CLINICAL RESEARCH STUDY

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Systolic Blood Pressure and Cardiovascular Outcomes During Treatment of Hypertension

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ABSTRACT

OBJECTIVE: Randomized controlled trials in hypertension demonstrate cardiovascular benefits when systolic blood pressures are reduced from higher values to < 160 mm Hg. The value of lower targets has not been fully defined, although major guidelines recommend achieving systolic blood pressures of < 140 mm Hg. This study was conducted to explore cardiovascular outcomes at differing on-treatment blood pressure levels.

METHODS: On the basis of a prespecified plan to explore relationships between clinical outcomes and systolic blood pressures, the pooled cohort of high-risk hypertensive patients (N = 10,705) in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial were divided into 4 strata of systolic blood pressure levels: >140 mm Hg, 130 to <140 mm Hg, 120 to <130 mm Hg, and 110 to <120 mm Hg. The primary end point was cardiovascular death or nonfatal myocardial infarction or stroke. Outcomes comparisons between the blood pressure groups were by Cox regression.

RESULTS: The mean patient age was 68 years, and the study duration was 35.7 months. The primary end point occurred in 171 of 3429 patients (5.0%) with systolic blood pressure in the 10 mm Hg range < 140 and in 179 of 2354 patients (7.6%) with systolic blood pressure ≥ 140 mm Hg (hazard ratio [HR], 0.62; 95% CI, 0.50-0.77; $P = .0001$). Likewise, cardiovascular death decreased by 36% ($P = .0147$), total myocardial infarction (fatal + nonfatal) decreased by 37% ($P = .0028$), and stroke decreased by 47% ($P = .0002$). Cardiovascular event rates in those with systolic blood pressure < 130 mm Hg were not different from those with systolic blood pressure < 140 mm Hg. However, compared with systolic blood pressure < 130 mm Hg, stroke incidence in those with systolic blood pressure < 120 mm Hg was lower (HR, 0.60; 95% CI, 0.35-1.01; $P = .0529$), but myocardial function was higher (HR, 1.52; 95% CI, 1.00-2.29; $P = .0437$), as were composite coronary events (myocardial infarction, hospitalized angina, or sudden death) (HR, 1.63; 95% CI, 1.18-2.24; $P = .0023$). The renal end point of a sustained > 50% increase in serum creatinine was significantly lower in those with systolic blood pressure < 140 mm Hg than in any of the other higher or lower blood pressure ranges.

CONCLUSIONS: In high-risk hypertensive patients, major cardiovascular events are significantly lower in those with systolic blood pressures < 140 mm Hg and < 130 mm Hg than in those with levels > 140 mm Hg. There are stroke benefits at levels < 120 mm Hg, but they are offset by increased coronary events. Renal function is best protected in the 130 to 139 mm Hg range.

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KEYWORDS: Blood pressure control; Cardiovascular events; Hypertension; Renal function; Stroke

The underlying assumption in treating hypertension is that reduction of blood pressure decreases the incidence of cardiovascular events, strokes, and chronic kidney disease. The strongest evidence for this has come from clinical trials in which patients with untreated systolic blood pressure values of ≥ 160 mm Hg had significant decreases in major clinical

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outcomes when their blood pressures were reduced to < 160 mm Hg.[1] However, this information is of limited value in deciding how to manage patients diagnosed with hypertension but whose systolic blood pressure levels are < 160 mm Hg.

Epidemiologic data indicate that the lowest incidence of cardiovascular and stroke events is at systolic blood pressures as low as 115 mm Hg.[2] However, this information does not predict what might happen when therapeutic interventions are used to achieve low blood pressure levels. Indeed, it has been reported that excessive reductions can be associated with increased coronary and other events.[3-6]

Guidelines for the treatment of hypertension in the United States[7] and Europe[8] recommend that patients be treated to maintain systolic blood pressure at < 140 mm Hg; moreover, they recommend that for patients with diabetes or chronic kidney disease, a target of < 130 mm Hg should be considered. However, a recent reappraisal of the European guidelines recommends a target of < 140 mm Hg for these high-risk patients.[9]

Only 1 authoritative trial has prospectively explored whether achieving low blood pressure targets is beneficial. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[10] randomized patients with diabetes to systolic blood pressure targets of < 140 or < 120 mm Hg. The primary end point of the study (cardiovascular death, nonfatal myocardial infarction, or stroke) was not different between the 2 blood pressure targets. However, the event rate for stroke as a single outcome was lower in patients with systolic blood pressure < 120 mm Hg.

Retrospective analyses of clinical trials have explored outcomes at different achieved blood pressures. In the Valsartan Antihypertensive Long-Term Use Evaluation trial, there were significantly fewer events for cardiovascular mortality, heart failure, and stroke in patients with achieved systolic blood pressure < 140 mm Hg compared with > 140 mm Hg.[11] The Ongoing Telmisartan Alone and in Combination with Ramipril Global EndPoint (ONTARGET) trial demonstrated that optimal cardiovascular outcomes occurred in the systolic range from 130 to 140 mm Hg, although stroke events decreased further at lower blood pressures.[3] Likewise, the International VErapamil SR-Trandolapril Study found that cardiovascular events were significantly lower at systolic blood pressures < 140 mm Hg than at > 140 mm Hg.[4]

CLINICAL SIGNIFICANCE

- There is a clear cardiovascular benefit in achieving systolic blood pressures < 140 mm Hg compared with > 140 mm Hg in treating high-risk hypertensive patients.
- Achieving a systolic blood pressure < 130 mm Hg has similar benefits, but reduced stroke rates at < 120 mm Hg seem to be offset by increased coronary events.
- Renal function in hypertensive patients is best preserved with systolic blood pressures from 130 to 139 mm Hg. Higher or lower blood pressures are associated with worsening renal outcomes.

The present report is based on the randomized controlled trial Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH).[12] We have measured and compared cardiovascular event rates in 4 patient groups: systolic blood pressures ≥ 140 mm Hg, 130 to < 140 mm Hg, 120 to < 130 mm Hg, and 110 to < 120 mm Hg.

MATERIALS AND METHODS

The analysis in the current report is based on data from ACCOMPLISH.[12] The original intention of ACCOMPLISH was to compare the outcome effects of the combination of an angiotensin-converting enzyme inhibitor plus amlodipine with the effects of the combination of the same angiotensin-converting enzyme inhibitor plus hydrochlorothiazide. The methods for this trial have been described.[12-14] A prespecified analysis for ACCOMPLISH was the subject of the present report, in particular the relationships of achieved blood pressure levels to cardiovascular and other clinical end points.

Conduct of the Study

ACCOMPLISH was designed, supervised, analyzed, and interpreted by an Executive Committee, all of whose members are among the academic authors of the current report (MW, GB, BP, EV, and KJ). The roles of key supporting committees for the trial and the role of the original sponsor (Novartis) have been described.[12-14] An institutional review board at each participating site approved the study protocol. The trial was officially registered (ClinicalTrials.gov, number NCT00170950).

Patients

The study was performed in hypertensive patients at high risk of cardiovascular events established by previously documented cardiovascular conditions, as described previously.[14]

Study Procedures

This was a randomized, controlled double-blind trial. Immediately after entering the study, patients were randomly assigned to 1 of 2 treatment arms: benazepril plus hydrochlorothiazide or benazepril plus amlodipine, although data from these 2 arms were pooled for the present report. After randomization, all previous antihypertensive therapies were discontinued completely and replaced immediately by one of the study's fixed combination therapies. The starting doses were benazepril 20 mg/d plus hydrochlorothiazide