THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Treatment of elevated blood pressure in the very elderly: less is better

Abstract

Risk of serious adverse cardiovascular events increases with advancing age and with higher blood pressure. Falls and other serious adverse events associated with postural hypotension also increase with age and with antihypertensive drug therapy. It is therefore important to know whether drug treatment improves not only cardiovascular outcomes, but also measures of net health which combine benefit and harm: total mortality and all patients with any serious adverse event (see Therapeutics Letter 42 at www.ti.ubc.ca). This Letter focuses on the best available evidence about drug treatment of elevated blood pressure in individuals over 79 years of age.

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What is the evidence for drug treatment of elevated blood pressure in patients 60 to 79 years of age?

A Cochrane review[1] published in 1998, quantified the morbidity and mortality benefit of anti-hypertensive drug therapy for hypertensive patients (systolic BP ≥160 mmHg) 60 years of age and older. It included 15 randomised controlled trials (RCT) of at least one-year duration, and 21,908 patients, mostly from 60 to 79 years old. Most trials were conducted in Western industrialised countries, lasted from three to six years, and evaluated either a diuretic or beta-blocker as the first-line therapy – with allowance for stepped care utilising other drug classes. This meta-analysis showed that therapy reduced both total mortality, RR 0.88 (95%CI 0.82, 0.98), ARR = 1.7%, NNT = 59 for five years; and combined total stroke and coronary heart disease, RR 0.73 (95%CI 0.68, 0.77), ARR = 5%, NNT = 20 for five years. No information was available for total serious adverse events.

This evidence for treatment of systolic BP ≥ 160 mmHg in people mostly aged 60–79 is considered robust and well established.

What is the evidence for drug treatment of elevated blood pressure in patients older than 79 years?

Until summer 2008, evidence for treating patients age 80 or older was based primarily on a sub-group meta-analysis[2] of RCTs from the Cochrane review cited above. This was published in 1999 and included data for 1,670 participants aged 80 years or older, derived from seven trials. This meta-analysis found a reduction in total stroke, RR 0.67 (95%CI 0.48, 0.93), but no decrease in mortality, RR 1.09 (95%CI 0.95, 1.25). The authors concluded that, because of the potential for an increase in mortality due to treatment, further trials were necessary.

What have we learned from the two HYVET studies?

The HYpertension in the Very Elderly Trial (HYVET) investigators designed two trials to determine whether antihypertensive treatment was beneficial in this older age group. The HYVET investigators began with a pilot open label multicentre RCT[3] published in 2003. It was conducted in 10 European countries, enrolling 1,283 patients with a sustained blood pressure of 160-219/90-109 mmHg. Patients were randomly allocated to one of three first-line treatments: thiazide diuretic, ACE inhibitor, or no treatment. Target blood pressure was < 150/80 mmHg; doses of the first-line drug could be doubled and slow release diltiazem could be added. The mean follow-up was 13 months. Total mortality did not differ in the two active treatment arms, compared with no treatment, RR 1.23 (95%CI 0.75, 2.01). Total serious adverse events were not reported. Total stroke was reduced in the two active treatment arms, compared with no treatment, RR 0.50 (95%CI 0.26, 0.95). These results did not answer the question regarding the effect of drug treatment on total mortality, but assisted in the design of the formal trial[4] published in August 2008.

HYVET[4] enrolled 3,845 patients ≥ 80 years with a sustained systolic blood pressure ≥ 160 mmHg from 13 countries in Western and Eastern Europe, China, Australasia and North Africa. Patients were randomised to active treatment or identical placebo. Active treatment consisted of the thiazide-like drug, sustained release indapamide 1.5 mg (equivalent to about 12.5 mg of hydrochlorothiazide), followed by stepped therapy with the ACE inhibitor perindopril 2 mg, increased to 4 mg if necessary. The target blood pressure was < 150/80 mmHg. Median follow-up was 1.8 years. In the active treatment group 26% required thiazide alone, 24% required thiazide plus 2 mg perindopril and 50% required thiazide plus 4 mg perindopril. Active therapy achieved a BP < 150/80 mmHg in

48% of people, while placebo therapy achieved a BP < 150/80 mmHg in 20% of people. The HYVET authors reported outcomes as hazard ratios and total events, rather than as people with at least one event. It is therefore impossible to calculate relative risk or absolute risk reduction except for mortality, for which patients can experience only one event. This trial showed that active therapy reduced total mortality, RR 0.82 (95%CI 0.69, 0.99), ARR = 2.2%, NNT = 48 for two years. The authors also reported the number of serious adverse events as 358 in the active treatment group and 448 in the placebo group. The primary outcome, total stroke, was not significantly reduced, HR 0.70 (95%CI 0.49, 1.01), but fatal and non-fatal heart failure was reduced, HR 0.36 (95%CI 0.22, 0.58). Adding these two HYVET studies to the Cochrane sub-group meta-analysis enlarged the review to nine RCTs comprising 6,798 participants aged ≥ 80. This new meta-analysis shows no effect on total mortality, RR 0.97 (95%CI 0.87, 1.08), but a significant reduction in total stroke, RR 0.67 (95%CI 0.54, 0.84). This translates into a 4% ARR for stroke, NNT = 25 for five years for an elderly population with an incidence of stroke of 12% over five years (incidence in the control group for the Systolic Hypertension in the Elderly trial[2] for people 80 and over).

CI = Confidence interval
RR = Relative risk
ARR = Absolute risk reduction
NNT = Number needed to treat to prevent one event
HR = Hazard ratio

Clinical interpretation

The overall evidence for lowering blood pressure in people ≥ 80 years with systolic BP ≥ 160 mmHg relates to individuals recruited for clinical trials who are relatively healthy. It is not relevant to the sick or frail elderly population. Pooled evidence demonstrates a reduction in the incidence of stroke, but no decrease in total mortality. This is reasonable justification for offering drug treatment to relatively healthy hypertensive elderly, as such patients uniformly want to avoid stroke. The best drug choice for management is not resolved by meta-analysis. However, the largest trial (HYVET[4]) and the only one that demonstrated a net health benefit by reducing both mortality and number of serious adverse events provides a relatively simple approach. Start with a low-dose thiazide followed by a low-dose ACE inhibitor. Double the dose of the ACE inhibitor once, if necessary to achieve a blood pressure < 150/80 mmHg. Using this approach one can expect that about half of patients will achieve a blood pressure of < 150/80 mmHg. This conservative approach to blood pressure management is corroborated by the recent observational study in Swedish individuals ≥ 85 years old, which suggests that systolic blood pressure in the range of 140 to 160 mmHg is optimal for the very elderly.[5]

Conclusions

For patients ≥ 80 years:

- Various antihypertensive therapies for primary prevention in relatively healthy patients with systolic BP > 160 mmHg reduced stroke, but had no proven effect on mortality.
- Using low-dose thiazide as first-line therapy followed by a low-medium dose ACE inhibitor reduced mortality as well as serious adverse events in one large RCT.
- With this regimen a blood pressure of < 150/80 mmHg can be expected in about 50% of patients.

The draft of this Therapeutics Letter was submitted for review to 60 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

References

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