LEARNING THE ROPES:

Should treatment with blood pressure lowering drugs be stopped in the very old?

BO CARLBERG

Department of Public Health and Clinical Medicine, Umeå University, Sweden

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Very few studies have investigated the effects of initiating, increasing, decreasing or stopping antihypertensive treatment in the very old (≥85 years). It is reasonable to assume that there still is a benefit from treatment in the very old, but increasing presence of co-morbidities and side effects will affect the risk/benefit ratio.

High blood pressure as a risk factor in very old

Even in high age, high blood pressure is a risk factor for stroke. A Swedish population-based study in very old with a mean age of 89 years found that, during a mean follow-up of 2.9 years, high blood pressure and atrial fibrillation were associated with an increased risk for stroke[1]. On the other hand, in many countries, most very eldery are already on treatment with blood pressure lowering drugs. Withdrawal of treatment is probably a much more common measure.

Effects of treatment with blood pressure lowering drugs in very old

The benefits from stopping antihypertensive treatment should be contrasted with the benefit from treating high blood pressure in the very old. The number of subjects aged 85+ in randomized controlled outcome trials of hypertension treatment is very small, and with uncertain results. The largest trial in this age group is the HYVET (HYpertension in the Very Elderly Trial) study[2]. It included subjects aged 80 or more, and active treatment resulted in lower total mortality and fewer cardiovascular events compared with subjects randomized to placebo. Also, there was no association between Frailty Index and the effects of treatment on the outcomes.

In the HYVET-subgroup of subjects aged 85 or more at randomization (n=1038), the treatment effects on cardiovascular outcomes were not statistically different from subjects aged 80-84. In a 1-year extended follow-up of 80 years + subjects, starting after finishing double blind treatment (baseline mean age 84.8 years), total mortality and cardiovascular mortality during the following year was lower in those previously randomized to active treatment, with a hazard ratio of 0,48 (95% confidence interval 0.26-0.87) and 0.19 (95% confidence interval 0.04-0.87), respectively. But, there were no significant differences in cardiovascular morbidity[3].

Which treatment regimen is the best in the very old?

With this very sparse data, it is not possible to gain specific evidence about potential differences between different antihypertensive drugs or treatment regimens in the very old compared with younger individuals. In the HYVET study, a thiazide-like diuretic (indapamide) and the ACE-inhibitor perindopril were used. Guidelines recommend using Angiotensin receptor blockers (ARB), ACE-inhibitors, diuretics and calcium antagonists. A systematic review of beta-blockers in older adults concluded that it could not be recommended to use beta-blockers as first line drugs in older adults[4]. However, there were no specific data from the very old.

Many hypertension guidelines recommend a combination pill containing two different drugs as initial blood pressure lowering drug therapy. The European Society of Hypertension Guideline have a quite strong recommendation for this initial combination therapy. However, due to the potential risk of initial hypotension and other side effects, they recommend that in people above 80 years and in frailer patients, initial monotherapy should be preferred.

Stopping treatment

In clinical practice, stopping antihypertensive drug treatment in old people is a very common measure. Reasons differ; symptomatic orthostatism, polypharmacy, hypotension due to a concomitant acute situation, other severe diseases etc. Very little is known about the effects on blood pressure, side effects, cognitive function or cardiovascular outcomes. There are a few observational studies in this area, but with this research question, it is very difficult to draw conclusions about the risks and benefits without a control group.

A Cochrane review titled "Withdrawal of antihypertensive drugs in older people", published in 2020 included randomized controlled trials of stopping antihypertensive drugs[5]. The review defined "older" as 50 years and older, and only three of the included trials were performed in studies with a mean age over 80 years. Of these, two included only subjects treated with diuretics and the indication could have been hypertension, heart failure or ankle edema. Thus, only one study covered the question about very old persons, the DANTE (Discontinuation of Antihypertensive Treatment in Elderly people) study[6].

The DANTE Study

DANTE included very old persons with drug treated hypertension, SBP below 160 mmHg, and a Mini-Mental State Examination score of 21-27 but not fulfilling the diagnostic criteria of dementia. The mean age was 81 years. Patients with heart failure or a history of myocardial infarction, CABG/PCI or stroke during the last three years were excluded. Participants (n=385) were randomized to continue or discontinue their blood pressure lowering drugs. Primary outcome was the change in a cognitive score from baseline to 4 months. The baseline mean SBP was 148 mmHg and increased by 5.4 mmHg in the discontinuation group and decreased by 2.0 mmHg in the control group.

Discontinuation of antihypertensive treatment did not improve cognitive function[6]. Nearly half of the patients with orthostatic hypotension in the discontinuation group could not discontinue all antihypertensive drugs. Therefore, the prevalence of orthostatic hypotension was not significantly reduced in the intention-to-treat analysis, but only in the as-treated analysis[7]. In total, there were only a few cardiovascular events during the four months of the study.

The OPTiMISE Study

Since then, the OPTiMISE (Optimizing Treatment in for Mild Systolic Hypertension in The Elderly) study has been published[8]. It included subjects with a mean age of 84.8 years with a SBP lower than 150 mmHg on 2 or more antihypertensive drugs. In addition, the physicians had to assess that the patient could benefit from treatment reduction due to polypharmacy, co-morbidity, nonadherence, frailty or dislike of medicines. Patients with heart failure due to left ventricular dysfunction, myocardial infarction or stroke during the last year, secondary hypertension or lacking capacity to consent were excluded.

Patients were randomized to follow a detailed medicine reduction scheme or to usual care for 12 weeks. In the end of the study, patients in the medication reduction group took 0.6 antihypertensive drugs fewer than the usual care group. Mean SBP at baseline was 130 mmHg and after 12 weeks, 3.4 mmHg higher in the deprescribing group compared with the usual care group. During this short follow-up, there were only a few cardiovascular events, but the number of patients experiencing at least 1 adverse event was significantly higher in the medication reduction group.

A cost-effectiveness estimation was performed with a Markov Modelling from a life-time time horizon. The conclusion from this analysis, besides

the uncertainty around many of the assumptions, was that antihypertensive medication reduction should not be attempted in all older patients. A more targeted approach should be required in routine practice.

The HYVET study revisited

Thus, there are very few randomized controlled studies examining the effects of stopping treatment with antihypertensive drugs in the very old. There are no studies with enough power to detect effects on cardiovascular outcomes.

Interestingly, the HYVET study mentioned above might give some more information. In total, 3845 subjects were randomized to active treatment or placebo. One third of the subjects had not been treated with antihypertensive drugs before randomization. They were thus randomized to start treatment or continue without treatment. Two thirds of the participants in the study were already on treatment before randomization. They could be regarded as being randomized to continue treatment of high blood pressure or stopping treatment. Interestingly, total mortality was reduced only in the last group (continue vs stopping treatment). Those who were randomized to continue treatment had lower mortality than those who were randomized to stop antihypertensive drugs (table). This was not a preplanned analysis, only one of many subgroup analyses and one should therefore be careful about interpreting the finding[9].

Epilogue

We know very little about the effect of stopping treatment with blood pressure lowering drugs in the very old or frail. There are sometimes obvious reasons for stopping or reducing treatment; symptomatic orthostatism, co-morbidity, nonadherence, dehydration, etc. However, it is always a risk/benefit estimation with many uncertain parameters. Also, with these sparse data, it is obvious that stopping treatment is often difficult to carry through and might be dangerous. When treatment is withdrawn, the effects on blood pressure, symptoms and signs have to be monitored.

Table. Subgroups, starting and stopping treatment with blood pressure lowering drugs in the HYVET study (table modified from ref 9, with permission)

	Subgroup HYVET Starting treatment vs no treatment (placebo) n=1359 Hazard Ratio (95% CI)	**Subgroup HYVET Continuing treatment vs stopping treatment (placebo) n=2486 Hazard Ratio (95% CI)**
All-cause mortality	0.95 (0.69-1.31)	O.71 (0.56-0.90)
Cardiovascular mortality	0.94 (0.61-1.47)	0.69 (0.50-0.97)
All cardiovascular events	0.69 (0.48-0.99)	0.65 (0.50-0.86)
Fatal or nonfatal Stroke	0.73 (0.39-1.36)	0.69 (0.44-1.07)
Fatal or nonfatal Myocardial infarction	No data	No data
Fatal or nonfatal Heart failure	0.28 (0.12-0.65)	0.42 (0.23-0.76)

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Bo Carlberg – bo.carlberg@umu.se

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