Systolic Blood Pressure and Cardiovascular Outcomes During Treatment of Hypertension

Michael A. Weber, MD,a George L. Bakris, MD,b Allen Hester, PhD,c Matthew R. Weir, MD,d Tsushung A. Hua, PhD,e Dion Zappe, PhD,e Bjorn Dahlof, MD,e Eric J. Velazquez, MD,f Bertram Pitt, MD,g Kenneth Jamerson, MDg

aSUNY Downstate College of Medicine, Brooklyn, NY; bThe University of Chicago Medicine, Chicago, Ill; cNovartis Pharmaceuticals, East Hanover, NJ; dUniversity of Maryland, Baltimore; eSahlgrenska University Hospital, Goteborg, Sweden; fDuke University School of Medicine, Durham, NC; gUniversity of Michigan, Ann Arbor.

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 (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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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
outcomes when their blood pressures were reduced to $<160$ mm Hg. 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. 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.

Guidelines for the treatment of hypertension in the United States and Europe 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.

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 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 Val- sartan 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. 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. 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.

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

**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.

**MATERIALS AND METHODS**

The analysis in the current report is based on data from ACCOMPLISH. The original intention of ACCOMPLISH was to compare the outcome effects of the combination of an angiotensin-converting enzyme inhibitor plus amiodipine with the effects of the combination of the same angiotensin-converting enzyme inhibitor plus hydrochlorothiazide. The methods for this trial have been described. 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. 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.

**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 amiodipine, 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
12.5 mg/d or amlodipine 5 mg/d. The protocol then mandated an increase in benazepril to 40 mg/d in both treatment arms at the following study visit. Thereafter, hydrochlorothiazide could be increased to 25 mg/d or amlodipine to 10 mg/d as required to achieve the target blood pressure of <140/90 mm Hg. For patients with diabetes or chronic kidney disease, a target blood pressure of <130/80 mm Hg was recommended but not mandated. If needed, investigators could add other antihypertensive agents (except angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, or thiazide diuretics). After an initial 3-month period during which all treatment intensifications were made, patients returned for visits after a further 3 months and then at 6-month intervals until the end of the trial. Blood pressure was measured by previously described methods.12

End Points
The primary study end point was the time to the first recorded event. For the analyses reported, this was the composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Death from cardiovascular causes was defined as sudden death from cardiac events or death from myocardial infarction, stroke, coronary interventions, heart failure, or other cardiovascular causes. Only the first event in an individual patient was counted toward the primary end point. In addition, there were analyses of secondary end points that were counted without censoring for previous occurrence of other end points. The secondary end points for this study were cardiovascular death, total mortality, total stroke (fatal or nonfatal), total myocardial infarction (fatal or nonfatal), clinical coronary events (total myocardial infarction, hospitalized angina pectoris, or sudden cardiac death), coronary revascularization, and increased serum creatinine (increase from baseline of >50%).

Analysis of Data
The study outcomes were adjudicated according to standard criteria by a clinical end points committee.12 Interim statistical analyses were performed at 6-month intervals for the trial’s Data Safety Monitoring Committee.12 This committee recommended early termination of the trial on the basis of evidence that the criteria for satisfying the trial’s stopping rules had been met.12

The principal observation in this analysis was the measurement of event rates in the pooled patient cohort of the primary end point and secondary end points within each of 4 on-treatment systolic blood pressure ranges: >140 mm Hg, 130 to <140 mm Hg, 120 to <130 mm Hg, and 110 to <120 mm Hg. We did not analyze data from patients with systolic values <110 mm Hg. Event rates in each of the ranges were compared with those in the adjacent ranges. In addition, event rates >140 mm Hg were compared with each of the other ranges. All patients were included according to the intention-to-treat principle. The analysis used Cox regressions to obtain the hazard ratios and the 95% confidence intervals (CIs) between values being compared.

Funding
The original ACCOMPLISH Trial was funded by Novartis. Their role in the conduct of this trial has been described.12 Novartis did not provide funding for the present analysis, although 3 authors (AH, TH, and DZ) are employees of the company.

RESULTS

Patient Numbers
The mean duration of treatment in this trial was 35.7 months. A total of 11,506 patients were enrolled. As shown in Figure 1, blood pressures after treatment titration were not available in 564 patients. In addition, we did not report outcomes in patients who achieved systolic blood pressures <110 mm Hg because there were too few (237) to permit meaningful analysis. Thus, there were 10,705 patients divided among the 4 groups of achieved systolic blood pressures (Figure 1).

Patient Characteristics
The principal clinical features of the patients in this trial are summarized in Table 1. All patients had histories of stroke, cardiovascular disease, chronic renal disease, or diabetes, or both disease and diabetes. The mean age of the cohort was 68 years, and the mean body mass index was 31. More detailed descriptions of the ACCOMPLISH cohort have been reported.12,13

Blood Pressures
The baseline and on-treatment systolic and diastolic blood pressures for each of the 4 study subgroups are listed in Table 2. Of the total cohort, 97% were receiving antihypertensive treatment at baseline.12 Across the 4 subgroups of ascending on-treatment blood pressures, a parallel trend for increasing blood pressures was observed in the baseline values. The differences in baseline systolic and diastolic blood pressures between each of the groups were significant (P < .0001 for all). In all 4 groups, blood pressures decreased significantly during the trial (P < .0001 for both systolic and diastolic blood pressures).

Clinical Outcomes According to Systolic Blood Pressure Groups
We compared the primary and secondary clinical end points by Cox regression analysis between patients with achieved systolic blood pressures >140 mm Hg, 130 to <140 mm Hg, 120 to <130 mm Hg, and 110 to <120 mm Hg. These data are shown in Figure 2. With the exception of coronary revascularization, all end points were significantly lower in the <140 mm Hg group than in the >140 mm Hg group. However, there were no significant differences be-
between the < 130 mm Hg and < 140 mm Hg groups, except for serum creatinine, which was higher in the < 130 mm Hg group. In comparing the < 120 mm Hg group with the < 130 mm Hg group, most outcomes tended to be higher in the < 120 mm Hg group and were significantly different for total myocardial infarction, clinical coronary events, and serum creatinine. Only stroke was lower in the < 120 mm Hg group.

The incidence of clinical events across the 4 systolic blood pressure groups, expressed as events per 1000 patient years, is shown in Figure 3 (primary end point, cardiovascular death, all-cause mortality, and total stroke) and Figure 4 (total myocardial infarction, clinical coronary events, coronary revascularization, and increased serum creatinine). In Figures 3 and 4, P values are shown for comparisons between the > 140 mm Hg group and each of the other systolic blood pressure groups, and P values (when significant) between adjacent groups also are shown.

**Adverse Events**

The treatments used in this trial, benazepril plus hydrochlorothiazide and benazepril plus amlodipine, were well tolerated. Adverse events during ACCOMPLISH have been described.12

**DISCUSSION**

The principal goal of this analysis was to explore the relationships between achieved systolic blood pressures and clinical outcomes in hypertensive patients. There was clear evidence that patients with a systolic blood pressure range from 130 to 139 mm Hg had significantly fewer events than those with a systolic blood pressure > 140 mm Hg. This applied not only to the primary end point but also to the secondary end points of cardiovascular death, all-cause mortality, total stroke, total myocardial infarction, clinical coronary events, and renal function. Only coronary revascularization was not different.

Systolic blood pressures < 130 mm Hg were not associated with lower event rates than pressures < 140 mm Hg. Our findings are consistent with those from the ONTARGET trial and International VErapamil SR-Trandolapril Study in which the nadir for the same primary end point as in this study was approximately 130 mm Hg.3,4 A further report from ONTARGET describing patients with diabetes con-
firmed that systolic blood pressures of approximately 130 mm Hg were associated with the fewest cardiovascular events.

Effects of Low Achieved Blood Pressures

We observed that systolic blood pressures in the 10 mm Hg range < 120 mm Hg, with the exception of stroke, provided no greater cardiovascular benefit than in the 10 mm Hg range < 130 mm Hg. The event rates for total myocardial infarction and major clinical coronary events (total myocardial infarction or unstable angina or sudden death) were significantly higher in those with levels < 120 mm Hg. These findings add emphasis to the ACCORD study, which found that, for the same primary end point as reported in the current article, a systolic blood pressure < 120 mm Hg was not different than < 140 mm Hg.

![Figure 2](https://example.com/figure2.png)

**Figure 2** Comparisons of clinical outcomes among groups of patients categorized by their achieved systolic blood pressures in the ACCOMPLISH trial. Hazard ratios were derived by Cox regression analysis. Definitions of the primary end point, clinical coronary events, and increased serum creatinine are given in the “Materials and Methods” section. BP = blood pressure; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.

**Table 2** Mean Baseline and On-treatment Systolic and Diastolic Blood Pressures for the Whole Study Cohort Divided into Subgroups of Achieved Systolic Blood Pressure

<table>
<thead>
<tr>
<th>No.</th>
<th>Baseline SBP (mm Hg), mean (SD)</th>
<th>Baseline DBP (mm Hg), mean (SD)</th>
<th>On-treatment SBP (mm Hg), mean (SD)</th>
<th>On-treatment DBP (mm Hg), mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1329</td>
<td>133.3 (15.02)</td>
<td>76.5 (10.13)</td>
<td>116.3 (2.73)</td>
<td>68.5 (5.98)</td>
</tr>
<tr>
<td>3593</td>
<td>140.7 (15.31)</td>
<td>79.2 (9.95)</td>
<td>125.5 (2.77)</td>
<td>71.2 (6.33)</td>
</tr>
<tr>
<td>3429</td>
<td>147.7 (16.22)</td>
<td>81.0 (10.62)</td>
<td>134.5 (2.83)</td>
<td>75.0 (6.89)</td>
</tr>
<tr>
<td>2354</td>
<td>158.3 (18.03)</td>
<td>82.8 (11.39)</td>
<td>150.2 (9.52)</td>
<td>78.8 (8.74)</td>
</tr>
</tbody>
</table>

| DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation. |
It is not clear why some cardiovascular outcomes increased at systolic blood pressures \( < 120 \text{ mm Hg} \) in ACCOMPLISH. Epidemiologic data indicate that the lowest cardiovascular event rates occur at systolic blood pressures of approximately 115 mm Hg, but these findings are derived from relatively healthy people compared with the high-risk patients in clinical trials.\(^2\) There has been speculation that the so-called J-curve effect seen in trials is due to low diastolic blood pressures during treatment causing increased coronary events in patients with preexisting disease,\(^1,6\) but in the present study it seems doubtful that the mean diastolic blood pressure of 69 mm Hg in patients with systolic blood pressures \( < 120 \text{ mm Hg} \) was sufficiently lower than the values of 72 and 75 mm Hg in the systolic groups \( < 130 \text{ and } < 140 \text{ mm Hg} \), respectively, to explain the higher event rates.

It also could be argued that the increased events in patients with systolic blood pressures \( < 120 \text{ mm Hg} \) might be a form of reverse causality, whereby the low blood pressures were actually due to existing heart disease, but this seems unlikely. The event rate (per 1000 patient years) in the present analysis for the primary end point in the patients with systolic blood pressures \( < 120 \text{ mm Hg} \) was 16.8, which clearly is not higher than the rate of 18.7 for the same end point in ACCORD patients randomized to \( < 120 \text{ mm Hg} \) and who achieved that goal by planned treatment titration.\(^10\)

**Effects on Stroke**

In ACCORD, stroke rates were significantly lower in those with a systolic blood pressure \( < 120 \text{ mm Hg} \) than in those with a level \( < 140 \text{ mm Hg} \).\(^10\) Likewise, in the present analysis we found stroke rates to be lowest at levels \( < 120 \text{ mm Hg} \). It is tempting to argue that the offsetting outcomes we observed at levels \( < 120 \text{ mm Hg} \)—higher coronary rates but lower stroke rates—could provide clinicians and patients with a context for deciding how aggressively to treat hypertension. Unfortunately, our data show that cardiac risk versus stroke risk does not seem to be an even trade. According to the data in Figures 3 and 4, achieving systolic blood pressure \( < 120 \text{ mm Hg} \) reduces stroke events (per 1000 patient years) by 2.9 but increases clinical coronary events by 5.7. So, theoretically, it would cost approximately 2 coronary events to prevent 1 stroke.

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**Figure 3** Event rates (per 1000 patient years) for major clinical outcomes in patients in ACCOMPLISH categorized according to their achieved systolic blood pressures. The P values for differences between adjacent groups are shown only if they are significant, but are shown for all comparisons between the \( > 140 \text{ mm Hg} \) group and each of the other groups. The definition of the primary end point is given in the “Materials and Methods” section.
Kidney Function

The clinical event that had the tightest connection to treatment blood pressures was elevation in serum creatinine, defined as a sustained increase of at least 50% from baseline. Because 90% of patients at baseline were already taking blockers of the renin-angiotensin system, drugs known to increase creatinine, the increases during the trial could not be attributed to initiating the trial’s angiotensin-converting enzyme inhibitor. Rather, changes in this index of renal function seem to be meaningful, especially because it has been reported that preventing increases of 50% or greater in creatinine predicts a slower progression of nephropathy and an increased time to dialysis.

Specifically, we found that on-treatment systolic blood pressures from 130 to 139 mm Hg, compared with >140 mm Hg, were associated with significantly lower adverse renal effects. However, there was actually a worsening in kidney function at levels <130 mm Hg, with yet a further deterioration at levels <120 mm Hg. This sharp J-shaped relationship defines a narrow range between 130 and 140 mm Hg as optimal for preserving kidney function. This observation clarifies a previous meta-analysis that demonstrated reduced worsening of kidney function at systolic blood pressures <140 mm Hg, although other data suggested that even lower blood pressure values could be beneficial in patients with substantial proteinuria. Of note, recent findings from a large patient cohort with stage 3 chronic kidney disease indicated that systolic blood pressures between 130 and 139 mm Hg were associated with optimal protection against progression to end-stage renal disease, coinciding closely with the present observations.

Study Limitations

The primary and some secondary end points reported differ from those in the original ACCOMPLISH report but were selected to be similar to those reported from other trials. Although analysis of the effects of achieved blood pressures on outcomes in ACCOMPLISH was prespecified, the decision to base our analysis on descending 10 mm Hg systolic ranges starting at 140 mm Hg was made post hoc. In fact, the only prospective comparison of different systolic blood pressure targets was ACCORD, which compared events at...
levels < 120 mm Hg with those at < 140 mm Hg. The present report included calculations of the outcomes effects of systolic blood pressures of < 130 mm Hg, < 120 mm Hg, and < 140 mm Hg. This could represent a useful contribution because systolic pressures of approximately 130 mm Hg might confer optimal cardiovascular protection.

CONCLUSIONS
This study demonstrates that cardiovascular outcomes in high-risk patients are effectively reduced at systolic blood pressures < 140 mm Hg. Pressures < 130 mm Hg provide similar benefits, but there are increased cardiac events < 120 mm Hg. The exceptions to these generalizations are stroke, which is lowest at < 120 mm Hg, and adverse renal changes, which are lowest at < 140 mm Hg but increase significantly in the lower blood pressure ranges.

References

Conflict of Interest: MAW consults for Boehringer-Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, and Takeda Pharmaceuticals, and provides speaking services for Daiichi Sankyo, Forest, and Takeda. GLB consults for Takeda, Abbott, Relapsya, Medtronic, Daiichi-Sankyo, and Novartis, and has grants from Forest and Takeda. AH, TH, and DZ are employees of Novartis. MRW consults for Amgen, Novartis, Pfizer, Daiichi-Sankyo, and MSD. BD consults for Novartis, Boehringer-Ingelheim, Bayer, and Vicore Pharma; owns stock in Mintage Scientific AB; and speaks for Novartis, MSD, Boehringer Ingelheim, Pfizer, Krka, Bayer, and Vicore. EJV is a consultant to Novartis. BP is a consultant to Novartis. KJ consults for Boehringer-Ingelheim, Forest, Novartis, XOMA, Pfizer, and InVase Therapeutics; speaks for Daiichi Sankyo, and receives research support from the National Heart, Lung, and Blood Institute, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, and Novartis.