Journal of the American Society of Hypertension 8(6) (2014) 437–447

Review Article

Top 10 landmark studies in hypertension

Elizabeth W. Edwards, MD, MBA[a], Donald J. DiPette, MD[a], Raymond R. Townsend, MD[b], and Debbie L. Cohen, MD[b,*]

[a]*Department of Medicine, University of South Carolina School of Medicine, Columbia, SC, USA; and*
[b]*Renal, Electrolyte, and Hypertension Division, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA*

Manuscript received March 3, 2014 and accepted March 10, 2014

Abstract

The field of hypertension has evolved considerably over the last 70 years, from a belief that elevated blood pressure was an inevitable consequence of aging and beneficial, to maintaining perfusion to overwhelming proof of the cardiovascular morbidity and mortality associated with elevated blood pressure. The authors reviewed the literature on hypertension and selected 10 studies pivotal in changing physicians' attitudes regarding the management, treatment, and outcomes of hypertensive patients. Four studies cover treatment initiation and blood pressure goals, two studies compare pharmacologic antihypertensive agents, and the final four address the approach to blood pressure control in special populations (diabetes mellitus and chronic kidney disease). The authors readily acknowledge the many other contributions to the field of hypertension not profiled here. J Am Soc Hypertens 2014;8(6):437–447. © 2014 American Society of Hypertension. All rights reserved.

Keywords: Blood pressure; clinical trials.

Introduction

Management of hypertension has evolved considerably over the last 70 years. In the mid-1940s, a reasonable systolic blood pressure was 100 plus the patient's age. Physicians assumed elevated blood pressure was the body's normal adaptation to stiffening and sclerotic arteries, and thus a beneficial compensatory mechanism to maintain organ perfusion.[1] To imagine the cardiovascular unawareness just seven decades ago is startling. Most physicians, including those prominent in the cardiovascular field, largely dismissed early data the American Society of Actuaries published in 1928 linking higher blood pressure to premature death.[2] At the time, cardiovascular disease was considered an inevitable consequence of aging. Furthermore, even as the medical community became aware of the cardiovascular consequences of hypertension, the first relatively tolerable pharmacologic antihypertensive agents, β-blockers and diuretics, were not developed until the 1950s.

Hypertension affects about one billion people worldwide. Data from the recent report of the National Health and Nutrition Examination Survey (NHANES), conducted in the United States from 2009–2010, estimates that approximately 30% of U.S. adults have hypertension, but only about half of those actually control their elevated blood pressure.[3] Approximately 20% of individuals with hypertension do not know they have the condition, increasing their risk for heart attack and stroke, the first and third leading causes of death in the U.S. Substantial differences exist between demographic subgroups, with adult men aged 18–44 years, Mexican Americans, foreign-born, and those without health insurance having a lower prevalence of control of their hypertension than their counterparts.[4] A recent predictive model showed that for every 10% increase in hypertension treatment, an additional 14,000 deaths per year in the adult population ages 25–79 years could be prevented.[5]

Hypertension is now a major and well-known risk factor for cardiovascular disease. Starting at 115/75 mm Hg each increase of 20/10 mm Hg in blood pressure doubles the risk of cardiovascular disease.[6] Treating a blood pressure above 140/90 mm Hg has been shown to reduce cardiovascular complications markedly. The first studies investigating the benefits of treating blood pressure were prospectively designed and rapidly demonstrated that pharmacologically lowering extremely high blood pressures dramatically reduced target organ damage.[7–9] The favorable results of

Grant Support: none.
Conflict of interest: none.

*Corresponding author: Debbie L. Cohen, MD, Renal, Electrolyte, and Hypertension Division, Perelman School of Medicine at the University of Pennsylvania, 1 Founders Building, 3400 Spruce St, Philadelphia, PA 19104. Tel: 215-615-0794; fax: 215-615-0349.
E-mail: debbie.cohen@uphs.upenn.edu

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2014.03.333

these initial studies prompted greater and more in-depth questions regarding the optimal blood pressure at which to initiate pharmacologic treatment; the optimal blood pressure goals; risk reduction in various age, gender, racial, and ethnic groups and those with concomitant disease states such as diabetes and chronic kidney disease; and what pharmacologic agents are best utilized and when. Over the ensuing years and to the present, multiple evidence-based studies have answered these questions. The intent of this paper is to review 10 landmark clinical studies (Table 1) that the authors believe have had the greatest impact in changing physicians' attitudes regarding hypertension.

We chose 10 landmark studies in three focus areas: (1) Treatment initiation and goals; (2) Comparison of pharmacologic antihypertensive agents; and (3) Approach in special populations (patients with diabetes mellitus and those with chronic kidney disease). The first focus area examines whether to treat hypertension, when to initiate therapy, which patients benefit from lowering blood pressure, and what the optimal blood pressure goal should be. The studies profiled include the Veterans Administration (VA) Cooperative Study (reported in three parts)[7–9]; the Hypertension, Detection, and Follow-up Program (HDFP) study[10,11]; Systolic Hypertension in the Elderly Program (SHEP) and its European counterpart (SYST-EUR; counted together because of their similarity)[12,13]; and the Hypertension Optimization Trial (HOT).[14] The second focus area discusses antihypertensive agents, classes, and combinations. The two studies in this focus area are the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[15] and the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial.[16] The third focus area examines whether blood pressure treatment and goals should differ for patients with diabetes mellitus (United Kingdom Prospective Diabetes Study Group [UKPDS][17] and Action to Control Cardiovascular Risk in Diabetes [ACCORD])[18] and chronic kidney disease (Modification of Diet in Renal Disease Study Group [MDRD][19] and African American Study of Kidney Disease and Hypertension Trial [AASK]).[20] We acknowledge that there are many other contributions to the field of hypertension that are not profiled.

Treatment Initiation and Goals

Whether to initiate treatment for non-malignant hypertension was a controversial question until the mid-1960s when the VA Cooperative Study Group answered that question with a resounding yes.[7] The VA Cooperative Study Group conducted a landmark trial—the first randomized, placebo-controlled, double-blind, multi-institutional pharmacologic efficacy trial in cardiovascular medicine. The study randomized 523 hypertensive men with diastolic blood pressures between 90 mm Hg and 129 mm Hg to treatment with hydrochlorothiazide, reserpine, and hydralazine, or placebo; results were published in three separate parts: the first included diastolic blood pressures between 115 and 129 mm Hg and the second and third included diastolic blood pressures between 90 and 114 mm Hg. The third part was a sub-analysis of the data and studied the influence of age, prior cardiovascular or renal abnormalities, and prior diastolic blood pressure in the 90–114 mm Hg group.[9] The first component of the study, published in 1967, reported the results on the 143 men with diastolic blood pressures between 115 and 129 mm Hg who received active pharmacologic treatment or placebo. Because of the striking advantage of treating these 143 men, researchers terminated the trial early and published their results: that active antihypertensive treatment favorably influenced the clinical course of these patients.[7] After 24 months of active treatment, blood pressure was reduced by 43/29.7 mm Hg in the active-treatment group, whereas there was no significant change in mean blood pressure readings in the placebo group. Twenty-seven severe, complicating events occurred in placebo-treated patients as compared with two in the active group. Four deaths occurred in the placebo-treated group and none in the actively treated patients. Other complications in the placebo group included grade III or IV hypertensive retinopathy, congestive heart failure, increasing azotemia, cerebrovascular thrombosis, transient ischemic attacks, cerebral hemorrhage, myocardial infarction, and severely elevated blood pressure. Severe complications in the active-treatment group were one cerebrovascular thrombosis and one case of multiple drug toxicity. This report was the first to establish clearly beneficial effects of pharmacologic treatment for severe hypertension.

The results of the second component of the VA Cooperative Study were published in 1970.[8] This study reported on the 380 men with diastolic blood pressures between 90 and 114 mm Hg who received active pharmacologic treatment or placebo. Fifteen percent of the patients dropped out of the study due to developing more severe hypertension or intolerance to therapy. The blood pressure in the treatment group decreased on average by 27.2/17.4 mm Hg, while the blood pressure in the placebo group increased on average by 4.2/1.2 mm Hg. Morbidity attributed mainly to heart failure, stroke, and renal failure was reduced from 55% in the placebo group to 18% in the treatment group over a 5-year period. Deaths were reduced from 35 in the control group to nine in the treatment group. Twenty patients in the placebo group developed serious diastolic hypertension of 125 mm Hg or higher compared with none in the treatment group. Pharmacologic treatment was more effective in preventing heart failure and stroke than coronary events, but the benefit was related to the level of pre-randomization blood pressure. The treated group benefitted, but not as dramatically as the 115–129 mm Hg group. This report focused on patients with mild to moderate diastolic hypertension, and, together with the first component of the VA