OBJECTIVE — Blood pressure ranges associated with cardiovascular disease (CVD) events in advanced type 2 diabetes are not clear. Our objective was to determine whether baseline and follow-up (On-Study) systolic blood pressure (SBP), diastolic blood pressure (DBP), and SBP combined with DBP predict CVD events in the Veterans Affairs Diabetes Trial (VADT).

RESEARCH DESIGN AND METHODS — Participants in the VADT \( (n = 1,791) \) with hypertension received stepped treatment to maintain blood pressure below the target of 130/80 mmHg in standard and intensive glycemic treatment groups. Blood pressure levels of all subjects at baseline and On-Study were analyzed to detect associations with CVD risk. The primary outcome was the time from randomization to the first occurrence of myocardial infarction, stroke, congestive heart failure, surgery for vascular disease, inoperable coronary disease, amputation for ischemic gangrene, or CVD death.

RESULTS — Separated SBP \( \geq 140 \) mmHg had significant risk at baseline (hazards ratio \([HR]\) 1.508, \( P < 0.001\)) and On-Study (HR 1.469, \( P = 0.002\)). DBP \(< 70 \) mmHg increased CVD events at baseline (HR 1.482, \( P < 0.001\)) and On-Study (HR 1.491, \( P < 0.001\)). Combined blood pressure categories indicated high risk for CVD events for SBP \( \geq 140 \) with DBP \(< 70 \) mmHg at baseline (HR 1.785, \( P = 0.03\)) and On-Study (HR 2.042, \( P = 0.003\)) and nearly all SBP with DBP \(< 70 \) mmHg.

CONCLUSIONS — Increased risk of CVD events with SBP \( \geq 140 \) mmHg emphasizes the urgency for treatment of systolic hypertension. Increased risk with DBP \(< 70 \) mmHg, even when combined with SBP in guideline-recommended target ranges, supports a new finding in patients with type 2 diabetes. The results emphasize that DBP \(< 70 \) mmHg in these patients was associated with elevated CVD risk and may best be avoided.

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Blood Pressure and Cardiovascular Disease Risk in the Veterans Affairs Diabetes Trial

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infection, stroke, congestive heart failure, surgery for vascular disease, inoperable coronary disease, amputation for ischemic gangrene, or CVD death. This study was approved by the Institutional Review Boards of each participating site, and all subjects gave informed consent.

Definition of BP categories
The ADA and JNC-7 target BP levels defined desirable measurements (9,10). Thus, 105–129/70–79 mmHg was considered the optimal target BP, 130–139 mmHg SBP as above target, and ≥140 mmHg as systolic hypertension among patients with type 2 diabetes. DBP ≥80 mmHg was above target and included patients with diastolic prehypertension (80–89 mmHg) and diastolic hypertension (≥90 mmHg). Low BP was defined as <105/<70 mmHg (12,13). The JNC-7 category of SBP prehypertension (120–139 mmHg) was used in selected additional analyses.

Statistical analysis
Two sets of analyses using Cox proportional hazard models (SAS, version 9.2 for Windows; SAS Institute, Cary, NC) were performed to assess BP as a predictor of time to first CVD event. Baseline-only measurements of SBP and DBP were used as covariates to predict time to first CVD event. Three baseline BP models were fitted: continuous SBP and DBP, categorical SBP and DBP separately, and categorical SBP and DBP cross-combinations. These models were useful in determining which level of baseline BP was predictive of the time to first CVD event. Next, both baseline and quarterly BP measures were used as time-varying (defined as On-Study) covariates in proportional-hazard models of time to first CVD event, including the subgroup analysis of the composite CVD end point risk associated with separate SBP and DBP. For the On-Study analysis, any missing BP data were imputed with the last observation carried forward. The same three models mentioned above were fitted with the time-varying BP data. The derived effects of BP on risk of event were an estimate of the effect of the BP level at the time of a given CVD event, rather than the BP at baseline. Hazard ratios (HRs), 95% CIs, and P values are reported. HRs are interpreted as percent increased risk per mmHg increase for continuous models and percent increased risk compared with the given reference category for categorical models.

RESULTS — At baseline, the mean age was 60.4 ± 8.7 years, BMI was 31 ± 4 kg/m², A1C was 9.4 ± 1.5%, and diabetes duration was 11.5 ± 7.5 years (mean ± SD). Of the patients, 40% had prior CVD events. Mean BP was 132/76 mmHg (supplementary Table 1). The cohort entering VADT had near-optimal mean BP. This was further reduced within 1 year and was maintained below target for up to 7 years with added BP treatment (1).

Separate SBP and DBP components as categorical variables at baseline and On-Study
To further characterize which BP ranges might be associated with significant risks for CVD events, we selected a range of separate SBP and DBP measurements to evaluate. Of note, at baseline and On-Study, there were expected significant increased risks for CVD for SBP ≥140 mmHg. SBP levels of 130–139 mmHg both at baseline and On-Study were not associated with increased risk (Table 2). In a separate analysis of the single BP components with different BP ranges, neither systolic (120–129 mmHg and 130–139 mmHg) nor diastolic prehypertension (80–89 mmHg) ranges were associated with significant increased risks for CVD events in this population (supplementary Table 2). Subgroup analysis of the composite end point indicated that myocardial infarction, congestive heart failure, cardiovascular death, and peripheral revascularization showed significant increased risk both at SBP ≥140 mmHg and DBP <70 mmHg. Amputation had significant increased risk only at ≥140 mmHg. Coronary revascularization, inoperable CAD, and stroke did not show significant increased risk at these BP’s (supplementary Table 3). A crucial finding at both baseline and On-Study was the significant increased risk for CVD associated with a DBP <70 mmHg. In the general population, an increased CVD risk has been reported for a DBP <70 mmHg, but a specific cutoff level of DBP has not been identified or reported (13,14).

Our evaluation of separate SBP and DBP measurements as categorical vari-

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Table 1—Baseline BP categories for the entire population

|   | SBP |   |   |   | All |
|---|-----|---|---|---|----|
|   | <105 | 105–129 | 130–139 | ≥140 | All |
| DBP | <70 | 44 | 29+ | 64 | 44 | 46 |
| 70–79 | 19 | 359 | 174 | 127 | 679 |
| ≥80 | —* | 151 | 170 | 337 | 658 |
| All | 63 | 804 | 408 | 508 | 1,783 |

Data are n. *No patients in this category.
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Table 2—HRs for separated SBP and DBP categories relative to each reference category at baseline and On-Study

| SBP (mmHg) | Baseline | | | On-Study | | |
| --- | --- | --- | --- | --- | --- | --- |
| HR | 95% CI | P | HR | 95% CI | P |
| <70 | 1.482 | 1.179–1.862 | <0.001 | 1.491 | 1.206–1.844 | <0.001 |
| ≥80 | 1.030 | 0.825–1.287 | 0.79 | 1.049 | 0.814–1.351 | 0.71 |
| <70 | 0.974 | 0.591–1.603 | 0.92 | 1.364 | 0.977–1.904 | 0.07 |
| 130–139 | 1.004 | 0.786–1.283 | 0.97 | 0.938 | 0.733–1.210 | 0.61 |
| ≥140 | 1.508 | 1.203–1.890 | <0.001 | 1.469 | 1.157–1.867 | 0.002 |

Table 3—HRs for combined SBP and DBP categories relative to a reference category at baseline and On-Study

| SBP (mmHg) | Baseline | | | On-Study | | |
| --- | --- | --- | --- | --- | --- | --- |
| HR | 95% CI | P | HR | 95% CI | P |
| 105–129/70–80 | Reference | 1.609 | 0.930–2.787 | 0.09 | 2.103 | 1.437–3.079 | <0.001 |
| <70/70–80 | 1.370 | 1.019–1.843 | 0.04 | 1.472 | 1.121–1.934 | 0.006 |
| 105–129/70–80 | 1.682 | 1.061–2.267 | 0.03 | 1.379 | 0.908–2.096 | 0.13 |
| 130–139/70–80 | 1.785 | 1.060–3.004 | 0.03 | 2.042 | 1.276–3.269 | 0.003 |
| ≥140/70–80 | 0.441 | 0.109–1.790 | 0.25 | 0.633 | 0.156–2.574 | 0.52 |
| <105/80 | 0.871 | 0.592–1.281 | 0.48 | 0.942 | 0.632–1.404 | 0.77 |
| 105–129/80 | 1.495 | 1.033–2.164 | 0.03 | 1.486 | 1.005–2.218 | 0.05 |
| <105/80* | 0.939 | 0.634–1.393 | 0.76 | 3.273 | 0.455–23.55 | 0.24 |
| 105–129/80* | 0.983 | 0.675–1.432 | 0.93 | 1.011 | 0.655–1.562 | 0.96 |
| ≥140/80* | 1.499 | 1.130–1.990 | 0.005 | 1.536 | 1.104–2.137 | 0.01 |

*Insufficient number in this BP category at baseline for analysis.

Combined BP components at baseline and On-Study

We tested ranges of combined BP components measured at baseline and On-Study to determine their utility in predicting CVD event in our patients (Table 3). Consistent with the single component measures, both baseline and On-Study SBP ≥140 mmHg increased the risk for a CVD event across all categories of DBP. At baseline, there was significant risk of CVD event for the DBP <70 mmHg associated with each SBP range and an increase in the HR with nonsignificance for the <105 mmHg range (HR 1.609, P = 0.09, Table 3).

On-Study, DBP <70 mmHg was associated with significant increased risk at any SBP range except for 130–139 mmHg (Table 3). At both baseline and On-Study, the BP range of 70–79 mmHg was not associated with a significant increase in risk with DBP <140 mmHg (Table 3). With DBP ≥80 mmHg, there was no significant risk increase with corresponding SBP ranges <140 mmHg at baseline and On-Study. Overall, with both BP components included at baseline and On-Study, the ranges of 105–129/70, ≥140/70–79, and ≥140/≥80 mmHg represented ranges associated with significant increased risks for CVD events in this population (Table 3). Finally, with DBP <70 mmHg, HRs were increased concordantly at baseline and On-Study, regardless of SBP levels.

Low DBP level investigation

An additional goal was to identify a potential cutoff for DBP <70 mmHg that had significant increased risk for CVD events. The Framingham Heart Study noted significant increased CVD risk in the adult general population with DBP <70 mmHg combined with SBP of 120–129 mmHg (HR 2.0), 130–139 mmHg (HR 1.9), and 140–159 mmHg (HR 3.0) (14). There was no definition of the lower limit of DBP before additional increased risk might occur. The European Guidelines for Hypertension assign an increased risk to DBP of 60–70 mmHg (13). A further division of the DBP ranges in our single-component BP analyses showed significant increased risk for DBP <60 and 60–69 mmHg, at baseline (HR 2.139, P < 0.001; HR 1.361, P = 0.02, respectively) and On-Study (HR 2.155, P < 0.001; HR 1.310, P = 0.02, respectively). To explore the potential cutoff level further, we carried out sensitivity analyses of the combined BP ranges by testing DBP <65 and <60 mmHg with the associated target BP ranges reviewed previously. Because of the smaller number of patients with SBP >130 mmHg, we were able to apply this analysis to only two groups of SBP ranges: SBP <105 mmHg and SBP 105–129 mmHg. Based on the sensitivity analysis, there were three interesting findings. First, in the target SBP/DBP group (105–129/<65 mmHg), the risk and significance remained similar at baseline (HR 1.453, P = 0.02) and On-Study (HR 1.557, P = 0.001). We did not explore this group further because statistical significance did not change with the different levels of DBP. Second, when the group with SBP <105 mmHg was examined with different DBP ranges, the HR and significance increased at baseline. With DBP <65 mmHg, the results were similar to <70 mmHg (HR 1.575, P = 0.14). However, with DBP <60 mmHg, the risk increased significantly (HR 2.903, P = 0.004). This implied that the cutoff point of DBP for further increased CVD risk was <60 mmHg with SBP <105 mmHg at baseline. Finally, the On-Study HR increased briskly with DBP <60 mmHg. When the DBP level was tested at <70, <65, and <60 mmHg, the HR increased from 2.103 to 2.198, and then to 2.825, respectively, while the P values remained
DBP of <60 mmHg as the likely cutoff associated with even greater significant risks for CVD events.

Combined components of SBP and DBP provided more specific BP categories for determination of CVD risk with baseline only and On-Study measurements. BP levels associated with the increased risk were consistent between baseline and On-Study measurements. We found that the risk of CVD events increased at SBP ≥140 mmHg and low extremes of DBP <70 mmHg when the two components were combined (Table 3). Our results that certain levels of BP components analyzed in combination are associated with higher CVD event risks are similar to the Framingham Heart Study findings (14). The information about baseline and On-Study BP risk categories will heighten physician awareness toward patients who need immediate and continuing BP treatment. The broad SBP and DBP target range of <130/<80 mmHg (9) and the wide normal range of <120/<80 mmHg lack defined lower limits (10,13). Our results raise awareness of the increased CVD risk of DBP <70 mmHg with 105–129/70–79 mmHg as a reasonable BP target range for patients with type 2 diabetes.

In the VADT patients, an SBP of 130–139 mmHg and a DBP of 80–89 mmHg were better tolerated, as underscored by the minimal changes in HRs and the lack of significance for these ranges whether reviewed as individual components or combined at baseline and On-Study (Tables 2 and 3, supplementary Tables 2 and 4). When BP components were evaluated separately at baseline, there were no significantly increased risks associated with DBP ≥80 mmHg (HR 1.030, P = 0.79) or with the SBP range of 130–139 (HR 1.004, P = 0.97) (Table 2). Analysis of specific baseline prehypertensive ranges for DBP of 80–89 mmHg (HR 1.071, P = 0.57) and SBP ranges of 120–139 mmHg broken down as 120–129 mmHg (HR 1.087, P = 0.56) and 130–139 mmHg (HR 1.081, P = 0.61) failed to show any significant increases in risk (supplementary Table 2). The same DBP and SBP ranges On-Study did not show significant increases in CVD event risk (supplementary Table 2). In a separate analysis of the combined BP components at baseline, SBP in the prehypertensive ranges (120–129 and 129–130 mmHg) were associated with increased risk only when combined with a DBP <70 mmHg (supplementary Table 4). There were no significant increases in CVD event risk when a DBP ≥80 mmHg was combined with SBP 120–129 mmHg or 130–139 mmHg On-Study (supplementary Table 4).

These nonintuitive findings conflict with reported increased CVD risk associated with these SBP and DBP levels in adult general populations (13,14). One contributing factor for this difference may be that many patients with BPs within these ranges already were on treatment with antihypertensive agents resulting in a decreased number. Patients with type 2 diabetes who are similar to VADT patients may tolerate more generous SBP (up to 139 mmHg) and DBP (up to 89 mmHg) target ranges. Our results underscore a dilemma for physicians who identify type 2 diabetic patients with mild increases in SBP (e.g., 130–139 or 140–145 mmHg) and DBP ≤60–69 mmHg. If they treat the SBP aggressively with attendant lowering of DBP, the consequence could be a shift of the patient into a higher CVD risk category (Table 3, supplementary Table 4). Longstanding increased arterial stiffness (manifested as increased pulse pressure) and CVD in these patients may render them less able to withstand vigorous BP lowering.

Increased arterial stiffness is common in the older population studied in the VADT, and the higher CVD risk in our patients with this presentation is common in a large general population (14). Our noted greater CVD risk of low DBP is underestimated in current guidelines that concentrate on the higher extremes of SBP and DBP. Another potential contributor to the increased CVD risk of low DBP is the existence of common genetic polymorphisms of single-nucleotide mutations associated with increased CVD risk and decreased DBP (15). This aspect will require further investigation in our population. BP control to target in patients with type 2 diabetes, with avoidance of excessive low DBP and SBP, decreases CVD risk. Long-term efforts to continue BP control are warranted, since the benefits of improved BP are not sustained unless the control is maintained (16).

Major strengths of this study included the large population with type 2 diabetes with frequent BP monitoring and adjustments for control, the longitudinal follow-up for up to 7 years On-Study, and the inclusion of a larger percentage of minorities than most studies of this type. A weakness was that the patients were not randomized to BP control groups or BP treatment. In addition, the results from
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this older, primarily male population may not be applicable to younger individuals and women. In our exploratory BP categorical analyses, lack of statistical significance did not prove lack of risk. Significance may have been attenuated by low power to detect a difference due to the small sample size in the higher BP categories coupled with the confounding treatment effect of BP control during the study. We did not look at the effects of lowering BP in patients in this analysis. A possible negative effect of antihypertensive treatments that excessively lower DBP must be considered. Future research questions include whether BP control changed outcomes for individual patients in higher-risk SBP or DBP categories. We also plan to investigate the potential associations of these high-risk BP categories with microvascular events.

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R.J.A. wrote the manuscript and researched data. G.D.B. researched and analyzed data, contributed to results, and reviewed/edit the manuscript. D.K. and T.E.M. researched data and reviewed/edit the manuscript. C.A. reviewed/edit the manuscript. W.D. reviewed/edit the manuscript and contributed to discussion.

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