Orthostatic Hypotension in Diabetics in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Blood Pressure Trial

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Orthostatic hypotension (OH) is a reduction of ≥20 mm Hg in systolic blood pressure (SBP) or a reduction of ≥10 mm Hg in diastolic blood pressure within 3 minutes of standing. OH may be caused by an excessive decrease in blood volume when a person is standing or from inadequate compensation for the reduction in cardiac preload associated with standing because of deficient stimulation of cardiopulmonary, aortic, and carotid baroreceptors, which reflexly increase sympathetic activity and decrease parasympathetic activity. OH may be associated with advanced age, diabetes mellitus, hypertension, neurological disorders, and medications such as antihypertensive drugs, antidepressants, anti-parkinsonian drugs, antipsychotics, nitrates, alcohol, cardiovascular disorders, endocrine disorders, dehydration, anemia, bedrest/deconditioning, and other disorders.

All older individuals taking antihypertensive drugs should routinely have blood pressure (BP) measured in the sitting position and within 3 minutes of standing. BP should not be measured immediately after eating to avoid postprandial hypotension being confused with OH. Both of these disorders may coexist. Postprandial hypotension is also associated with falls, syncope, coronary events, stroke, and all-cause mortality at long-term follow-up. OH may cause postural instability, falls, and syncope. OH is also associated with an increased incidence of all-cause mortality, coronary events, heart failure, and stroke. The prevalence of OH in 12433 individuals in the Atherosclerosis Risk in Communities study was 4.9%. At 6-year mean follow-up, individuals with OH had a 3.49x increased risk of coronary heart disease. After controlling for age, ethnicity, sex, comorbid conditions, and cardiovascular risk factors, the hazard ratio for coronary heart disease was increased by 1.85x. A meta-analysis of 13 prospective studies included 121913 individuals. At 5-year median follow-up of 65174 individuals, OH increased all-cause mortality by 1.50x. At 6.4-year median follow-up of 49512 individuals, OH increased coronary heart disease by 1.41x. At 6.8 to 24-year mean follow-up of 50096 individuals, OH increased heart failure by 2.25x. At 6.8-year median follow-up of 58300 individuals, OH increased stroke by 1.64x.

The ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) trial randomized 4733 diabetics, mean age 62.1 years, to lower SBP to <120 mm Hg or to <140 mm Hg. After 1 year, the SBP was 119.3 mm Hg with intensive BP control (IBPC) versus 133.5 mm Hg with standard therapy. The annual rates of the primary outcome (non-fatal myocardial infarction, nonfatal stroke, or cardiovascular death) were 1.87% with IBPC versus 2.09% with standard therapy (a 12% insignificant reduction). The annual rates of stroke (a prespecified secondary outcome) were 0.32% with IBPC versus 0.53% with standard therapy (a 41% reduction).

A post hoc analysis of data from ACCORD BP showed that the primary cardiovascular disease outcome was 26% less in individuals randomized to IBPC and standard glycemia goals than in individuals randomized to standard therapy and standard glycemia goals. In addition, an SBP of <120 mm Hg in ACCORD BP was associated with a 39% reduced risk of electrocardiographic left ventricular hypertrophy. Reduction of left ventricular hypertrophy has been found to reduce cardiovascular events.

The excellent study by Fleg et al investigated the prevalence, incidence, and prognostic significance of OH in the ACCORD BP trial. Orthostatic blood pressure measurements were made in 1321 individuals at baseline, in 2625 individuals at 12 months, in 3702 individuals at 48 months, and in 926 individuals at all 3 visits. The smaller number of orthostatic blood pressure measurements at baseline and at 12 months was because of this investigation not beginning until 44 months after the ACCORD BP trial began. The prevalence of OH at a specific visit was defined based on the occurrence of consensus OH at that visit, regardless of whether OH had been previously diagnosed. The incidence of OH at a specific follow-up visit was defined as the occurrence of consensus OH at that visit in individuals examined previously who had not been shown to have OH.

The prevalence of OH was 17.8% at baseline, 10.4% at 12 months, 12.8% at 48 months, and 20% at ≥1 visit. At baseline, the prevalence of OH was 19.3% in individuals treated with IBPC versus 16.1% in those treated with standard therapy (P not significant). At 12 months, the prevalence of OH was 9.5% in individuals treated with IBPC versus 11.4% in those treated with standard therapy (P not significant). At 48 months, the prevalence of OH was 12.2% in individuals treated with IBPC versus 13.5% in those treated with standard therapy (P not

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significant). At 12 months, the incidence of OH was 8.0% in individuals treated with IBPC versus 9.9% in those treated with standard therapy (P not significant). At 48 months, the incidence of OH was 9.9% in individuals treated with IBPC versus 11.0% in those treated with standard therapy (P not significant). Dizziness on standing for the BP measurement was similar for both treatment groups at baseline and at 6 months but was higher with IBPC at 48 months (5.7%) than with standard therapy (4.1%). Therefore, many individuals with OH in this study were asymptomatic. Regression analysis showed that female sex, higher SBP, hemoglobin A1c, current smoking, and use of β-blockers, α-blockers, and insulin were associated with an increased likelihood of OH and black race with a decreased likelihood of OH.

This important study also showed that OH was associated with a 1.62x increased all-cause mortality and with a 1.85x increased heart failure death or hospitalization but not with nonfatal myocardial infarction, stroke, cardiovascular death, or their composite.

The SPRINT (Systolic Blood Pressure Intervention Trial) randomized 9361 individuals with an SBP of 130 to 180 mm Hg and increased cardiovascular risk but without diabetes mellitus to an SBP goal of <120 mm Hg versus <140 mm Hg. The same automated oscillometric device (Omron HEM-907) was used to measure BP in SPRINT as in ACCORD BP. At 1 year, the mean SBP was 121.4 mm Hg with IBPC and 136.2 mm Hg with standard therapy. The intervention was stopped early after the median follow-up of 3.26 years.

In SPRINT, the prevalence of OH alone was 16.6% with IBPC versus 18.3% with standard BP treatment (a 12% decrease). The prevalence of OH with dizziness was 1.3% with IBPC versus 1.5% with standard BP treatment (P not significant).

In SPRINT, the primary composite outcome of myocardial infarction, other acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes was reduced to 25% by IBPC. IBPC reduced all-cause mortality 27%, heart failure 38%, cardiovascular death 43%, and the primary composite outcome or death 22%. IBPC reduced the primary outcome by 33% in individuals aged ≥75 years and by 20% in individuals aged 50 to 74 years.

Unfortunately, SPRINT excluded diabetics from their trial. The sample size was approximately twice larger in SPRINT (9361 persons) than in ACCORD BP (4733 individuals), and there were important methodological differences between both of these trials. The participants in SPRINT were older (mean age 67.9 years) than in ACCORD BP (mean age 62.1 years). The participants in ACCORD BP were at lower risk than the participants in SPRINT. Participants with dyslipidemia were assigned to the lipid arm and excluded from the BP arm in ACCORD BP. Participants with a serum creatinine above 1.5 mg/dL were also excluded from ACCORD BP. ACCORD BP often used the diuretic hydrochlorothiazide, whereas SPRINT primarily used the diuretic chlorthalidon.

In conclusion, a randomized clinical trial using a similar number of participants and design used in SPRINT needs to be performed in older hypertensive diabetics to investigate whether the SBP goal should be <120 mm Hg or <140 mm Hg. On the basis of the available data, I recommend lowering the SBP in older hypertensive diabetics at increased cardiovascular risk to <130 mm Hg or to <120 mm Hg, with more intensive monitoring for serious adverse events. The excellent study by Fleg et al reassures us that hypertensive diabetics treated to an SBP goal of <120 mm Hg will not have a higher prevalence or incidence of OH than those treated to an SBP goal of <140 mm Hg. This study showed that hypertensive diabetics treated to an SBP goal of <120 mm Hg had a tendency to decreased incidence of OH.

Disclosures

None.

References


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