Editorial

Treatment of hypertension in the elderly: new findings in older subjects

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The Australian National Blood Pressure Study (ANBP) was one of the first trials to demonstrate benefits from blood pressure lowering, primarily with diuretic and beta-blocker therapy[1]. Since this time, treatment of hypertension has moved from the specialist arena to the family practice environment and new agents have been developed for the control of hypertension. In the early 1990's these treatments had been clearly shown to confer cardiovascular outcome benefits, particularly in the elderly who are at greatest risk of cardiovascular events[2-5]. At the time this study commenced, newer agents such as angiotensin-converting enzyme (ACE)-inhibitors and calcium channel blockers were being widely adopted in practice for the treatment of hypertension, despite a total absence of evidence to demonstrate advantages over older agents[6]. Thus the ANBP2 was one of a number of outcome trials starting in the mid 1990's to investigate the benefits of ACE-inhibitor with diuretic therapy for the treatment of hypertension in the elderly.

A total of 1594 family medical practices throughout Australia were involved in ANBP2. The study adopted a prospective, randomized open-label study design with the blinding of endpoint assessments (PROBE)[7,8]. Study inclusion criteria were: average untreated sitting blood pressure at the two "study entry" visits of ≥ 160 mmHg systolic and/or ≥ 90 mmHg diastolic (if systolic was ≥ 140 mmHg), no recent cardiovascular morbidity (within 6 months), and willing to give informed consent. Exclusion criteria included: any life-threatening illness, contraindication to an ACE-inhibitor or diuretic, plasma creatinine > 2.5 mg/dl, malignant hypertension, or dementia. Subjects were randomized by telephone from a central location to either ACE-inhibitor-based or diuretic-based treatment. Drug treatments were based on either ACE-inhibitor or diuretic therapy with the choice of agent and starting dose at the discretion of the general practitioner[9]. In order to achieve a blood pressure target of < 140/90 mmHg, dose titration or additional agents including beta-blockers, calcium channel blockers and alpha-blockers were recommended in both groups and were at the discretion of the general practitioner. Initial and subsequent cardiovascular events were included in the primary endpoint of "all cardiovascular events or any death". Cox regression was used to model multiple times to events with randomized group as the principal predictor[10]. Endpoints were collected by study nurses who reviewed general practitioner case notes, hospital records and death certificates.

In order to identify the 6083 subjects randomized to ANBP2, 54 282 subjects were screened by study nurses. The treatment groups were well balanced in terms of entry blood pressure (mean ± SD) 168 ± 13/91 ± 8 mmHg and other baseline characteristics. Sixty-two percent had been on previous antihypertensive therapy, 8% had previous coronary heart disease events, 5% previous cerebrovascular disease, and 7% were diagnosed diabetics (Table I). At the end of the observation period, 60% remained on allocated drug treatment (58% ACE-inhibitor and 62% diuretic) and 35% ACE-inhibitor and 37% diuretic subjects required more than one agent. Additional

Table I. Baseline characteristics of the second Australian National Blood Pressure Study population.

	ACE-inhibitor (n = 3044)	Diuretic (n = 3039)	Total (n = 6083)
Sex (M/F) (%)	50/50	48/52	49/51
Age (years)	72.0	71.9	71.9
65-74 (%)	70	70	70
75-84 (%)	30	30	30
Blood pressure (mmHg)			
Systolic	167 ± 13	168 ± 13	168 ± 13
Diastolic	91 ± 8	91 ± 8	91 ± 8
Previously treated (%)	62	62	62
Body mass index (kg/m^2)	27 ± 4	27 ± 4	27 ± 4
Smoking (%)			
Current	7	7	7
Ex-smokers	46	45	45
Alcohol (%)			
Current	74	72	73
Ex-drinkers	6	7	6
Physically active (%)	78	76	77
Coronary heart disease* (%)	8	8	8
Cerebrovascular disease** (%)	5	4	5
Diabetes mellitus (%)	8	7	7
Hypercholesterolemia (%)	38	36	37
Lipid-lowering drugs	13	13	13

Values are expressed as means ± SD. * defined as myocardial infarction, angina, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty; ** defined as stroke or transient ischemic attack.

antihypertensive drugs used in the ACE-inhibitor and diuretic groups respectively were calcium channel blockers (22.9 and 24.9%), beta-blockers (10.8 and 13.7%) and angiotensin receptor blockers (14 and 12.4%).

Clinically relevant and highly significant blood pressure reductions of the same magnitude (-26/-12 mmHg) were observed in both ACE-inhibitor and diuretic groups. ACE-inhibitor treatment was associated with an 11% reduction in the rate of all cardiovascular events or death compared to diuretic treatment (hazard ratio-HR 0.89; 95% confidence interval-CI 0.79-1.00, p = 0.05) (Fig. 1). A similar effect for ACE-inhibitor treatment in comparison to diuretic was observed for all first cardiovascular events or death 0.89 (95% CI 0.79-1.01, p = 0.06), particularly for all first myocardial infarctions (adjusted HR 0.68; 95% CI 0.47-0.98, p = 0.04).

There was no difference between the two treatment groups in fatal cardiovascular events with the exception of fatal strokes which were higher with ACE-inhibitor treatment (adjusted HR 1.91; 95% CI 1.04-3.50, p = 0.04). However, ACE-inhibitor treatment was associated with a 14% reduction in first non-fatal cardiovascular events (adjusted HR 0.86; 95% CI 0.77-0.99, p = 0.03) and a 32% reduction in first non-fatal myocardial infarctions (adjusted HR 0.68; 95% CI 0.47-0.99, p = 0.05).

Of interest, males had almost twice as many events as females (907 vs 524 total events) and effects of ACE-

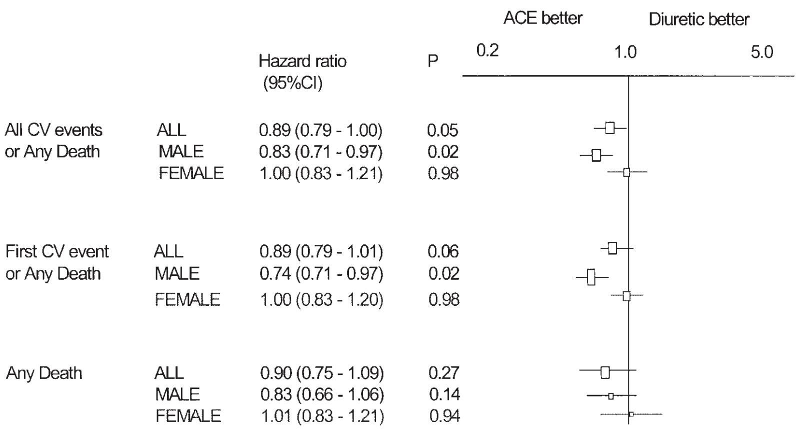

Figure 1. *Primary results for all subjects, males and females. ACE = angiotensin-converting enzyme; CI = confidence interval; CV = cardiovascular.*

inhibitor treatment were more evident in males (HR 0.83; 95% CI 0.71-0.97, p = 0.02) than in females (HR 1.00; 95% CI 0.83-1.21, p = 0.98) (Fig. 1). Cause specific and fatal and non-fatal differences between treatment groups were, as with the main outcomes of the study, only observed in males.

Overall, the results of other comparative studies in the elderly are consistent with the current findings, however ANBP2 is the first to demonstrate differences of a clinically relevant magnitude[11,12]. Also, these findings do not reflect those of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study which reported on the superiority of diuretic therapy over ACE-inhibitor in a similar age subgroup[13].

Whilst ANBP2 was ongoing two other studies were published comparing ACE-inhibitor-based therapy of hypertension with "conventional" treatment in elderly subjects: the Swedish Trial in Old Patients with Hypertension (STOP)-2[11] study and the Captopril Prevention Project (CAPPP)[12]. Whilst direct comparison is difficult as the primary outcome for each of the studies is different, the results of ANBP2 are consistent with the findings from these studies. STOP-2 showed no difference in the primary cardiovascular mortality outcome, however there was a trend for benefits in all myocardial infarction, all stroke, and heart failure frequency with ACE-inhibition. The CAPPP study also showed no difference in the combined cardiovascular morbidity and mortality primary endpoint, however trends were observed in favor of ACE-inhibitor treatment for fatal cardiovascular events, all cardiac events and new-onset diabetes. Randomization inequalities particularly in baseline blood pressure make interpretation of the CAPPP study findings difficult. Other factors such as trial design, patient entry criteria, endpoint definition, and alpha-error may be contributing to the differences observed between the ANBP2 findings and those from these two other studies.

Shortly prior to the publication of ANBP2, the principle findings from the ALLHAT were published[13]. Whilst ALLHAT was not specifically a trial in elderly hypertensives, there were a considerable number in the 65-84 year age range given that this was the largest antihypertensive trial undertaken. ALLHAT's findings suggested that in the elderly subgroups, diuretics were not only as effective as ACE-inhibitors but may be better in preventing heart failure and stroke. ANBP2's findings demonstrated modest benefits in favor of ACE-inhibition for all cardiovascular events and death. Important differences in the study populations, study design, additional antihypertensive agents used, on-treatment blood pressure control and endpoint definitions are likely to be major contributors to differences observed in study outcomes. ANBP2 has been conducted entirely in the family practice setting where the treating physician has the responsibility to manage the patient in terms of dosage changes and choice of additional therapy to control hypertension. Where combination therapy was required, the combinations that have been used were sensible and it is likely that these results will reflect those in a "real-world" setting with relatively healthy elderly hypertensives. Unlike ALLHAT and other recent antihypertensive treatment trials, the population in this trial is relatively healthy, active and overall had few previous cardiovascular events, low rates of diabetes and therefore the benefit could be expected to be less but more generally applicable to the increasing numbers of persons over the age of 65 years.

The findings of the recently reported Heart Outcomes Prevention Evaluation (HOPE)[14] and Losartan Intervention for Endpoint reduction in hypertension (LIFE)[15] trials suggest that ACE-inhibition confers benefits in high-risk subjects above that derived from blood pressure lowering. Possible mechanisms influencing these outcomes may include lipid neutrality[16,17], left ventricular hypertrophy reduction[18], enhancing insulin sensitivity[17] and influencing the atherosclerotic process such as plaque stability and endothelial function[19]. The findings from ANBP2 also suggest that ACE-inhibition may be beneficial in elderly hypertensive patients beyond the effects on blood pressure lowering.

In conclusion, a modest outcome advantage for ACE-inhibitor-based therapy, particularly for males, over a diuretic-based regimen was observed in elderly hypertensives despite similar reductions in blood pressure. This finding was observed in the setting of usual family practice where most elderly hypertensive patients are managed. The message from ANBP2, which complements and balances ALLHAT, is that general practitioners will utilize a wide variety of agents from any specific class of antihypertensive therapy to lower blood pressure and in many patients more than one agent will be required to achieve blood pressure control. The actual dose and combination of therapy for individual patients to achieve blood pressure control is likely to remain as part of the "art" of medicine – the "science" has demonstrated that lowering blood pressure by whatever means is beneficial for long-term outcomes in hypertensive patients.

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