Short- and Long-Term Survival in Treated Elderly Hypertensive Patients With or Without Diabetes: Findings From the Second Australian National Blood Pressure Study

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BACKGROUND
We sought to determine the incidence of newly diagnosed diabetes in treated elderly hypertensive patients and the prognostic impact of diabetes on long-term survival.

METHODS
The Second Australian National Blood Pressure (ANBP2) study randomized 6,083 hypertensive patients aged 65–84 years to angiotensin-converting enzyme inhibitor (ACEI) or thiazide diuretic–based therapy and followed them for a median of 4.1 years. Long-term survival was determined in 5,678 patients over an additional median of 6.9 years after ANBP2 (post-trial).

RESULTS
After ANBP2, the cohort was classified into preexisting (7.2%), newly diagnosed (5.6%), and no diabetes (87.2%) groups. A 44% higher incidence of newly diagnosed diabetes was observed in patients randomized to thiazide diuretic compared with ACEI-based treatment. The other predictors of newly diagnosed diabetes were having a higher body mass index, having a higher random blood glucose, and living in a regional location compared to major cities (a geographical classification based on accessibility) at study entry. After completion of ANBP2, compared with those with no diabetes, the preexisting diabetes group experienced higher cardiovascular (hazards ratio (HR) = 1.65; 95% confidence interval (CI) = 1.03–2.65) and all-cause mortality (HR = 1.40; 95% CI = 1.02–1.92) when adjusted for age, sex, and treatment. A similar pattern was observed after including the post-trial period for cardiovascular (HR = 1.52; 95% CI = 1.20–1.93) and all-cause mortality (HR = 1.50; 95% CI = 1.29–1.73). However, when the newly diagnosed group was compared with the no diabetes group, no significant difference was observed in cardiovascular (HR = 0.33; 95% CI = 0.11–1.05) or all-cause mortality (HR = 0.76; 95% CI = 0.47–1.23) either during the ANBP2 trial or including post-trial follow-up (cardiovascular: HR = 0.82; 95% CI = 0.58–1.17; all-cause mortality: HR = 1.04; 95% CI = 0.85–1.27).

CONCLUSIONS
Long-term presence of diabetes reduces survival. Compared with thiazide diuretics, ACEI-based antihypertensives may delay the development of diabetes in those at risk and thus potentially improve cardiovascular outcome in the elderly.

Keywords: blood pressure; elderly; hypertension; mortality; newly diagnosed diabetes; preexisting diabetes.

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Diabetes is a global health problem and its prevalence is on the rise in both high- and low-income countries. 1 High blood pressure (BP) frequently coexists with diabetes, and the risk of developing diabetes is greater in those with hypertension than in those with normal BP. 2, 3 The coexistence of diabetes and hypertension substantially increases the risk of cardiovascular disease and all-cause mortality, and the magnitude of this risk increase appears to be more than simply additive. 4, 5 A number of studies have shown a reduction in the risk of cardiovascular events and mortality in cohorts with diabetes for specific antihypertensive drug classes, notably renin-angiotensin system antagonists and calcium channel blockers, 6–12 which have also been found to be associated with a lower risk of diabetes development in hypertensive populations without preexisting diabetes. 13, 14

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Although a number of hypertension treatment trials have reported the associated incidence of newly diagnosed diabetes,16–17 there is a limited amount of information on the long-term prognostic impact of newly diagnosed diabetes in treated hypertensive patients because of the relatively short duration of follow-up after the onset of diabetes.15,16 Moreover, data are limited in the elderly, who have a higher prevalence of hypertension and increased risk of diabetes.18–20

The aim of this study was to determine the incidence of newly diagnosed diabetes and examine factors predicting its development in older people with hypertension who are in the 7th–9th decades of life. In addition, this study examined the implications of newly diagnosed diabetes for short-term and long-term survival of elderly persons treated for hypertension.

METHODS

Study design and participants

The study design and main findings from the Second Australian National Blood Pressure (ANBP2) study have been published previously.21 A total of 6,083 hypertensive patients aged 65–84 years were enrolled in the PROBE designed study and randomized to either angiotensin-converting enzyme inhibitor (ACEI)–based (n = 3,044) or diuretic-based (n = 3,039) treatment.22 Study inclusion criteria included average untreated BP at the 2 study entry visits of ≥160 mm Hg systolic and/or ≥90 mm Hg diastolic (if systolic was ≥140 mm Hg), having no recent cardiovascular morbidity (within 6 months), and willing to give informed consent. The ACEI, enalapril, and the diuretic, hydrochlorothiazide, were recommended as initial therapy; however, choice of the specific agent and dose within these 2 classes was determined by the family practitioner. To achieve goal BP, addition of other antihypertensive drugs was recommended in both groups.

After the completion of ANBP2, consenting participants of this elderly cohort entered a follow-up study to assess the progression of hypertension in the 8th and later decades of life and to investigate factors associated with all-cause and cardiovascular morbidity and mortality. The diagnosis of new diabetes and its outcome were not prespecified in the study design and main findings from the Second Australian National Blood Pressure (ANBP2) study have been published previously.21

Definition of diabetes

Patients were classified as having preexisting diabetes if they had been identified as having diabetes at study entry (randomization) and were classified as having newly diagnosed diabetes if they developed diabetes during the ANBP2 in-trial phase. Patients who remained free from diabetes during the ANBP2 study were classified as having no diabetes. The diagnosis of newly diagnosed diabetes was based on the following criteria: (i) being diagnosed or treated for diabetes by their family practitioners or (ii) first incidence of a random plasma glucose concentration ≥11.1 mmol/L (≥200 mg/dl).

Subject follow-up, survival, and endpoint measurement

In the ANBP2 clinical trial phase, the cohort was followed for a median of 4.1 years. Data on prescribed medications, BP measurements, laboratory tests, and any cardiovascular events were collected during the follow-up visits. An endpoint committee blinded to drug treatment adjudicated all potential study endpoints. The endpoint events considered during the clinical trial phase were (i) any first nonfatal cardiovascular event, (ii) any cardiovascular mortality, and (iii) all-cause mortality.

After conclusion of the clinical trial, long-term survival and events (post-trial) were determined by (i) linkage to the Australian Institute of Health and Welfare National Death Index (death registry) and (ii) information received from the participants and their family physicians by questionnaire (n = 1,858, post-trial follow-up phase). The National Death Index provided International Classification of Disease, 10th Edition coding to classify cause of death. Major nonfatal cardiovascular events occurring since clinical trial closure were identified from the family physicians and participants questionnaires.

Statistical analysis

The risk of newly diagnosed diabetes and its predictors were identified among those who were free of diabetes at study entry (n = 5,642). Multivariable Cox regression analysis was undertaken after univariable analysis to identify the predictors of newly diagnosed diabetes. Covariables included baseline (18 variables) (Table 1) and in-study variables (e.g., use of multiple antihypertensives, target BP achievement).

Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for cardiovascular and all-cause mortality were estimated using Cox proportional hazard models for patients with preexisting and newly diagnosed diabetes compared with patients without diabetes during the clinical trial phase (Analysis A, short-term), then together with post-trial follow-up (Analysis B, long-term), and also considering only the post-trial follow-up period (Analysis C, extended period only). These analyses were adjusted for clustering of patients within family practices and potential risk factors such as age, sex, and treatment regimen. The intention-to-treat principle was used for all analyses. Kaplan–Meier survival curves were plotted after the end of the clinical trial phase for all-cause and cardiovascular mortality by diabetes groups (no diabetes, preexisting diabetes, and newly diagnosed diabetes), and the log-rank test was used to compare the curves. We repeated Analyses A–C by stratifying patients for randomized treatment regimen to assess whether there was any difference by drug treatment between the groups.

We also conducted a subanalysis to identify the association of newly diagnosed diabetes with first nonfatal events stratified by randomized treatment regimen among the participants: (i) during the ANBP2 clinical trial (n = 6,083) and (ii) during the post-trial follow-up period (n = 1,858 subjects with completed questionnaires). Any nonfatal events occurring during the post-trial phase were censored at 30 June for the respective year because exact date was not recorded.
Further analysis was conducted after inclusion of the duration of diabetes as a covariable in Analyses A–C for those patients with diabetes (preexisting and newly diagnosed). All analyses were performed using Stata version 11.2 for Windows.

**RESULTS**

A total of 441 (7.2%) subjects had diabetes at ANBP2 study entry (preexisting diabetes). During in-trial follow-up of the clinical trial phase, a further 339 subjects (5.6%) were diagnosed with diabetes (newly diagnosed diabetes). The remaining 87.2% of the patients (n = 5,303) remained free from diabetes throughout the trial period. Table 1 describes patient characteristics at the time of study entry classified by diabetes status: preexisting, newly diagnosed, and no diabetes. In the newly diagnosed diabetes patients, the duration of diabetes was a median of 2.4 years at the conclusion of the clinical trial phase and a median of 8.8 years for post-trial follow-up, whereas, in those with preexisting diabetes, the duration of diabetes was a median of 9.4 years at the conclusion of clinical trial phase and a median of 15.4 years for post-trial follow-up.
The average BP (systolic/diastolic) of patients at randomization and during the study period was 168/91 mm Hg and 145/81 mm Hg, respectively. Twenty-nine percent (n = 1,762) of patients achieved average on-study systolic BP <140 mm Hg, and 96% (n = 5,845) achieved diastolic BP <90 mm Hg. At the closure of the clinical trial, 45% (n = 2,754) of the patients were receiving >1 antihypertensive drug.

**Newly diagnosed diabetes**

The incidence rate of newly diagnosed diabetes was 14.5 per 1,000 patient-years (1.45% per year) during the clinical trial phase. One hundred thirty-nine subjects in the ACEI-based (11.9 per 1,000 patient-years) and 200 subjects in the diuretic-based (17.2 per 1,000 patient-years) groups developed diabetes. The diuretic-based group had a 44% greater rate in the development of newly diagnosed diabetes (P = 0.001) than the ACEI-based group. The cumulative hazards for the development of diabetes in both treatment groups over the study period are illustrated in Figure 1.

The results of univariable Cox regression are presented in Supplementary Table S1. After multivariable analysis, predictors of the development of newly diagnosed diabetes were: allocation to the diuretic-based group (HR = 1.89; 95% CI = 1.46–2.43; P < 0.001) vs. the ACEI-based group; higher body mass index (BMI) (BMI ≥ 30 kg/m² vs. BMI <25 kg/m²: HR = 3.41, 95% CI = 2.38–4.89, P < 0.001; BMI 25–29 kg/m² vs. BMI <25 kg/m²: HR = 1.71, 95% CI = 1.22–2.40, P = 0.002); a unit increase in random blood glucose of 1 mmol/L at study entry (HR = 1.51; 95% CI = 1.42–1.61; P < 0.001), and living in a regional location, a geographical classification based on accessibility/remoteness index of Australia (HR = 1.46; 95% CI = 1.13–1.90; P = 0.004) compared with living in a major city at study entry. To assess the incremental effect of developing newly diagnosed diabetes, we assigned 1 point for each of the predictors (except treatment group) (Supplementary Table S2). In these hypertensive patients, the incidence of newly diagnosed diabetes increased with the number of risk factors from 2.9% without any risk factors to 13.6% for ≥2 risk factors.

**Survival outcome**

During the clinical trial phase (Analysis A) for a median period of 4.1 years (interquartile range (IQR) = 3.9–4.6), death from all causes occurred in 405 patients (15.7 per 1,000 patient-years), with cardiovascular-related deaths occurring in 166 patients (6.4 per 1,000 patient-years). Both all-cause and cardiovascular-related mortality were higher in patients with preexisting diabetes than in those free of diabetes (Table 2, Analysis A). There was no significant difference in observed all-cause and cardiovascular mortality in hypertensive patients with newly diagnosed diabetes compared with those with no diabetes (Table 2, Analysis A).

After the inclusion of data from the post-trial follow-up period (Analysis B), over a median of 10.8 years (IQR = 9.6–11.4 years) there were 1,830 deaths (30.4 per 1,000 patient-years) from all causes, of which 803 deaths (13.3 per 1,000 patient-years) were cardiovascular related. The risk of all-cause and cardiovascular-related mortality remained significantly higher in the preexisting diabetes group than in the no diabetes group (Table 2, Analysis B). In addition, there was no significant difference in the long-term post-trial survival for those with newly diagnosed diabetes compared with those with no diabetes.

Similar findings were observed when the analysis was restricted only to the post-trial phase (Table 2, Analysis C) for a median of 6.9 years (IQR = 6.1–6.9 years). Survival by year after the end of the clinical trial phase is presented in Figure 2. Significant differences between diabetes subgroups regarding the incidence of all-cause mortality (Figure 2a) (overall log-rank test P < 0.001) and cardiovascular mortality were observed (Figure 2b) (overall log-rank test P = 0.01). The stratified analyses by assigned treatment groups on observed fatal events are presented in Supplementary Table.
Diabetes and Survival in Elderly Hypertensives

No difference was observed in the HR for fatal events in treatment groups for newly diagnosed diabetes and those who remained free from diabetes.

The subanalysis conducted to explore the association of preexisting and newly diagnosed diabetes on first nonfatal cardiovascular event during the ANBP2 clinical trial showed that the presence of preexisting diabetes significantly increased the hazards of events compared with those with no diabetes (HR = 1.57; 95% CI = 1.24–1.99; P < 0.001), but this was not observed in those with newly diagnosed diabetes. However, no other differences were observed for nonfatal events during the post-trial follow-up period (Supplementary Table S4) between those with and without diabetes. Overall incidence rates for nonfatal events were higher among those receiving diuretics (Supplementary Table S4) in the stratified analysis by randomized treatment regimen. However, no differences were observed on first nonfatal cardiovascular events (including both periods) in subjects receiving ACEI vs. diuretics.

Further analysis using Cox regression after inclusion of diabetes duration as a covariable in the Analyses A–C revealed that the newly diagnosed diabetes group experienced significantly less cardiovascular and all-cause mortality in comparison with patients with preexisting diabetes (Supplementary Table S5).

**DISCUSSION**

This study in elderly hypertensive patients participating in the ANBP2 clinical trial examined the incidence of newly diagnosed diabetes after entering the trial, risk factors for its development, mortality outcome, and nonfatal...
cardiovascular events at a median of 4.1 years (end of clinical trial) and a long-term mortality outcome over an additional median of 6.9 years (post-trial follow-up). During the clinical trial phase, the incidence of newly diagnosed diabetes was 5.6% across all randomized patients and was 44% higher in those receiving diuretic-based antihypertensive therapy vs. those receiving ACEI-based therapy. The development of newly diagnosed diabetes was predicted by commencing antihypertensive treatment with a diuretic and by a higher BMI, a higher random blood glucose level, and living in a regional area at trial entry. Those with preexisting diabetes at study entry were more likely to experience cardiovascular and all-cause mortality during both clinical trial (short-term) and including post-trial (long-term) follow-up than those without diabetes throughout the clinical trial period (no diabetes group). A similar finding for first nonfatal cardiovascular event was observed in the preexisting diabetes group during the clinical trial but not during the post-trial follow-up. In contrast, there were no differences in cardiovascular and all-cause mortality and in first nonfatal cardiovascular events during the clinical trial or the post-trial follow-up in those who developed newly diagnosed diabetes compared with those in the no diabetes group.

The observed incidence of newly diagnosed diabetes during the clinical trial was 1.45% per year in these elderly treated hypertensive patients, although these differences in incidence rates are significantly impacted by differences in diagnostic criteria for diabetes and population characteristics.8,24–26 The age-standardized incidence rate of newly diagnosed diabetes in Australia is 0.7% per year.27 In the elderly hypertensive patients participating in the ANBP2 trial, the presence of higher BMI and a higher blood glucose level at study entry, both suggestive of a metabolic syndrome, predicted newly diagnosed diabetes, which is consistent with other reports that show that obesity is a significant predictor of newly diagnosed diabetes28,29 as is the metabolic syndrome.17,30,31 Participants living in regional areas as compared with large metropolitan areas were also more likely to have newly diagnosed diabetes. Although we do not have a clear explanation for this association, a higher prevalence of diabetes has been previously reported in regional areas in Australia.32

A key finding of this study is that being treated with a thiazide diuretic–based antihypertensive regimen (in comparison with an ACEI-based regimen) was also an independent predictor of newly diagnosed diabetes. Thiazide diuretics have been previously reported as a predictor for the development of newly diagnosed diabetes in younger hypertensive populations,8,13,14 and this study has now also shown this finding to relate to older hypertensive patients. This effect of thiazide diuretics has been attributed to effects on both insulin secretion and glucose metabolism.33 The observation suggests that treatment with thiazide diuretics may unmask newly diagnosed diabetes in those who are already at risk of development of diabetes, such as those who are obese and/or those who already have higher blood glucose levels.
As expected, those who entered the ANBP2 trial with preexisting diabetes had a higher mortality rate at the end of the trial and including post-trial long-term follow-up (10 years in total). However, for those with newly diagnosed diabetes (during the clinical trial), there was no significant increase in mortality risk or nonfatal cardiovascular events observed by the end of the clinical trial or with longer term follow-up compared with those with no diabetes. The association of newly diagnosed diabetes with fatal outcomes is controversial. Little or no effect of newly diagnosed diabetes on mortality has been reported from previous studies, whereas others have reported an increased mortality. Moreover, some studies have found no effect of newly diagnosed diabetes on fatal events but have reported an increase in nonfatal events. One prominent confounding factor suggested for the lack of an adverse effect of newly diagnosed diabetes on outcome is the short duration of follow-up of study participants after the development of newly diagnosed diabetes. Earlier studies have also suggested that, in elderly patients who already are at higher risks of cardiovascular events because of their age, to observe any additional effect on outcome at least a decade of exposure to newly diagnosed diabetes is required. In addition, in older subjects, competing risks for mortality, such as cancer and dementia, may mitigate the adverse effect of diabetes on survival in newly diagnosed diabetes patients in their 7th and 8th decades of life.

There are some limitations of our study that should be noted. First, the definition of newly diagnosed diabetes is based on either random plasma glucose concentration or use of an antidiabetic agent by the patient or notification/treatment of the patient for diabetes by his/her family practitioner. Thus there is a chance of a misclassification of the trial and including post-trial long-term follow-up because of the rapidly aging population and the increases in obesity seen in many societies. Given the health, social, and economic burden imposed by diabetes, delaying the onset of diabetes may have a significant public health impact.

These findings suggest that even in advanced age, diuretic-based BP-lowering medication may confer a cardio-metabolic detriment, with increased rates of newly diagnosed diabetes compared with ACEI-based therapy, particularly in the presence of other risk factors for diabetes. Our study also showed that a longer duration of diabetes was associated with poor survival. Consideration of the individual patient's risk factors for diabetes is important in the choice of therapies for chronic diseases such as hypertension. In those at high risk of diabetes, initiating therapy for hypertension with an ACEI, an angiotensin receptor antagonist, or a calcium channel antagonist may be more appropriate than commencing with a thiazide diuretic in both older and younger hypertensive patients.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at American Journal of Hypertension (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

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