**Supplementary Figure 1**.

 (a)

 (b)

**Supplementary Table 1**. HRs for blood pressure variables and risk of CHF in the treated and non-treated groups, ACCORD.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Model-1**Age Adjustment | **Model-2**Multivariate Adjustment | **Model-3**Model 2 + cumulative mean BP |
|  BP arm |
|  | HR (95% C.I.) | P-value | HR (95% C.I.)  | P-value | HR (95% C.I.)  | P-value |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| CV-SBP | 1.10 (0.94-1.29) | 0.24 | 1.10 (0.92-1.33) | 0.30 | 1.14 (0.95-1.38) | 0.16 |
| ARV-SBP | 1.18 (1.00-1.37) | **0.04** | 1.18 (0.99-1.41) | 0.07 | 1.20 (1.01-1.43) | **0.04** |
| CV-DBP | 1.24 (1.07-1.45) | **0.006** | 1.12 (0.93-1.34) | 0.24 | 1.12 (0.93-1.35) | 0.09 |
| ARV-DBP | 1.20 (1.03-1.41) | **0.02** | 1.10 (0.92-1.32) | 0.29 | 1.11 (0.92-1.32) | 0.27 |
| Non-BP arm |
| CV-SBP | 1.31 (1.19-1.43) | **<0.001** | 1.22 (1.07-1.39) | **0.003** | 1.28 (1.12-1.50) | **<0.001** |
| ARV-SBP | 1.29 (1.19-1.41) | **<0.001** | 1.22 (1.08-1.38) | **0.001** | 1.27 (1.12-1.44) | **<0.001** |
| CV-DBP | 1.28 (1.17-1.40) | **<0.001** | 1.25 (1.10-1.43) | **<0.001** | 1.25 (1.10-1.42) | **<0.001** |
| ARV-DBP | 1.25 (1.15-1.36) | **<0.001** | 1.24 (1.10-1.40) | **<0.001** | 1.24 (1.10-1.40) | **<0.001** |

Blood pressure variables that were significant in age-adjusted models (Model-1) were further adjusted for baseline factors that showed significant associations in Table 1 (Model-2). In Model-3, models were additionally adjusted for cumulative mean of blood pressure. P-values <0.05 (bold font) are considered significant. CV: coefficient of variation; ARV: average real variability.BP arm: those randomized to blood pressure lowering arm; Non-BP arm: those not participating in blood pressure lowering.

**Supplementary Table 2.** Baseline characteristics in the VADT by incident HF status.

|  |  |  |
| --- | --- | --- |
|  |  | P-value |
|  | **No (*n*=1,448)** | **Yes (*n*=102)** |
| **Age (years)** | 59.7 (8.5) | 64.3 (8.5) | <0.0001 |
| **Intensive treatment (%)** | 50 | 46 | 0.54 |
| **Male (% Yes)** | 97 | 100 | 0.07 |
| **Non-Hispanic White (%)** | 60 | 79 | <0.0001 |
| **Diabetes duration (years)** | 11 (7.5) | 13 (7.3) | 0.07 |
| **CVD History (%)** | 35 | 73 | <0.0001 |
| **Hypertension History (%)** | 71 | 82 | 0.01 |
| **Smoking** |   |   | 0.91 |
|  **Current smoker (%)** | 17 | 18 |  |
|  **Previous smoker (%)** | 56 | 53 |  |
|  **Pack-years** | 14 (0-40) | 23 (0-55) | 0.02 |
| **BMI (kg/m2)** | 31.2 (4.5) | 32.0 (4.4) | 0.09 |
| **SBP (mmHg)** | 131 (16) | 136 (20) | 0.02 |
| **DBP (mmHg)** | 76 (10) | 75 (12) | 0.31 |
| **HDL cholesterol (mg/dL)** | 36 (10) | 33 (8) | <0.0001 |
| **LDL cholesterol (mg/dL)** | 108 (32) | 109 (34) | 0.78 |
| **Total cholesterol (mg/dL)** | 183 (44) | 184 (40) | 0.80 |
| **Triglycerides (mg/dL)** | 166 (78) | 188 (89) | 0.01 |
| **Glycated hemoglobin level (%)** | 9.4 (1.5) | 9.6 (1.5) | 0.07 |
| **Albumin to creatinine ratio (mg/g) (mg/g)** | 16 (6-56) | 56.5 (21-205) | <0.0001 |
| **eGFR (ml/min/1.73 m2)** | 83 (22) | 74 (19) | <0.0001 |

BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CVD: Cardiovascular disease; eGFR: estimated glomerular filtration rate from Modification of Diet in Renal Disease Study (MDRD) equation.

Data presented are mean, SD, or median (IQR) or %

After median of 5.6 years, HbA1c values of 6.9% in the intensive group and 8.4% in the standard group were achieved **Supplementary Table 3.** Hazard ratios for the association of blood pressure variables with CHF estimated by Cox proportional hazards model in the VADT (*n* = 1,550).

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Model-1**Age Adjustment | **Model-2**Multivariate Adjustment  | **Model-3**Model 2 + Cumulative mean BP |
|  |
|  | HR (95% C.I.) | P-value | HR (95% C.I.)  | P-value | HR (95% C.I.)  | P-value |
| Cum. mean SBP | 1.03 (1.02-1.05) | **<0.001** | 1.03 (1.01-1.05) | **0.02** | - | - |
| Cum. max SBP | 1.00 (0.99-1.01) | 0.98 | 0.98 (0.97-1.00) | **0.03** | 0.92 (0.89-0.94) | **<0.001** |
| CV-SBP  | 1.10 (0.92-1.32) | 0.31 | 1.03 (0.85-1.24) | 0.77 | 1.02 (0.85-1.23) | 0.82 |
| ARV-SBP | 1.14 (0.95-1.36) | 0.15 | 1.06 (0.88-1.27) | 0.56 | 1.03 (0.86-1.24) | 0.75 |
|  |
|  |  |  |  |  |  |  |
| Cum. mean DBP | 0.99 (0.96-1.03) | 0.65 | 1.01 (0.97-1.05) | 0.71 | - | - |
| Cum. max DBP | 0.95 (0.93-0.98) | **<0.001** | 0.94 (0.91-0.97) | **<0.001** | 0.81 (0.76-0.86) | **<0.001** |
| CV-DBP  | 1.14 (1.07-1.22) | **<0.001** | 1.07 (0.99-1.16) | 0.10 | 1.09 (1.00-1.18) | **0.04** |
| ARV-DBP | 1.20 (1.11-1.30) | **<0.001** | 1.16 (1.06-1.27) | **0.001** | 1.16 (1.06-1.27) | **0.001** |

Hazard ratios (HR) (95% confidence interval (95% CI)), and p-values estimated by Cox proportional hazards model in the VADT. Those with history of heart failure at baseline were excluded. Blood pressure variables that were significant in age-adjusted models (Model-1) were further adjusted for baseline factors that showed significant associations in Supplementary Table 2 (Model-2). In Model-3, models were additionally adjusted for cumulative mean of blood pressure. P-values <0.05 (bold font) are considered significant. CV: coefficient of variation; ARV: average real variability

**Supplementary Table 4.** Hazard ratios (HRs) for blood pressure variables and risk of CHF in those with and without a history of CVD and both DBP < 70 mmHg and SBP < 140 mmHg in ACCORD

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Model-1**Age Adjustment | **Model-2**Multivariate Adjustment | **Model-3**Model 2 + cumulative mean BP |
|  |
|  | HR (95% C.I.) | P-value | HR (95% C.I.)  | P-value | HR (95% C.I.)  | P-value |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *With CVD hx*CV-SBP | 1.55 (1.27-1.90) | **<0.001** | 1.52 (1.24-1.86) | **<0.001** | 1.52 (1.24-1.86) | **<0.001** |
| ARV-SBP | 1.42 (1.17-1.73) | **<0.001** | 1.39 (1.14-1.68) | **<0.001** | 1.40 (1.15-1.70) | **<0.001** |
| CV-DBP | 1.37 (1.22-1.53) | **<0.001** | 1.39 (1.22-1.57) | **<0.001** | 1.40 (1.23-1.60) | **<0.001** |
| ARV-DBP | 1.31 (1.15-1.50) | **<0.001** | 1.33 (1.15-1.53) | **<0.001** | 1.33 (1.15-1.55) | **<0.001** |
| *Without CVD hx*CV-SBP | 1.11 (0.81-1.52) | 0.51 | 1.02 (0.73-1.42) | 0.91 | 1.02 (0.73-1.41) | 0.92 |
| ARV-SBP | 1.25 (0.95-1.65) | 0.11 | 1.17 (0.88-1.55) | 0.28 | 1.15 (0.87-1.53) | 0.32 |
| CV-DBP | 1.19 (0.89-1.58) | 0.24 | 1.17 (0.86-1.60) | 0.32 | 1.13 (0.83-1.54) | 0.42 |
| ARV-DBP | 1.21 (0.92-1.58) | 0.17 | 1.19 (0.88-1.60) | 0.24 | 1.16 (0.86-1.55) | 0.33 |

CV: coefficient of variation; ARV: average real variability; top panel shows the result in those with CVD history at baseline, bottom panel shows the result in those without CVD history at baseline. P-values <0.05 (bold font) are considered significant

**Supplementary Table 5.** Definitions of measures of variability. Let $X\_{ij}$ denote the blood pressure value for subject $i$ at visit $j$. Time dependent variability measures for subject $i$ at visit $j$ are defined as follows:

|  |  |  |
| --- | --- | --- |
| **Measure** |  |  |
| Mean |  |  $ \overbar{X}\_{ij}= \frac{\sum\_{l=1}^{j}X\_{il} }{j}$ |
| Var; SD | Variance; standard deviation | $Var\_{ij}= \frac{\sum\_{l=1}^{j}(X\_{il}-\overbar{X}\_{ij})^{2}}{j-1}$, $ SD\_{ij} = \sqrt{Var\_{ij}}$ |
| CV | Coefficient of variation | $$\frac{SD\_{ij}}{\overbar{X}\_{ij}},$$ |
| ARV | Average real variability | $$\frac{1}{j-1}\sum\_{l}^{j-1}|X\_{l+1}-X\_{l}|/\overbar{X}\_{ij}$$ |