intention strategies.
Hypertension in elderly diabetics

Treatment surveillance

Recommendations concern:

– angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists: The risk of deteriorating renal function and hyperkalaemia with angiotensin converting enzyme inhibitors appears to be increased in the elderly subject. Because of this, serum creatinine and potassium should be measured one or two weeks after instituting treatment or increasing dosage, then systematically once a year.

– thiazidic or loop diuretics: Blood chemistry one or two weeks after introducing treatment, then at least once a year. The risk would be greater in the event of co-prescription of potentially nephrotoxic drugs (NSAID for example).

Cognitive functions

In patients aged over 75 years, cognitive function should be evaluated (MMS) because of the impact of cognitive decline or dementia on observance and the risk of therapeutic error.

Choice of combination treatment

In regard to combination treatment, the elderly subject is not an exception. The combination must provide an additive or synergistic effect, be well tolerated, and if possible validated by clinical trials. A combination strategy can be proposed if the pressure goals are not attained and lower pressure is well tolerated, particularly in terms of orthostatic hypotension and risk of falls.

Combinations recommended by the AFSSAPS [36] are presented in Figure 1.

In specific situations, a three-drug regimen may be necessary: Good observance and compliance with dietary recommendations (sodium intake, alcohol, calorie intake, body mass index) must be verified before prescribing a three-drug regimen.

Questions warranting further study

Up to what age should patients be treated?

The beneficial effect of therapeutic management of risk factors is difficult to demonstrate in populations of very old subjects in terms of mortality, but inversely, there is no evidence of a significant increase in mortality in patients over 80 years given antihypertensive treatment. The most clearly demonstrated benefit concerns the prevention of stroke which, in the elderly subject, is a major cause of disability. Tolerance to antihypertensive treatment in the elderly subject warrants further study.

The frail or very sick elderly subject

This type of patient has not been included in any of the published studies. It would be reasonable to assume that prevention of stroke would be useful in frail patients. It is also clear that tolerance to treatment in these patients often taking multiple medications must be carefully monitored. More work is needed in this population. For the time being, European guidelines have considered that the goal of 150/90 mmHg is reasonable in these subjects [1].

Conclusion

The elderly diabetic subject benefits from therapeutic management of hypertension as least as much as, if not more than the non-diabetic or younger patient. For the very old frail patient, many questions remain open. Beyond this particular population, the objectives and modalities of therapeutic management do not differ fundamentally from those adopted for middle-aged subjects with type 2 diabetes mellitus, but in terms of tolerance to treatment, and in particular the risk of orthostatic hypotension, dehydration, electrolyte imbalance and renal failure, this population must benefit from reinforced surveillance.

Figure 1
Therapeutic combinations recommended by the AFSSAPS [36]. (Bold lines designate an additive effect on blood pressure lowering). ARA II: angiotensin II receptor antagonists. ACEI: angiotensin converting enzyme inhibitors. CGB: calcium channel blockers.
References


