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

ROBERT J. ANDERSON, MD[1]
GIDEON D. BAHN, PHD[2]
THOMAS E. MORITZ, MS[2]
DERRICK KAUFMAN, MS[2]
CARLOS ABRAIRA, MD[3]
WILLIAM DUCKWORTH, MD[4]
FOR THE VADT STUDY GROUP

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 ≥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 ≥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 ≥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.

Diabetes Care 34:34–38, 2011

Based on results of recent interventional trials (1–3), the question of whether or not intensive glucose control significantly reduces the risk of cardiovascular disease (CVD) in all patients with type 2 diabetes remains controversial. It may be beneficial in subgroups of these patients when severe hypoglycemia is avoided. Blood pressure (BP) control is consistently correlated with CVD events in studies of risk factors in type 2 diabetes. In the UK Prospective Diabetes Study, BP control was twice as effective as glucose control in preventing any diabetes end points (4,5). The Hypertension Optimal Treatment (HOT) study and the Appropriate Blood Pressure Control in Diabetes (ABCD) trial support improved BP control as a significant CVD event preventive factor in patients with diabetes (6–8). Both the American Diabetes Association (ADA) and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recommend treatment of BP in patients with diabetes to a target of <130/<80 mmHg (9,10). Current evidence supports a systolic blood pressure (SBP) level of <140 mmHg, but there is sparse information to guide physicians as to how far the SBP and diastolic blood pressure (DBP) can be lowered safely and whether lower BP levels might be associated with increased risk. We analyzed the BP data collected during the Veterans Affairs Diabetes Trial (VADT) to learn whether specific levels of BP in patients with type 2 diabetes predict CVD events.

The VADT is a 20-center 1,791-patient prospective study of intensive versus standard glucose treatment in patients with suboptimal responses to maximum oral agents or insulin. The main objective was to assess the benefit of intensive glucose control for up to 7 years on CVD events in patients with advanced type 2 diabetes. Other objectives included the assessment of the effects on microvascular and neurological complications, cognitive function, quality of life, and cost-effectiveness. BP, lipids, diet, and lifestyle were treated identically in both arms. By improving BP control in an identical manner in both glucose arms, VADT excluded the effect of BP differences in CVD events between treatment arms and reduced the overall risk of macrovascular complications during the trial. The initial results were published recently (1).

RESEARCH DESIGN AND METHODS

— Randomization for VADT began in 2000. In all, 1,791 individuals were included in the study. The design of VADT and the results have been reported elsewhere (1,11). Baseline characteristics of subjects are detailed in supplementary Table 1 (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-1420/DC1). All who entered the trial with new or treated hypertension were given stepped treatment to maintain BP below 130/80 mmHg. After starting with ACE inhibitors or angiotensin II receptor blockers, the following agents were added as needed: diuretics, cardioselective β-blockers, calcium channel blockers, clonidine, hydralazine, and minoxidil. The primary outcome was the time from randomization to the first occurrence of myocardial

From the [1]Section of Endocrinology, VA Medical Center, Omaha, Nebraska; the [2]Cooperative Studies Program Coordinating Center, Hines VA Hospital, Hines, Illinois; [3]Research Service, VA Medical Center, Miami, Florida; and the [4]Section of Endocrinology, VA Medical Center, Phoenix, Arizona.
Corresponding author: Robert J. Anderson, robert.anderson4@va.gov.
Received 19 July 2010 and accepted 28 September 2010. Published ahead of print at http://care.diabetesjournals.org on 8 November 2010. DOI: 10.2337/dc10-1420. Clinical trial registry no.: NCT00032487, clinicaltrials.gov.

Table 1—*Baseline BP categories for the entire population*

	SBP				
	<105	105–129	130–139	≥140	All
DBP					
<70	44	294	64	44	446
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.

infarction, 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/m^2, 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 BP components and interaction of BP components (SBP and DBP) as continuous variables at baseline and 7 years On-Study

All patients in both the standard and intensive treatment groups were included in the analyses, regardless of BP medicine treatment, to facilitate the ability to predict CVD event risk associated with BP. An initial analysis of the continuous SBP and DBP as separate components along with the interaction of SBP and DBP components was done to test whether there was an association between the BP readings and primary outcomes. The continuous SBP, DBP, and interaction of components (SBP × DBP) was significant both at baseline ($P = 0.02$, $P < 0.001$, and $P < 0.001$, respectively) and On-Study ($P = 0.002$, $P < 0.001$, and $P < 0.001$, respectively). These analyses demonstrated significant likelihood estimates that SBP alone, DBP alone, and their interaction were related to the risk of CVD events. We further investigated the readings as separate SBP and DBP categorical components and as combined SBP and DBP categorical components to determine what range of BP would be associated with significant risk of CVD events.

BP categories

Hypertension, defined as current treatment for hypertension or a BP of ≥140/90 mmHg, was present in 72% of patients (1). BP ranges and numbers of patients in each category are listed in Table 1. Categories were chosen to be in accord with ADA and JNC-7 treatment target levels (9,10). With the designation of prehypertension (SBP 120–139 mmHg/DBP 80–89 mmHg), there was some overlap of systolic prehypertension with our target range of 105–129/70–79 mmHg (9).

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 BPs (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-

Table 2—*HRs for separated SBP and DBP categories relative to each reference category at baseline and On-Study*

	Baseline			On-Study		
	HR	95% CI	*P*	HR	95% CI	*P*
DBP (mmHg)						
70–79	Reference			Reference		
<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
SBP (mmHg)						
105–129	Reference			Reference		
<105	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	0.733–1.201	0.61
≥140	1.508	1.203–1.890	<0.001	1.469	1.157–1.867	0.002

ables noted in Table 2 indicated a significant increased risk of CVD at SBP ≥140 mmHg and DBP <70 mmHg when each BP category was analyzed in comparison with the target ranges. Combinations of two continuous variables (SBP and DBP) noted previously were also significant, which indicated that the effect of an increasing SBP depended on the level of DBP. Evidence from the Framingham Heart Study supported the combined BP components versus single components as superior for predicting CVD risk in the general population (14).

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 SBP <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, ≥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.

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

	Baseline			On-Study		
BP (mmHg)	HR	95% CI	*P*	HR	95% CI	*P*
105–129/70–79	Reference			Reference		
<105/<70	1.609	0.930–2.787	0.09	2.103	1.437–3.079	<0.001
105–129/<70	1.370	1.019–1.843	0.04	1.472	1.121–1.934	0.006
130–139/<70	1.682	1.061–2.667	0.03	1.379	0.908–2.096	0.13
≥140/<70	1.785	1.060–3.004	0.03	2.042	1.276–3.269	0.003
<105/70–79	0.441	0.109–1.790	0.25	0.633	0.156–2.574	0.52
130–139/70–79	0.871	0.592–1.281	0.48	0.942	0.632–1.404	0.77
≥140/70–79	1.495	1.033–2.164	0.03	1.486	1.005–2.198	0.05
<105/≥80*				3.273	0.455–23.55	0.24
105–129/≥80	0.939	0.634–1.393	0.76	1.011	0.655–1.562	0.96
130–139/≥80	0.983	0.675–1.432	0.93	0.957	0.611–1.497	0.85
≥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.

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

significant at <0.001 at each point. The results supported the conclusion that a DBP of <70 mmHg is the level at which CVD risk begins to increase significantly, with further enhanced significant risks with DBP <60 mmHg at baseline and On-Study in these patients with type 2 diabetes.

CONCLUSIONS — When the VADT BP data were analyzed with respect to the target BP (105–129/70–79 mmHg), SBP ≥140 mmHg, as a single component and combined with any DBP, indicated an increased risk for CVD events in these type 2 diabetic patients at baseline and On-Study. The results underlined the need for treatment of type 2 diabetic patients with SBP ≥140 mmHg and elevated DBP into the target range as recommended in ADA and JNC-7 BP guidelines (9,10). Patients in VADT with high SBP and low DBP were at increased risk for CVD events.

Our results support the identification of a new category of high CVD event risk for the group of type 2 diabetic patients with low DBP. Single component and combined SBP and DBP analyses both identified DBP <70 mmHg as a significant increased risk for primary outcomes both at baseline and On-Study (Tables 2 and 3). Further breakdown of the DBP levels as a single component showed a DBP of 60–69 mmHg with significant increased risks at baseline and On-Study (supplementary Table 2). In the same analyses, the single-component DBP <60 mmHg was associated with the highest risk (supplementary Table 2). The separate analysis of DBP combined with SBP highlighted <60 mmHg as the DBP with the highest significant risk of CVD events at baseline and On-Study. Combined BP components of <105/<60 mmHg harbored the greatest increased risk at baseline (HR 2.903, $P = 0.004$) and On-Study (HR 2.825, $P < 0.001$). Our findings regarding DBP support the Framingham Heart Study, which identified DBP <70 mmHg associated with isolated systolic hypertension and prehypertension as high-risk categories for CVD events in the population in which 2.3% had diabetes (14). The European guidelines also noted that a DBP of 60–70 mmHg should be regarded as an additional risk when associated with isolated systolic hypertension (13). Our results extend the high-risk DBP designation to our population of patients with type 2 diabetes. We identify a DBP of <70 mmHg as the cutoff for deleterious levels of DBP and a DBP <60 mmHg as a 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

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.

Acknowledgments— This study was supported by the VA Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development. Additional support was received from the American Diabetes Association and the National Eye Institute of the National Institutes of Health. Pharmaceutical, other supplies, and financial assistance were provided by GlaxoSmithKline, Novo Nordisk, Roche Diagnostics, sanofi-aventis, Amylin, and Kos Pharmaceuticals. These companies had no role in the design of the study, in the accrual or analysis of the data, or in the preparation of the manuscript.

R.J.A. received clinical research funding from Roche Pharmaceuticals. All funds were administered by the Nebraska Educational Biomedical Research Association, a nonprofit VA Foundation. C.A. received honoraria from the American Diabetes Association, Aventis, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

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

These results were presented in part in abstract form at the Clinical Trial Symposium (#S-19-4) of the 92nd Annual Meeting of the Endocrine Society, San Diego, California, 19 June 2010.

We thank the veteran patients who volunteered for this study. Without their dedication, the VADT could not have been done. We acknowledge the data management support of Lizy Thottapurathu, Ken Bukowski, and Mary Biondic, all at the Cooperative Studies Program Coordinating Center, Hines VA Hospital, Hines, IL, and the manuscript preparation assistance of Cindy Pietsch, MS, VA Medical Center, Omaha, NE.

References

1. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Jennifer Marks, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD, for the VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
2. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
3. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
4. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–713
5. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
6. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S, for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755–1762
7. Mehler PSM, Coll JRP, Estacio RM, Esler AP, Schrier RWM, Hiatt WRM. Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. Circulation 2003;107:753–756
8. Estacio RM, Jeffers BW, Gifford N, Schrier RWM. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care 2000;23(Suppl. 2):B54–B64
9. American Diabetes Association. Standards of medical care in diabetes—2009. Diabetes Care 2009;32(Suppl. 1):S13–S61
10. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003;289:2560–2571
11. Abraira C, Duckworth W, McCarren M, Emanuele N, Arca D, Reda D, Henderson W, for the VADT Investigators. Design of the cooperative study on glycemic control and complications in diabetes mellitus type 2: Veterans Affairs Diabetes Trial. J Diabetes Complications 2003;17:314–322
12. Castelli WP. Epidemiology of coronary heart disease: the Framingham study. Am J Med 1984;76:4–12
13. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HAJS, Zanchetti A. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007;28:1462–1536
14. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. Circulation 2009;119:243–250
15. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Köttgen A, Vasan RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FUS, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJG, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JCM, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. Nat Genet 2009;41:677–687
16. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med 2008;359:1565–1576