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Treatment

Recent Clinical Trials

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Clinical trials evaluate the operational utility of administered treatments. The specific trials reviewed in this section provide answers to questions that directly influence evidence–based care of patients with hypertension. These questions include: (1) the definition of patient populations in which treatment is beneficial; (2) the value of a specific treatment or treatment strategy in reducing cardiovascular risk and; (3) the relative value of available treatments in achieving therapeutic objectives.

The Hypertension in the Very Elderly Trial (HYVET)

HYVET evaluated the usefulness of antihypertensive therapy versus placebo in individuals >80 years of age with a baseline systolic blood pressure (SBP) ≥160 mm Hg. The initial protocol required concurrent elevation in diastolic blood pressure (DBP; 90–109 mm Hg); a protocol amendment approved during the recruitment phase allowed inclusion of patients with isolated systolic hypertension. Subjects were randomized to receive the diuretic, indapamide (sustained–release) 1.5 mg/d or placebo. The angiotensin–converting enzyme (ACE) inhibitor, perindopril (2–4 mg) was added, if needed, to subjects in the active treatment group who did not reach the BP treatment goal of <150/80 mm Hg. The mean BP difference between the active treatment and placebo groups was 15.0/6.1 mm Hg after 2 years of follow–up; only 48% of patients in the active treatment group achieved goal BP.

The study was stopped early after a mean follow–up of 2.1 years due to the unexpected finding of a significant mortality reduction in subjects randomized to active therapy. Major reductions in key cardiovascular endpoints were also documented (Table 1) Stroke, the primary endpoint, was reduced by 30%, heart failure by 64%, and overall mortality by 21%. Stroke reduction was of borderline significance ($P = .06$), apparently attributable to reduced statistical power related to early study termination. The 39% reduction in fatal stoke ($P = .046$) made a significant contribution to overall mortality reduction. During a 1–year extension phase, in which all patients received active therapy, BPs in the two treatment arms converged, and there was no difference in the occurrence of stroke or other cardiovascular endpoints. However, a significant mortality advantage was retained in patients originally randomized to active treatment.

Comment

Previous studies, including Swedish Trial of Old People with Hypertension-2 (STOP-2), Systolic Hypertension in the Elderly Program (SHEP), and Systolic Hypertension in Europe (Syst-Eur), in subjects 60 years of age and above, established the benefit of antihypertensive therapy in older patients with both systolic/diastolic and isolated systolic hypertension. In the subset of the 'very' elderly, those 80 years of age and above, observational studies suggested that BP and mortality risk were inversely related; that is, the higher the BP the lower the mortality seen. It was not known, however, whether this relationship was due to comorbidities (eg, heart failure) that both reduced BP and increased mortality, or represented a true protective effect of elevated BP in the very elderly.

The results of HYVET demonstrated important reductions in the incidence of stroke and heart failure in addition to overall mortality reduction with BP reduction. Questions remain, however, about the optimal threshold for treatment and BP targets in this patient subgroup. Patients were included in HYVET only if their baseline SBP was

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Table 1
Primary and secondary outcomes of Action to Control Cardiovascular Disease in Diabetes (ACCORD) Blood Pressure (BP)

Outcome	Intensive Therapy (n = 2362), events, n	Intensive Therapy (n = 2362), %/y	Standard Therapy (n = 2371), events, n	Standard Therapy (n = 2371), %/y	Hazard Ratio	*P*
Primary outcome	208	1.87	237	2.09	0.88	.20
Prespecified secondary outcomes						
Non–fatal myocardial infarction	126	1.13	146	1.28	0.87	.25
Stroke						
Any	36	0.32	62	0.53	0.59	.01
Non–fatal	34	0.30	55	0.47	0.63	.03
Death						
Any cause	150	1.28	144	1.19	1.07	.55
Cardiovascular cause	60	0.52	58	0.49	1.06	.74

>160 mm Hg, leaving unanswered the question as to whether patients with SBP 140–160 mm Hg should receive routine antihypertensive therapy. The optimal targets for BP reduction likewise remain unclear; HYVET used a BP target of 150/80 mm Hg, and this was achieved in fewer than half of the treated patients. Despite these limitations, the study adds to the growing body of evidence that antihypertensive therapy is indicated in elderly patients regardless of age, although the exact threshold and BP targets for antihypertensive medication initiation and the BP goals achieved remain unclear. Diuretic–based treatment with addition of an ACE inhibitor as needed is an effective treatment strategy.

The Action to Control Cardiovascular Disease in Diabetes (ACCORD)

ACCORD was a prospective clinical endpoint study that randomized 'high–risk' participants with diabetes at 77 clinical sites in North America to receive either intensive or standard glycemic control (NEJM 2008;358:2545-2559). To be included in ACCORD, patients had to have had stable adult–onset diabetes for at least 3 months, had a glycohemoglobin of at least 7.5% but not more than 11%, be at least 40 years of age with established cardiovascular (CV) disease or at least 55 years of age with evidence of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for CV disease (dyslipidemia, hypertension, smoking, or obesity). A serum creatinine of >1.5 mg/dL or a body mass index (BMI) >45 were exclusion criteria. In addition to being randomized to one of two glycemic targets, subjects were also randomized in either a lipid (which had first priority) or BP trial.

Patients in ACCORD BP had to have an SBP between 130 and 180 mm Hg, and be taking no more than three antihypertensive medications. Patients were assigned to an SBP goal <140 mm Hg (standard arm) or <120 mm Hg (intensive arm). Both groups were treated in open–label fashion with approved and commonly used antihypertensive medications.

After randomization, participants assigned to the intensive arm were seen monthly for the first 4 months and every 2 months thereafter, whereas standard participants were seen and had BP assessed at months 1 and 4, and every 4 months thereafter. At each management visit, BP was based on the average of three measurements using an automated device (Omron 907) after subjects rested and were seated in a chair for 5 minutes.

The primary endpoint was a composite of non–fatal myocardial infarction (MI), non–fatal stroke, or CV death. There were eight pre–specified secondary outcomes. With a planned sample size of 4200 participants, the ACCORD BP trial was designed to have 94% power to detect a 20% difference in the rate of the primary outcome at 5 years, with an assumed primary event rate of 4% per year in the standard therapy group.

Of the 10,251 overall ACCORD subjects, 4733 were assigned to the BP study (2362 to intensive BP control and 2371 to standard BP control). Mean age of the subjects included in the BP study was 62.2 years with 48% female, 61% non–Hispanic white, 24% black, and 7% Hispanic. Approximately one–third had a history of CV disease at baseline. Mean baseline A1C was 8.3%, mean baseline low–density lipoprotein cholesterol (LDL–C) was 110 mg/dL, and mean BP on entry was 139/76 mm Hg. One year after randomization, and essentially throughout the remainder of the trial, the average SBP was 119.3 mm Hg for the intensive group and 133.5 mm Hg for the standard group, with the corresponding achieved DBP 64.4 mm Hg in the intensive group and 70.5 mm Hg in the standard group. The mean difference in BP between groups was 14.2/6.1 mm Hg, which was associated with a mean difference of 1.1 antihypertensive medications/patient at the end of the trial (3.4 and 2.3 antihypertensive medications used in the intensive and