

## **Hypertension in diabetes mellitus**

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Hypertension and diabetes mellitus (DM) are two of the most important risk factors for cardiovascular disease (CVD) and are commonly found in the same patient. Often, they are accompanied by other elements of the metabolic syndrome, further increasing the risk of CVD and renal disease. Worldwide, the prevalence of hypertension is projected to increase from less than 1 billion to approximately 1.5 billion by 2025 and the prevalence of DM is expected to rise from approximately 170 million to almost 400 million by 2030<sup>1,2</sup>.

Weight loss and increased physical activity are effective in prevention and treatment of both hypertension and DM. They should be combined with reduced sodium intake, moderation in alcohol consumption, and increased potassium intake<sup>3</sup>.

Compared to placebo, blood pressure (BP) lowering with diuretics, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB) reduces the risk of CVD in persons with and without DM<sup>4,5</sup>. The pattern for diuretics versus placebo is displayed in figure 1.

Compared to placebo or CCB, ACEI and ARB are more effective in reducing the incidence of microalbuminuria during the treatment of hypertension in patients with DM<sup>6</sup>. However, it is unclear whether this provides any special benefit in preventing CVD. With a sample size of 42,418 participants, including 15,297 participants with DM, experience in the Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT) provides the largest comparison of treatment with representative agents from four classes of antihypertensive drug therapy (diuretics-chlorthalidone, ACEI-lisinopril, CCB-amlodipine and  $\alpha$ -receptor blockers-doazosin). The diuretic versus  $\alpha$ -receptor blocker therapy comparison was discontinued prematurely because of a higher relative risk of CVD in the  $\alpha$ -receptor blocker group. There was no evidence of superiority for treatment with ACEI or CCB compared to diuretic in the overall group or in subgroups with DM, impaired fasting glucose, or normoglycemia<sup>7</sup> (fig. 2). In contrast, CVD (especially heart failure) was more common during treatment with CCB and ACEI compared to diuretic, overall and in the subgroups with or without DM. In the subgroup with DM, the relative risk (95% confidence interval [CI]) for incidence of heart failure in those treated with CCB vs. diuretic was 1.42 (1.23-1.64) and in those treated with ACEI vs. diuretic was 1.22 (1.05-1.42).

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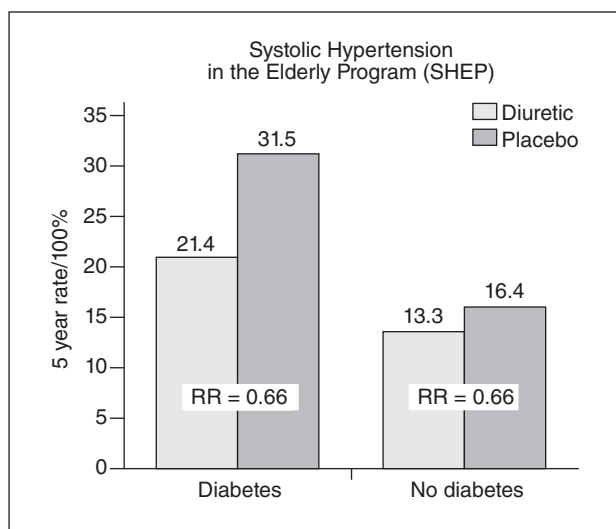


Fig. 1. Incidence of major cardiovascular events by treatment group for adults with hypertension who did or did not have diabetes mellitus at baseline. RR: relative risk. (Adapted from Curb et al<sup>4</sup>.)

Metabolic consequences, including a tendency for hyperglycemia and hypokalemia, are a recognized consequence of diuretic therapy. In ALLHAT, the 4 and 6-year cumulative incidence of DM (fasting blood sugar  $\geq 126$  mg/dl) in study participants without DM ( $<126$  mg/dl) at baseline was 11.0 and 13.8% for those assigned to diuretic, 9.3 and 12.0% for those assigned to CCB, and 7.8 and 11.0% for those assigned to ACEI. If one assumes the CCB to be metabolically neutral, only about 15% of the DM associated with diuretic use in ALLHAT was due to the drug itself. Meta-analysis has demonstrated a consistent pattern for a higher incidence of hyperglycemia during diuretic therapy compared to placebo and ACEI or ARB<sup>8,9</sup>. Whether diuretic induced hyperglycemia and DM has the same CVD risk implications as non drug induced DM is uncertain. In ALLHAT, the relative risk (RR) of coronary heart disease (CHD) in study participants who developed new onset DM was lower in those assigned to diuretic (1.46; 95% CI, 0.88-2.42) compared to their counterparts assigned to CCB (1.71; 95% CI, 0.87-3.34) or ACEI (2.23; 95% CI, 1.07-4.62), albeit an interaction term yielded no statistically significant difference between the three treatment assignments<sup>8</sup>. The Systolic Hypertension in the Elderly Program (SHEP) follow up study provides experience from a long-term (average = 14.3 years) follow-up in which those treated with diuretic were relatively "uncontaminated" by addition of other agents<sup>10</sup>. SHEP participants with prevalent DM at baseline assigned to diuretic treatment experienced a lower RR of CVD mortality compared to their counterparts assigned to placebo (0.69; 95% CI, 0.68-0.95). Those assigned to placebo who developed new onset DM during the 5 years of treatment in the trial experienced a significant increase in RR of CVD

(1.56; 1.11-2.18) during follow up. In contrast, those assigned to diuretic did not (1.04; 95% CI, 0.75-1.46). In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, rosiglitazone was associated with a 60% reduction in DM or death whereas treatment with an ACEI improved post-challenge 2 hour glucose levels but failed to have a positive impact on the primary outcome. Compared with placebo, ACEI treatment lowered fasting glucose by  $< 1$  mg/dl, an effect that would not be expected to influence CVD risk.

Hypokalemia, leading to reduced insulin secretion, may be an important causative mechanism for diuretic induced hyperglycemia and DM. In a quantitative review of 20 placebo-controlled and 39 active-controlled trials, there was a linear relationship between decrease in potassium and increase in blood glucose, with an approximately 10 mg/dl increase in glucose for every 1 mEq/l decrease in potassium<sup>11</sup>. A US National Heart, Lung, and Blood Institute Working Group recommended conduct of a short-term clinical trial to determine whether prevention of hypokalemia can minimize or prevent diuretic induced hyperglycemia<sup>12</sup>.

Most patients with DM and hypertension require 2 or more antihypertensive medications to control their BP. Combination of a diuretic and ACEI or ARB is logical and can be supplemented by a CCB or other drugs to attain the desired level of BP control. Achievement of good BP control may be more important than choice of the agents needed to reach that goal. Compared to their counterparts assigned to a BP goal  $< 180/105$  mmHg, study participants in the United Kingdom Prospective Diabetes Study (UKPDS) with DM and hypertension assigned to a goal BP  $< 150/85$  mmHg experienced a 44% lower incidence of stroke, a 21% reduction in myocardial infarction, and a 47% decrease in microvascular complications<sup>13</sup>. The clinical trial was conducted over a 10 year period from 1987 to 1997. During the next 10 years, from 1997 to 2007, between-group differences in BP disappeared gradually and the previously noted benefits were lost<sup>14</sup>. These findings underscore the importance of not only achieving but maintaining good BP control to attain the expected benefits of antihypertensive therapy. More recently designed clinical trials have documented the benefit of BP lowering in DM patients with hypertension who have a lower starting level of BP. For example, in the ADVANCE trial 11,140 patients with type 2 diabetes and treated hypertension (average systolic/diastolic BP = 145/81 mmHg) were randomized to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to their current antihypertensive drug therapy. Compared with those assigned to placebo, study participants assigned to active therapy had a mean reduction in systolic BP of 5.6 mmHg and diastolic BP of 2.2 mmHg. Relative risk of a major macrovascular or microvascular event was 0.91 in the active treatment group compared to placebo (95% CI, 0.83-1.00). The ACCORD trial is

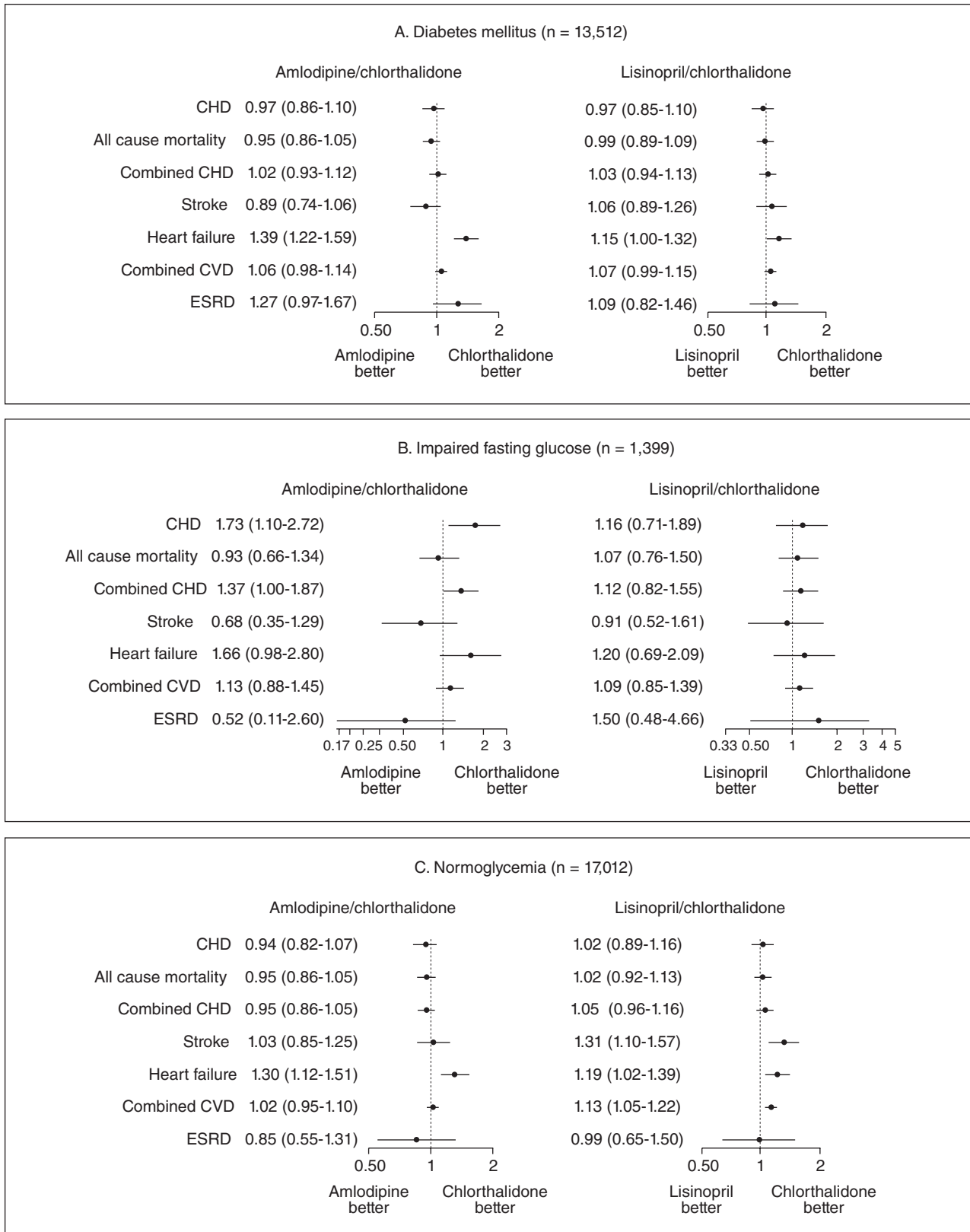


Fig. 2. Relative risks (95% CI) for nondiuretic compared with diuretic treatment of hypertension in ALLHAT participants with diabetes mellitus (A), impaired fasting glucose (B), and normoglycemia (C) at baseline. CHD: coronary heart disease (CHD death and nonfatal myocardial infarction); combined CHD: CHD, coronary revascularization, or hospitalized angina; combined CVD: combined CHD, stroke, other treated angina, heart failure, or peripheral arterial disease; ESRD: end-stage renal disease. (Adapted from Whelton et al<sup>7</sup>.)

evaluating the benefit of intensive (systolic BP < 120 mmHg) versus standard (systolic BP < 140 mmHg) BP control in approximately 5,000 study participants with DM and hypertension. Results are expected in 2010. At this time, the scientific evidence in favor of the Joint National Committee for Prevention, Detection and Treatment of Hypertension recommendation that the BP goal for treatment of hypertension in patients with DM and/or chronic renal disease be < 130/80 mmHg is incomplete. However, the recommendation seems reasonable in the context of existing knowledge from observational prospective studies as well as clinical trials.

In summary, hypertension is common in persons with DM and is often accompanied by other components of the metabolic syndrome. Lifestyle change should be a starting point for prevention and treatment of hypertension, especially in persons with DM. Diuretics, alone or in combination with other antihypertensive agents, are effective for treatment of uncomplicated hypertension in persons with or without DM. ACEI and ARBs are good choices for treatment of hypertension in individuals with DM and heavy proteinuria. Most patients with DM and hypertension require 2 or more antihypertensive medications and inclusion of a diuretic in such combinations makes good sense. The modest hyperglycemia that is sometimes encountered during diuretic therapy may be due to hypokalemia and does not appear to carry the same risk implications as non-drug induced hyperglycemia and DM. Increasingly, clinical trial and observational evidence favors intensive treatment of hypertension in adults with DM aimed at achieving lower levels of BP than is warranted in their counterparts without DM.

### Conflict of interest

The author declares he has no conflict of interest.

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