# Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial

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## Summary

**Background** The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial showed that initial antihypertensive therapy with benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide in reducing cardiovascular morbidity and mortality. We assessed the effects of these drug combinations on progression of chronic kidney disease.

**Methods** ACCOMPLISH was a double-blind, randomised trial undertaken in five countries (USA, Sweden, Norway, Denmark, and Finland). 11 506 patients with hypertension who were at high risk for cardiovascular events were randomly assigned via a central, telephone-based interactive voice response system in a 1:1 ratio to receive benazepril (20 mg) plus amlodipine (5 mg; n=5744) or benazepril (20 mg) plus hydrochlorothiazide (12·5 mg; n=5762), orally once daily. Drug doses were force-titrated for patients to attain recommended blood pressure goals. Progression of chronic kidney disease, a prespecified endpoint, was defined as doubling of serum creatinine concentration or end-stage renal disease (estimated glomerular filtration rate <15 mL/min/1·73 m² or need for dialysis). Analysis was by intention to treat (ITT). This trial is registered with ClinicalTrials.gov, number NCT00170950.

**Findings** The trial was terminated early (mean follow-up 2·9 years [SD 0·4]) because of superior efficacy of benazepril plus amlodipine compared with benazepril plus hydrochlorothiazide. At trial completion, vital status was not known for 143 (1%) patients who were lost to follow-up (benazepril plus amlodipine, n=70; benazepril plus hydrochlorothiazide, n=73). All randomised patients were included in the ITT analysis. There were 113 (2·0%) events of chronic kidney disease progression in the benazepril plus amlodipine group compared with 215 (3·7%) in the benazepril plus hydrochlorothiazide group (HR 0·52, 0·41–0·65, p<0·0001). The most frequent adverse event in patients with chronic kidney disease was peripheral oedema (benazepril plus amlodipine, 189 of 561, 33·7%; benazepril plus hydrochlorothiazide, 85 of 532, 16·0%). In patients with chronic kidney disease, angio-oedema was more frequent in the benazepril plus amlodipine group than in the benazepril plus hydrochlorothiazide group. In patients without chronic kidney disease, dizziness, hypokalaemia, and hypotension were more frequent in the benazepril plus hydrochlorothiazide group than in the benazepril plus amlodipine group.

**Interpretation** Initial antihypertensive treatment with benazepril plus amlodipine should be considered in preference to benazepril plus hydrochlorothiazide since it slows progression of nephropathy to a greater extent.

**Funding** Novartis.

*Lancet* 2010; 375: 1173–81

Published Online February 18, 2010 DOI:10.1016/S0140-6736(09)62100-0

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## Introduction

Current guidelines for management of hypertension in Europe and the USA recommend initial antihypertensive therapy with a combination of two drugs for patients whose blood pressure is 20/10 mm Hg above their treatment goal.[1,2] The US guidelines recommend that a thiazide diuretic be included in the initial combination,[1] whereas experimental and clinical evidence suggests that other combinations—ie, a renin-angiotensin system blocker such as an angiotensin-converting enzyme (ACE) inhibitor and a dihydropyridine calcium-channel blocker—effectively reduce blood pressure and have vasculoprotective effects.[3,4]

Patients with chronic kidney disease usually need combination antihypertensive therapy to achieve the recommended blood pressure goal of less than 130/80 mm Hg;[5,6] however, patients with this disease who were treated with three antihypertensive agents did not achieve the recommended blood pressure goals in clinical trials.[7] Patients with albuminuria above 33·9 mg/mmol, whether or not they have chronic kidney disease, need additional antihypertensive treatment to achieve blood pressure goals, whereas those with normoalbuminuria do not need such treatment.[8,9]

Most studies in patients with advanced stage nephropathy support the initial use of renin-angiotensin

system blockers in combination with diuretics to reduce blood pressure.[5,6,10] However, no studies have compared the effect of initial treatment with two different fixed-dose combinations of antihypertensive drugs on progression of chronic kidney disease. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial compared the effectiveness of a maximally titrated, fixed-dose combination of the ACE inhibitor benazepril and the dihydropyridine calcium-channel blocker amlodipine with the combination of benazepril and hydrochlorothiazide in reducing cardiovascular morbidity and mortality. The trial was stopped early because of a 20% reduction in cardiovascular risk recorded in the benazepril plus amlodipine group.[11]

As part of the prespecified analyses of the ACCOMPLISH trial,[12] we examined the effects of the drug combinations at the approved maximum doses on chronic kidney disease outcomes in a large population of patients who were at high risk for cardiovascular events. We report the frequency of the composite endpoint of progression of chronic kidney disease, defined as doubling of serum creatinine concentration or end-stage renal disease (estimated glomerular filtration rate [eGFR] <15 mL/min/1·73 m² or need for dialysis). Additionally, we report this outcome in combination with cardiovascular mortality or all-cause mortality, and report changes in surrogate markers of progression of chronic kidney disease, such as changes in eGFR and albuminuria.

## Methods

### Patients

The rationale and study design for the ACCOMPLISH trial have been reported in detail elsewhere.[12] Briefly, ACCOMPLISH was a prospective, randomised, double-blind clinical trial undertaken in five countries (USA, Sweden, Norway, Denmark, and Finland). Men or women aged 55 years or older of any ethnic background were eligible for enrolment. All enrolled patients had hypertension and were at high risk for cardiovascular events; patients were included if they had a history of coronary events, myocardial infarction, revascularisation, stroke, chronic kidney disease, peripheral arterial disease, left ventricular hypertrophy, or diabetes. Detailed eligibility criteria have been described elsewhere.[12] All patients provided written informed consent approved by the respective institutional review boards of the trial centres before enrolment.

### Randomisation and masking

Between October, 2003, and May, 2005, eligible patients were randomly assigned in a global 1:1 ratio to one of two treatment groups, with assignments made centrally by telephone by use of the interactive voice response system (IVRS). A group external to the study sponsor generated the randomisation sequence and all individuals involved in the conduct of the trial were masked to treatment assignments for the duration of the study. The randomisation list was reviewed by the sponsor's biostatistics section for quality assurance and locked after approval. Randomisation data were kept strictly confidential, accessible only to authorised individuals, until the time of unblinding.

The pre-generated randomisation sequence was programmed via algorithm into the telephone system. To assign a patient to a study group, investigational sites needed to call directly into the telephone system and enter demographic data for the patient. The investigator received details of randomisation group, which were also confirmed by fax. The randomisation number was written on the space provided on the drug label. This randomisation number also determined delivery and assignments of masked study drug at each visit (packaged in identical blister packs for each treatment group). During the trial, the IVRS immediately reported the occurrence of any emergency code breaks to the principal investigator and the monitor for the site. Only when the study had been completed, the data file verified, and protocol violations determined were the drug codes broken and made available for data analysis.

### Procedures

Patients were randomly assigned to receive either a single pill combination of benazepril (20 mg) plus amlodipine (5 mg) or a combination of benazepril (20 mg) plus hydrochlorothiazide (12·5 mg) daily, without washout of previous medications.

1 month after randomisation, the benazepril component in both groups was force titrated to 40 mg. 2 months after randomisation, investigators could titrate doses of either drug to the maximum, if needed, to achieve a target blood pressure of less than 140/90 mm Hg (or <130/80 mm Hg for patients with diabetes or chronic kidney disease). 3 months after randomisation and until the end of the trial, add-on antihypertensive agents, consisting of β blockers, α blockers, clonidine, and spironolactone, were allowed. β blockers were recommended as a second agent in both groups to achieve blood pressure targets. Once-daily loop diuretics could be given for volume management. After the initial 3-month titration period, patients returned at 6 months and then at 6-month intervals until the end of the trial.[12] Patient follow-up for assessment of endpoints continued until the end of the trial, even if study medication had been permanently discontinued.

### Endpoints

The primary endpoint of the main ACCOMPLISH trial was time to first event of composite cardiovascular morbidity and mortality (sudden cardiac death, myocardial infarction, stroke, coronary intervention, congestive heart failure, or other cardiovascular causes).[11,12] The prespecified, intention-to-treat, chronic kidney disease endpoint was time to first event of doubling of serum creatinine concentration or end-stage renal disease,

| | Patients with chronic kidney disease (n=1093) | | | Patients without chronic kidney disease (n=10 389) | | | Comparison of chronic kidney disease *vs* no chronic kidney disease | | |
|---|---|---|---|---|---|---|---|---|---|
| | All (n=1093) | Benazepril plus amlodipine (n=561) | Benazepril plus hydrochlorothiazide (n=532) | All (n=10 389) | Benazepril plus amlodipine (n=5171) | Benazepril plus hydrochlorothiazide (n=5218) | $\chi^2$ test | *F* statistic | p value |
| Men | 734 (67·2%)* | 366 (65·2%) | 368 (69·2%) | 6217 (59·8%) | 3076 (59·5%) | 3141 (60·2%) | 22·14 (men *vs* women) | .. | <0·0001 |
| Ethnic origin | | | | | | | | | |
| Black | 218 (19·9%)* | 106 (18·9%) | 112 (21·1%) | 1194 (11·5%) | 587 (11·4%) | 607 (11·6%) | 65·51 (black *vs* non-black) | .. | <0·0001 |
| White | 844 (77·2%)* | 441 (78·6%) | 403 (75·8%) | 8751 (84·2%) | 4368 (84·5%) | 4383 (84·0%) | 35·43 (white *vs* non-white) | .. | <0·0001 |
| Other | 31 (2·8%)† | 14 (2·5%) | 17 (3·2%) | 444 (4·3%) | 216 (4·2%) | 228 (4·4%) | 5·15 (other *vs* black or white) | .. | 0·0232 |
| Region | | | | | | | | | |
| USA | 839 (76·8%)* | 428 (76·3%) | 411 (77·3%) | 7293 (70·2%) | 3627 (70·1%) | 3666 (70·3%) | 20·61 (USA *vs* Nordic countries) | .. | <0·0001 |
| Nordic countries | 254 (23·2%) | 133 (23·7%) | 121 (22·7%) | 3096 (29·8%) | 1544 (29·9%) | 1552 (29·7%) | .. | .. | .. |
| Age (years) | 70·9 (7·52)* | 71·3 (7·7) | 70·6 (7·3) | 68·1 (6·73) | 68·1 (6·7) | 68·1 (6·8) | .. | 169·21 | <0·0001 |
| ≥65 | 834 (76·3%)* | 433 (77·2%) | 401 (75·4%) | 6788 (65·3%) | 3371 (65·2%) | 3417 (65·5%) | 53·29 (≥65 *vs* <65) | .. | <0·0001 |
| ≥75 | 354 (32·4%)* | 200 (35·7%) | 154 (28·9%) | 1929 (18·6%) | 957 (18·5%) | 972 (18·6%) | 118·58 (≥75 *vs* <75) | .. | <0·0001 |
| Body-mass index (kg/m²)‡ | 31·1 (6·4) | 31·3 (6·6) | 31·0 (6·2) | 30·9 (6·2) | 30·9 (6·2) | 30·9 (6·2) | .. | 1·32 | 0·2510 |
| <30 | 522 (47·8%) | 256 (45·6%) | 266 (50·1%) | 5240 (50·5%) | 2591 (50·2%) | 2649 (50·9%) | 2·97 (<30 *vs* ≥30) | .. | 0·0847 |
| ≥30 | 570 (52·2%) | 305 (54·4%) | 265 (49·9%) | 5127 (49·5%) | 2573 (49·8%) | 2554 (49·1%) | .. | .. | .. |
| Blood pressure (mm Hg) | | | | | | | | | |
| Systolic | 145·0 (20·3) | 145·1 (20·2) | 145·0 (20·5) | 145·4 (18·0) | 145·3 (18·2) | 145·4 (17·8) | .. | 0·40 | 0·5282 |
| Diastolic | 78·4 (11·0)* | 78·6 (11·2) | 78·1 (10·7) | 80·2 (10·7) | 80·3 (10·8) | 80·2 (10·6) | .. | 28·74 | <0·0001 |
| Heart rate (beats per min) | 69·3 (11·2)† | 69·4 (10·9) | 69·1 (11·6) | 70·5 (10·9) | 70·6 (10·9) | 70·5 (11·0) | .. | 12·95 | 0·0003 |
| eGFR (mL/min/1·73 m²) | 45·1 (8·8)* | 45·2 (8·9) | 45·1 (8·8) | 82·5 (19·0) | 82·6 (18·7) | 82·5 (19·3) | .. | 4143·3 | <0·0001 |
| Serum creatinine (μmol/L) | 139·7 (26·5)* | 138·8 (23·0) | 140·6 (22·1) | 81·33 (17·7) | 81·3 (15·9) | 82·2 (16·8) | .. | 11 329 | <0·0001 |
| Fasting glucose (mmol/L) | 6·88 (2·64)† | 6·82 (2·64) | 6·94 (2·63) | 7·09 (2·58) | 7·13 (2·63) | 7·06 (2·54) | .. | 6·87 | 0·0088 |
| UACR (mg/mmol)§ | 28·8 (70·3)* | 30·8 (77·2) | 26·7 (59·8) | 8·7 (29·5) | 8·8 (29·2) | 8·6 (29·9) | .. | 251·9 | <0·0001 |
| <3·39 | 421 (46·8%)* | 226 (49·1%) | 195 (44·4%) | 5306 (69·6%) | 2665 (69·3%) | 2641 (70·0%) | 189·77 (<3·39 *vs* ≥3·39) | .. | <0·0001 |
| 3·39–33·9 | 311 (34·6%) | 148 (32·2%) | 163 (37·1%) | 1896 (24·9%) | 961 (25·0%) | 935 (24·8%) | .. | .. | .. |
| >33·9 | 167 (18·6%)* | 86 (18·7%) | 81 (18·5%) | 418 (5·5%) | 219 (5·7%) | 199 (5·3%) | 215·46 (≤33·9 *vs* >33·9) | .. | <0·0001 |

Data are n (%) or mean (SD). eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio. Data shown are for all randomised patients with creatinine concentration measurements at baseline. Chronic kidney disease is defined as baseline serum creatinine concentration more than 106·1 μmol/L in women and more than 114·9 μmol/L in men. All results shown are based on tests with one degree of freedom for $\chi^2$ and numerator of *F* test. Denominator degrees of freedom for *F* test are 11 435 to 11 480, apart from 8517 for UACR. *p<0·0001 compared with no chronic kidney disease group. †p<0·05 compared with no chronic kidney disease group. ‡Body-mass index was calculated as a function of weight and height. 11 459 (99·6%) of randomised patients (patients with chronic kidney disease, n=1092; patients without chronic kidney disease, n=10 367) had baseline measurements for creatinine, weight, and height. §Percentage based on all patients with baseline values. 2769 (26·7%) patients without chronic kidney disease and 194 (17·7%) with chronic kidney disease had no UACR measurements at baseline.

***Table 1:*** **Baseline characteristics of patients**

defined as eGFR less than 15 mL/min/1·73 m² or need for chronic dialysis. This endpoint was defined before the data and safety monitoring board recommended early termination of the trial. Because of this early termination, the follow-up period in this trial is about 1 year shorter than that in previous trials reporting chronic kidney disease outcomes.[13–15]

Other endpoints were progression of chronic kidney disease plus death (all-cause or cardiovascular), change in albuminuria, and change in eGFR. Additionally, progression of chronic kidney disease was assessed in the subset of patients with more advanced chronic kidney disease at baseline. Chronic kidney disease was defined by the upper limit of normal for the laboratory values—ie, a serum creatinine concentration more than 106·1 μmol/L (eGFR ≤46 mL/min/1·73 m²) in women and more than 114·9 μmol/L (eGFR ≤55 mL/min/1·73 m²) in men. Additionally, the chronic kidney disease endpoint was assessed in those aged 65 years or older because of an interaction noted in the analysis between age and the combined endpoint of progression of chronic kidney disease and mortality.

Measurements of urine albumin were made after randomisation only if urinary albumin-to-creatinine ratio (UACR) was 3·39 mg/mmol or more at screening. UACR was assessed by use of a single morning urine specimen, in accordance with published guidelines.[2,16] All urine albumin and creatinine samples were measured in the central laboratory—albumin by an immunoturbidimetric method[17] and creatinine by a modified Jaffe method.[18]

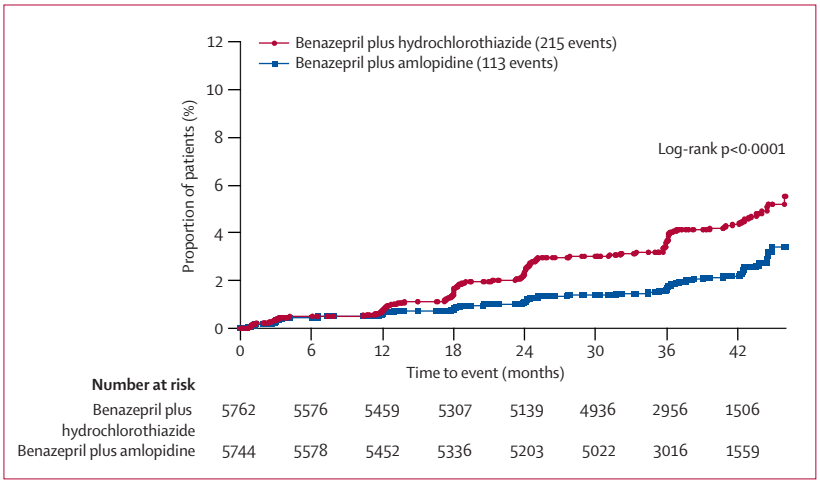


***Figure 1:*** **Kaplan-Meier curves for progression of chronic kidney disease for the intention-to-treat population**
Progression of chronic kidney disease was defined as doubling of serum creatinine concentration, estimated glomerular filtration rate less than 15 mL/min/1·73 m², or need for dialysis.

### Statistical analysis

ACCOMPLISH was an event-driven trial designed to accrue 1642 patients with primary events, providing 90% power to detect a 15% risk reduction for the benazepril plus amlodipine group at a two-sided significance level of 0·05, on the assumption of an annual event rate of 3·5% for the benazepril plus hydrochlorothiazide group.[12] A central committee whose members were unaware of study group assignments adjudicated all prespecified endpoints by use of standard criteria. An independent data monitoring committee met twice a year. 4-yearly formal interim analyses for efficacy were originally prespecified. The analysis of the main composite endpoint, its components, and all other efficacy endpoints followed the intention-to-treat principle. We imputed missing values by carrying the last observation forward. We used Kaplan-Meier methods to construct cumulative time-to-event curves for the two groups and the main comparison was based on a log-rank test. Univariate Cox regression was used to estimate treatment hazard ratios (HRs) and 95% CIs. Model assessment for proportionality of hazard was based on plots of log (–log [survival]) versus log (time).[19,20]

For the analysis of chronic kidney disease, continuous data are given as mean (SD) and categorical data as actual number of events and percentages. In the main analysis in this report, we used a time-to-event approach and included all randomised participants (intention to treat). Treatment comparisons with regard to data for time to first event were similar to those done for the primary endpoint in the main ACCOMPLISH trial,[11] including the use of log-rank tests and Cox regression of time to occurrence of first event for estimation of the HR and 95% CI. Time-to-event analyses were done for each endpoint, without censoring for previous events of other types, so that all patients were included with complete information about the respective endpoints. Analyses on prespecified subgroups were done with the Cox regression model, with factors for treatment, subgroup, and interactions. All p values were two-sided. We concluded superior efficacy for the benazepril plus amlodipine treatment group if the log-rank test was significant with risk reduction. Specific details about the statistical analyses are reported elsewhere.[11,12]

Comparisons between treatment groups for categorical data were done with the $\chi^2$ test. For continuous variables, comparisons between treatment groups were done with *F* tests. Urine albumin concentrations and urine albumin-creatinine ratios were not normally distributed; therefore, values were log-transformed before analysis. For log-transformed data, the geometric mean and 95% CI are presented. All analyses were done with SPSS version 16. This study is registered with ClinicalTrials.gov, number NCT00170950.

### Role of the funding source

This trial was designed by the ACCOMPLISH executive committee, all of whom are authors of this report. The sponsor of the trial was Novartis, which undertook all data collection and provided statistical analyses. All data analyses, however, were under the direction of the first author. The authors had full access to all the data for the entire trial, not only those data used in the current analysis. The sponsor had no role in determining journal submission of this work. The corresponding author and the executive commitee had final responsibility for the decision to submit for publication. The authors, with no direct input from the sponsor, interpreted the data and wrote the report.

## Results

In the main trial, 13 782 patients were screened and 11 506 were randomly assigned to treatment (benazepril plus amlodipine, n=5744; benazepril plus hydrochlorothiazide, n=5762). Mean follow-up was 2·9 years (SD 0·4). At trial completion, vital status was not known for 143 (1%) patients who were lost to follow-up (benazepril plus amlodipine, n=70; benazepril plus hydrochlorothiazide, n=73). Patients who were lost to follow-up did not differ from those who completed the study in terms of baseline characteristics. All randomised patients were included in the intention-to-treat analysis. Patient baseline characteristics, primary endpoints for the trial, blood pressure levels, and safety data are reported elsewhere.[11] Mean blood pressure after dose adjustment was 131·6/73·3 mm Hg (SD 18·2/10·3) in the benazepril plus amlodipine group and 132·5/74·4 mm Hg (17·9/11·2) in the benazepril plus hydrochlorothiazide group (mean difference 0·9/1·1 mm Hg, p<0·0013). Blood pressure control was achieved by 4119 (75%) patients in the benazepril plus amlodipine group and 3963 (72%) patients in the benazepril plus hydrochlorothiazide group.

11 482 patients had data for creatinine concentration at baseline. Table 1 shows the baseline characteristics of patients with and without advanced chronic kidney disease. Patients with chronic kidney disease had a mean

eGFR of 45·1 mL/min/1·73 m² (IQR 39·5–51·9). Compared with those without chronic kidney disease, patients with chronic kidney disease had a lower eGFR and were more likely to be male, black, have a higher mean age, be older than 75 years, and have albuminuria more than 33·9 mg/mmol. In the subgroup of patients with chronic kidney disease, there were no demographic differences between treatment groups. Patients with chronic kidney disease had a similar rate of diabetes to those without the disease (58·9% *vs* 60·5%; p=0·302). Cardiovascular mortality was higher for patients with chronic kidney disease than for those without (46 deaths, 4·2%, *vs* 194 deaths, 1·9%; HR 1·64, 95% CI 1·15–2·34; p<0·0001), as was all-cause mortality (91 deaths, 8·3%, *vs* 406 deaths, 3·9%; HR 1·70, 1·33–2·18; p<0·0001).

In the intention-to-treat population, there were fewer chronic kidney disease events (figure 1) and fewer combined cardiovascular deaths and chronic kidney disease events (figure 2) in the benazepril plus amlodipine group than in the benazepril plus hydrochlorothiazide group. Table 2 shows the frequency of chronic kidney disease outcomes in the intention-to-treat population and in those aged 65 years or older. There were 113 (2·0%) chronic kidney disease events in the benazepril plus amlodipine group compared with 215 (3·7%) events in the benazepril plus hydrochlorothiazide group (HR 0·52, 95% CI 0·41–0·65, p<0·0001).

The combined endpoint of progression of chronic kidney disease and all-cause mortality was also lower in the benazepril plus amlodipine group (346 events, 6·0%) than in the benazepril plus hydrochlorothiazide group (465 events, 8·1%; HR 0·73, 95% CI 0·64–0·84; p<0·0001). The rate of chronic kidney disease events in 7640 participants who were 65 years or older (208 events, 2·7%) did not differ from the rate in patients who were younger than 65 years (118 events, 3·1%; HR 0·85, 0·68–1·07; p=0·189). However, there was an interaction (p=0·011) between older age (≥65 years) and the combined endpoint of progression of chronic kidney disease and all-cause mortality.

In patients with chronic kidney disease, more than half of patients in each treatment group had diabetic nephropathy (benazepril plus amlodipine, 335 of 561, 59·7%; benazepril plus hydrochlorothiazide, 309 of 532, 58·1%). However, in such patients, progression of chronic kidney disease did not differ between groups: there were 16 (4·8%) events in the benazepril plus amlodipine group compared with 17 (5·5%) events in the benazepril plus hydrochlorothiazide group (HR 0·78, 95% CI 0·38–1·56; p=0·48). Incorporation of cardiovascular mortality into the endpoint did not change its significance (benazepril plus amlodipine, 28 events, 8·4%; benazepril plus hydrochlorothiazide, 30 events, 9·7%; HR 0·79, 0·47–1·34; p=0·39).

The blood pressure target in patients with chronic kidney disease was less than 130/80 mm Hg. Figure 3 shows the changes in systolic and diastolic blood pressure during the trial in this subgroup of patients. In patients who achieved the blood pressure target, no differences in the proportion with office systolic blood pressure control were seen between groups throughout the study or at the final visit (benazepril plus amlodipine, n=220, 39·2%; benazepril plus hydrochlorothiazide, n=198, 37·2%; p=0·37). In patients with chronic kidney disease aged 65 years or older, mean blood pressure was lower in the benazepril plus amlodipine group (133·1/71·2 mm Hg [SD 16·7/10·3]) than in the benazepril plus hydrochlorothiazide group (134·4/73·2 mm Hg [18·2/11·3]; p=0·004).

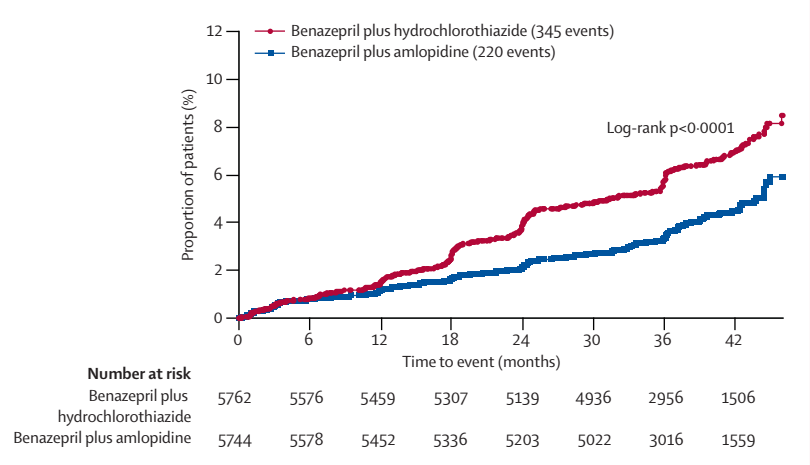


***Figure 2:*** **Kaplan-Meier curves for progression of chronic kidney disease plus cardiovascular death for the intention-to-treat population**
Progression of chronic kidney disease was defined as doubling of serum creatinine concentration, estimated glomerular filtration rate less than 15 mL/min/1·73 m², or dialysis.

Baseline eGFRs for the intention-to-treat population were similar between groups (benazepril plus amlodipine, 79 mL/min/1·73 m² [SD 21·2]; benazepril plus hydrochlorothiazide, 79·0 mL/min/1·73 m² [21·5]). There was a slower decline in eGFR after 2·9 years of treatment in the benazepril plus amlodipine group (–0·88 mL/min/1·73 m² [15·6]) than in the benazepril plus hydrochlorothiazide group (–4·22 mL/min/1·73 m² [16·3]; p=0·01). In patients with chronic kidney disease (ie, those with a mean eGFR at baseline of 45·1 mL/min/1·73 m² [8·8]), progression of chronic kidney disease was slower in the benazepril plus amlodipine group (1·6 mL/min/1·73 m² [12·7]) than in the benazepril plus hydrochlorothiazide group (–2·3 mL/min/1·73 m² [10·6]; p=0·001).

69·6% of patients without chronic kidney disease had normoalbuminuria (UACR <3·39 mg/mmol) and 81·4% of patients with chronic kidney disease had normoalbuminuria or microalbuminuria (UACR 3·39–33·9 mg/mmol; table 1). Thus, only 5·1% (585 patients) of the total population had albuminuria more than 33·9 mg/mmol. In 446 (76·2%) of those patients with baseline albuminuria more than 33·9 mg/mmol who were assessed at the final visit, there was a reduction in UACR from baseline in the benazepril plus hydrochlorothiazide group (median change –63·8%,

| | Benazepril plus amlodipine | Benazepril plus hydrochlorothiazide | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|
| **Intention-to-treat population (N=11 506)*** | | | | |
| Main endpoint of progression of chronic kidney disease | 113 (1·97%) | 215 (3·73%) | 0·52 (0·41–0·65) | <0·0001 |
| Doubling of serum creatinine concentration | 105 (1·83%) | 208 (3·61%) | 0·51 (0·39–0·63) | <0·0001 |
| Dialysis | 7 (0·12%) | 13 (0·23%) | 0·53 (0·21–1·35) | 0·180 |
| eGFR <15 mL/min/1·73 m² | 18 (0·31%) | 17 (0·30%) | 1·06 (0·54–2·05) | 0·868 |
| Progression of chronic kidney disease and cardiovascular death | 220 (3·83%) | 345 (5·99%) | 0·63 (0·53–0·74) | <0·0001 |
| Progression of chronic kidney disease and all-cause mortality | 346 (6·02%) | 465 (8·07%) | 0·73 (0·64–0·84) | <0·0001 |
| **Patients aged ≥65 years (n=7640)†** | | | | |
| Main endpoint of progression of chronic kidney disease | 70 (1·83%) | 138 (3·62%) | 0·50 (0·37–0·67) | <0·0001 |
| Doubling of serum creatinine concentration | 66 (1·73%) | 132 (3·46%) | 0·49 (0·37–0·67) | <0·0001 |
| Dialysis | 3 (0·08%) | 10 (0·26%) | 0·30 (0·08–1·09) | 0·053 |
| eGFR <15 mL/min/1·73 m² | 11 (0·29%) | 11 (0·29%) | 1·00 (0·43–2·31) | 0·99 |
| Progression of chronic kidney disease and cardiovascular death | 160 (4·18%) | 234 (6·13%) | 0·68 (0·55–0·83) | 0·0002 |
| Progression of chronic kidney disease and all-cause mortality | 266 (6·96%) | 327 (8·57%) | 0·81 (0·68–0·95) | 0·010 |

Data are n (%). Progression of chronic kidney disease was defined as doubling of serum creatinine concentration, estimated glomerular filtration rate [eGFR] <15 mL/min/1·73 m², or need for dialysis. *Benazepril plus amlodipine, n=5744; benazepril plus hydrochlorothiazide, n=5762. †Benazepril plus amlodipine, n=3824; benazepril plus hydrochlorothiazide, n=3816.

***Table 2:*** **Outcomes in the intention-to-treat population and in patients aged 65 years or older**

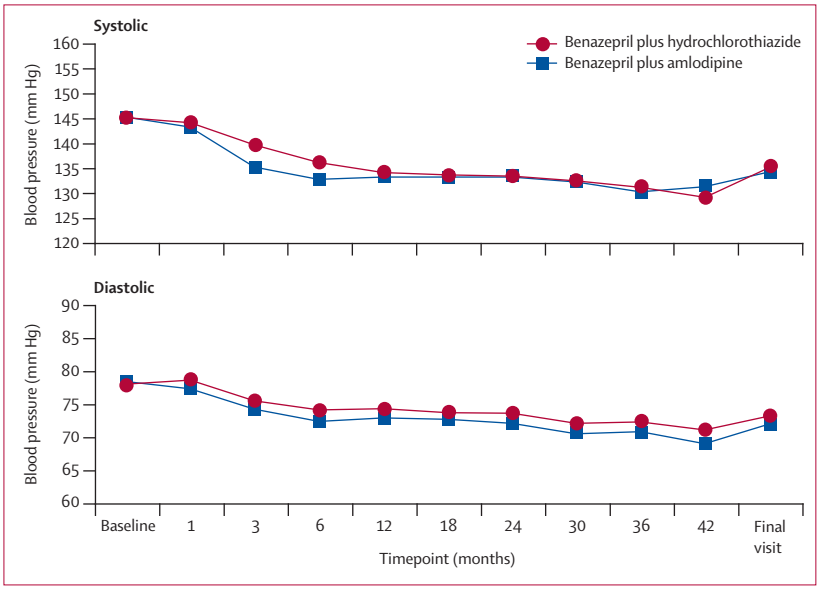


***Figure 3:*** **Changes in blood pressure throughout the trial in patients with chronic kidney disease**

IQR –89·7 to 4·5; n=217) compared with a median change of –29·0% (IQR –73·3 to 66·8; n=229) in the benazepril plus amlodipine group (p<0·0001 for ratio of log mean change from baseline). In 409 (97·1%) of 421 patients in the chronic kidney disease subgroup who were assessed at the final visit, a reduction in UACR from baseline was noted in the benazepril plus hydrochlorothiazide group (median change –26·8%, IQR –71·2 to 67·0; n=202) whereas an increase was seen in the benazepril plus amlodipine group (median change 2·9%, IQR –55·3 to 226·6; n=207; p=0·0001 for ratio of log mean change from baseline).

Of the 2207 patients with baseline microalbuminuria, a smaller proportion in the benazepril plus amlodipine group became normoalbuminuric than in the benazepril plus hydrochlorothiazide group (n=463, 41·7%, *vs* n=750, 68·3%; p=0·0016). Similarly, in 585 patients who had baseline albuminuria in excess of 33·9 mg/mmol, the proportion of patients that reverted to microalbuminuria or became normoalbuminuric differed between groups (n=146, 49·7%, *vs* n=251, 89·6%; p=0·0012).

Table 3 shows the frequency of adverse events. The most frequent adverse event in patients with chronic kidney disease was peripheral oedema (benazepril plus amlodipine, n=189, 33·7%; benazepril plus hydrochlorothiazide, n=85, 16·0%). In patients without chronic kidney disease, dizziness, hypokalaemia, and hypotension were more frequent in the benazepril plus hydrochlorothiazide group than in the benazepril plus amlodipine group. Conversely, in patients with chronic kidney disease, angio-oedema was more frequent in the benazepril plus amlodipine group than in the benazepril plus hydrochlorothiazide group.

## Discussion

This trial shows that in patients with hypertension at high risk for cardiovascular events, combination treatment with benazepril plus amlodipine reduces progression of chronic kidney disease more effectively than does benazepril plus hydrochlorothiazide. This benefit was also seen when cardiovascular or all-cause mortality were assessed with progression of chronic kidney disease. Differences in blood pressure control throughout the study could not account for these findings.

Although reduction of blood pressure is essential to slow progression of chronic kidney disease, antihypertensive

| | Patients with chronic kidney disease | | | Patients without chronic kidney disease | | |
|---|---|---|---|---|---|---|
| | Benazepril plus amlodipine (n=561) | Benazepril plus hydrochlorothiazide (n=532) | p value | Benazepril plus amlodipine (n=5171) | Benazepril plus hydrochlorothiazide (n=5218) | p value |
| Peripheral oedema | 189 (33·7%) | 85 (16·0%) | <0·0001 | 1603 (31·0%) | 686 (13·1%) | <0·0001 |
| Dizziness | 141 (25·1%) | 129 (24·2%) | 0·73 | 1048 (20·3%) | 1329 (25·5%) | <0·0001 |
| Dry cough | 120 (21·4%) | 93 (17·5%) | 0·10 | 1056 (20·4%) | 1125 (21·6%) | 0·14 |
| Hypotension | 24 (4·3%) | 29 (5·5%) | 0·36 | 118 (2·3%) | 178 (3·4%) | 0·0005 |
| Hyperkalaemia | 12 (2·1%) | 12 (2·3%) | 0·89 | 22 (0·4%) | 21 (0·4%) | 0·85 |
| Hypokalaemia | 0 | 1 (0·2%) | 0·30 | 3 (0·1%) | 16 (0·3%) | 0·003 |
| Angio-oedema | 9 (1·6%) | 2 (0·4%) | 0·04 | 44 (0·9%) | 32 (0·6%) | 0·15 |
| Allergic reaction to study drugs | 1 (0·2%) | 2 (0·4%) | 0·53 | 23 (0·4%) | 23 (0·4%) | 0·97 |

Data are n (%).

*Table 3:* **Adverse events**

agents that block the renin-angiotensin system in patients with advanced nephropathy and albuminuria of more than 33·9 mg/mmol show additional protection from progression.[10,13–15,21,22] By contrast, use of a dihydropyridine calcium-channel blocker (without a renin-angiotensin system blocker) does not slow progression of chronic kidney disease to the same extent as a renin-angiotensin system blocker alone, despite similar reduction in blood pressure.[23,24] Patients with advanced nephropathy with albuminuria above 33·9 mg/mmol, however, require multiple antihypertensive drugs to achieve recommended blood pressure targets.[6] Moreover, in a post-hoc analysis of a trial in patients with diabetic nephropathy and albuminuria above 33·9 mg/mmol, the combination of a dihydropyridine calcium-channel blocker with a renin-angiotensin system blocker yielded chronic kidney disease outcomes similar to that of a renin-angiotensin system blocker in combination with a diuretic drug.[24]

Other trials assessing progression of chronic kidney disease in hypertensive patients with nephropathy and normoalbuminuria or microalbuminuria show similar outcomes to our study when assessed by the same criteria.[25,26] For example, The Appropriate Blood Pressure Control in Diabetes (ABCD) trial did not show a significant difference between the enalapril and nitrendipine groups in chronic kidney disease outcomes at similar blood pressures to those achieved in this trial.[26] This result is consistent with our findings in that the subgroup with diabetes did not have any unique outcome, although, like the ABCD trial, our participants had predominantly normoalbuminuria or microalbuminuria.

The age at which patients start dialysis has been steadily increasing over the past two decades—from 62 years in 1990 to 68 years in 2008—and is projected to further increase by 2015.[27] Furthermore, although our data are consistent with previous reports of higher rates of cardiovascular and all-cause mortality in patients with an eGFR below 60 mL/min/1·73 m², more people survive such events nowadays; therefore, morbidity, including worsening kidney function, is also higher. In this trial, 32·4% of patients with chronic kidney disease—ie, those with an eGFR at or below 45 mL/min/1·73 m²—were older than 75 years of age. Our data suggest that people in this age group have better chronic kidney disease outcomes when treated with benazepril plus amlodipine than when treated with benazepril plus hydrochlorothiazide. Moreover, in this older subgroup, dizziness and hypotension were more frequent in patients assigned to benazepril plus hydrochlorothiazide than in those assigned to benazepril plus amlodipine. Although the study was not powered for definitive outcomes regarding progression of chronic kidney disease in elderly people, it provides data in this age group for alternative treatments and safety parameters in the context of chronic kidney disease outcomes.

All randomised trials that show reduced rates of chronic kidney disease progression with renin-angiotensin system blockers have been in patients with albuminuria of more than 33·9 mg/mmol.[5] A 30% reduction or more in albuminuria in those with more than 33·9 mg/mmol albuminuria in addition to reduction in blood pressure is a consistent finding in these trials; this finding accords with a slowed progression of chronic kidney disease.[5] This relation, however, has not been shown in people with normoalbuminuria or microalbuminuria.[28] The absence of an association is the main reason that microalbuminuria is not accepted as a surrogate marker of progression of nephropathy.[29]

Although frequency of albuminuria was reduced in both treatment groups, the magnitude of reduction was less than 30% and the overall reduction was greater in the benazepril plus hydrochlorothiazide group than in the benazepril plus amlodipine group. This finding accords with results reported by the Gauging Albuminuria Reduction with Lotrel in Diabetic Patients with Hypertension (GUARD) study, which randomised 332 patients with hypertension, type 2 diabetes, and UACR 2·26–56·5 mg/mmol to benazepril plus amlodipine or benazepril plus hydrochlorothiazide; patients were followed up for 1 year.[30] Results from this study, and results from our trial, differed from those reported in other trials

for reasons that are not clear. A factor that might have contributed to the disparate results is that the level of albuminuria might have been too low, since more than 80% of patients in our trial had a concentration of urine albumin in the normal or microalbuminuria range. Additionally, the higher frequency of side-effects related to volume depletion in the benazepril plus hydrochlorothiazide group—ie, dizziness and hypotension—might have contributed to a greater reduction in eGFR in the intention-to-treat analysis, however, that alone would not account for these differences. Sodium intake and urine osmolarity might have also been a factor since they are known to affect albuminuria; however, but these factors were not assessed in these trials.[31]

After the first year of the ACCOMPLISH trial, we noted that the decline in eGFR in the benazepril plus amlodipine group was slower than the decline in the benazepril plus hydrochlorothiazide group. This differential change in eGFR was not related clinically to chronic kidney disease events.

A strength of our study is that the chronic kidney disease endpoints were prespecified and end-stage renal disease was used as part of the definition. Change in progression of chronic kidney disease and albuminuria were also prespecified and carefully measured throughout the trial. However, a limitation is that the trial was not powered as a chronic kidney disease outcome study. Although a substantial proportion of patients had eGFR less than 60 mL/min/1·73 m², only a very small proportion had albuminuria above 33·9 mg/mmol. Most clinical and epidemiological studies have suggested that the greater the concentration of urine albumin, the greater the likelihood of progression of chronic kidney disease.[6,32] The early termination of the study probably diminished our ability to discern a significant difference in the progression to end-stage renal disease or need for dialysis that might have occurred at a later timepoint as seen in studies with long-term follow-up.

Thus, patients with hypertension, chronic kidney disease, and minimal or no albuminuria, who achieved blood pressure 130/80 mm Hg with an initial combination of benazepril plus amlodipine have lower rates of cardiovascular events and slower progression of chronic kidney disease than do patients treated with a combination of benazepril plus hydrochlorothiazide. A prospective study in patients with more advanced proteinuric nephropathy is needed to establish the superiority between these two different antihypertensive combination treatments on progression of chronic kidney disease.

#### Contributors

All authors were members of the trial's executive or steering committee (apart from PAS) and contributed to the discussions and interpretation of the data, and to the writing of the report. The analyses were planned by GLB, PAS, MRW, RYK, Y-TC, and MAW. PAS assisted members of the executive committee in drafting the report and in data analysis and interpretation. Data were analysed by Y-TC and statistical staff. All authors had full access to the data in the study. No medical writers or other individuals were involved in the design, analysis, or writing of this report.

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#### Conflicts of interest

Authors have received research grants or consulting or lecture fees from Novartis (GLB, MRW, MAW, BD, BP, KJ, and EJV), Diachi-Sankyo (GLB, MRW, MAW, KJ), Merck (GLB, MRW, MAW, BD), and Boeringher Ingelheim (GLB, MRW, MAW), all companies that manufacture combination products involving angiotensin-receptor blockers with either amlodipine or hydrochlorothiazide. LSB, RYK, VS, and YTC are employees of Novartis.

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