Personal and Historical Perspectives

Reminiscences of the Veterans Administration
Trial of the Treatment of Hypertension

Edward D. Freis

In 1966 F. J. Inglefinger, A. S. Relman, and M. Finland published a book Controversy in Internal Medicine. Even at that late date, the authors of one of the chapters vigorously defended the position that the drug treatment of essential hypertension was of no benefit. The question was hotly debated during the 1950s and 1960s. In fact, many authorities strongly opposed such treatment, arguing that it was first necessary to find the cause or causes of hypertension before it could be treated effectively. This controversy provided the stimulus for the Veterans Administration (VA) Cooperative Study on Antihypertensive Agents. The idea to carry out a controlled trial evolved gradually; it began with a trip to Germany.

In the 1950s, I accompanied Dr. Hubert Pipberger, a VA colleague who has contributed much to computer electrocardiography, on a visit to Bonn. Hubert and I had been attending a European Meeting on Cardiology, and on the way back, he decided to visit Dr. C. Martini, one of the pioneers in controlled clinical trials, who was then quite elderly but still mentally alert. It was the first time I had heard a discussion of this relatively new method. I was only mildly interested, and the highlight of the visit for me was a delicious homemade glazed apple cake made by Frau Martini.

On the way home, Hubert raised my consciousness further regarding the power of statistical analysis and clinical trials. I became more interested but still did not make the connection that these methods could be applied to solve controversial questions regarding the treatment of hypertension. Nevertheless, out of curiosity, I began to read R. Fisher and especially Bradford Hill, whose commonsense approach inspired me more than any other biostatistician.

Early Multiclinic Trials in the Veterans Administration

Even at that time, the VA had already demonstrated leadership in controlled clinical trials: the VA multiclinic evaluations of antituberculosis drugs, which demonstrated beyond doubt their long-term efficacy. Most importantly for me, they demonstrated that valid long-term outpatient controlled trials were practical in the VA setting. The idea then finally hit me that if a clinical trial could be done in antituberculosis therapy, why not in the treatment of hypertension?

The department of biostatistics at VA Central Office consisted of Jack Williams, who had been involved in the antituberculosis drug trials. Williams was only too happy to work with me as I seemed to be his only client. He accepted all my suggestions both good and bad. Unfortunately, he died prematurely and unexpectedly before the initial study was completed. He was replaced by an experienced and critical biostatistician, Lawrence Shaw, who was assisted by R. Tewksbury, an elderly gentleman with whom I made site visits. During our travels, one of the main topics of his conversation was the depth of the false bottom of whiskey glasses. “Only in New York City do you get your honest measure,” he often told me.

Larry Shaw was not at all intimidated by the physicians in the study. He enforced rigorous statistical design and methods of analysis, and we owe much to him for the successful outcome. When he came on board, he pointed out that we had been trying to answer too many questions in a single study. For example, we attempted to determine the relative efficacy of several antihypertensive agents and, in the same study, tried to answer the question as to whether drug treatment prevents complications in essential hypertension. For a variety of reasons, these two objectives could not validly be combined in a single study. In 1962, we decided to begin a new trial directed solely at the question of whether treatment reduces morbidity and mortality in mild-to-severe hypertension excluding malignant hypertension.

Climate of Medical Opinion Before the Seventies

The reason for including a wide spectrum of severity in treating hypertension resulted from the climate of medical opinion at the time. The era of chemotherapy for hypertension was still in its infancy, and most physicians were primarily interested in an etiologic diagnosis of hypertension. Their
Many farsighted physicians, including Horace Smirk, specifically with antihypertensive drugs was scornfully referred to as "treating the manometer." I can recall in the fifties and even in the sixties some world-famous medical institutions that directed their entire energies toward the search for a surgical cure for the different forms of secondary hypertension such as renovascular hypertension or pheochromocytoma. If none was found, which was usually the case, the patient was discharged, often without any attempt at antihypertensive medication. Research grants were rewarded almost exclusively to those who sought the causes of hypertension.

Academia neglected to consider, however, several rather important issues. First, by far the most common type of hypertension was the essential variety, whose causes were elusive and have remained so to this day. Second, and more important, while the causes of essential hypertension remained unknown, there was good evidence obtained, particularly in patients with malignant hypertension, that reduction of a markedly elevated blood pressure with drugs resulted in remission of many signs and symptoms, including clearing of hemorrhages and exudates in the optic fundi, remission of congestive heart failure, and disappearance of occipital headache. It seemed reasonable to some of us that, if these pathological manifestations of hypertension were reversible by reducing the blood pressure, they probably were caused by the elevated blood pressure, per se, regardless of the ultimate pathogenesis of the hypertension. Our motto became "Control the hypertension and control the disease." Although not in the majority, many farsighted physicians, including Horace Smirk, Irvine Page and his associates, Arthur Corcoran and Harriet Dustan, George Pickering, and others, while not giving up the search for causes, had the same philosophy.

At the first international meeting on hypertension in 1961 in Prague, I sought the opinion of two leaders in the field concerning the advisability of a placebo-controlled multiclinic trial. One was Horace Smirk from New Zealand, who was then the leading advocate of antihypertensive drug treatment. His response was, "It is unethical to use placebo when we already know that drug treatment is beneficial." It seemed to me that, unfortunately, the majority of practicing physicians did not accept this view, but I could see that it would be useless to argue with him. I next approached George Pickering. He listened attentively and at the end simply smiled and nodded his head affirmatively. I thanked him and walked away further convinced that the study was worthwhile.

The opposing school, headed by Drs. W. Goldring and H. Chasis, would have none of this.\(^{1}\) They vigorously continued to support the view that we cannot treat hypertension unless we know the cause. Their influence was so great that they dominated medical opinion until 1970 when our VA Cooperative Study on results in moderate hypertension was published.

**Evolution of the Morbidity-Mortality Trial**

The organization of our initial cooperative studies,\(^{2,3}\) which were in actuality a learning experience, began in 1956. Participating physicians were recruited mostly at a meeting of the Chiefs of Medical Services of the VA. There were a few long-term multiclinic trials in the literature at that time but none in hypertension. We, therefore, had few models to follow. Although our early trials provided some information on the relative efficacy of the drugs available in the late 1950s, they were unconvincing in answering our most important question, "What effect does drug treatment have on morbidity and mortality in hypertension?"

For these reasons, we began a new study devoted solely to the effects of treatment on morbidity-mortality in hypertension. As we didn't have the funds to rent a meeting room, a group of us met in the lobby of the Seaview Hotel during the meetings of the American Federation for Clinical Research in Atlantic City in the spring of 1962. The general plan of the study was decided on. It was to include essential hypertension of all degrees of severity from 90–129 mm Hg diastolic blood pressure but exclude malignant hypertension. Patients with severe complications of hypertension were also excluded.

To eliminate the white-coat effect on blood pressure, the patients were initially hospitalized for 1 week with blood pressure recorded five times daily. They were then returned to the outpatient clinic for 3 weeks, where the baseline blood pressures were recorded. The treatment was a combination of hydrochlorothiazide, hydralazine, and reserpine that had been found to be highly effective and generally well tolerated in our previous trials. The study was randomized and double-blind. Compliance was checked by pill counts and by incorporating riboflavin in the tablets, which causes the urine to fluoresce when viewed under ultraviolet light.

We began to admit patients in January 1964. At the end of the first year into the study, we began to hear disturbing rumors about excessive mortality in one subgroup of patients. This subgroup comprised the placebo patients with entry diastolic blood pressure between 115 and 129 mm Hg. By the time we met for an emergency meeting, the number of morbid events, all of them serious, was 27 (four fatal) in the control group versus two in the treated group. The results of this subgroup were published in 1967.\(^{4}\) We regretted that we could not have recognized and terminated this group of patients from the trial sooner, but the events occurred so rapidly they caught us by surprise. The remaining patients with baseline diastolic blood pressure between 90 and 114 mm Hg remained in the trial for an average period of 2 years longer. We did not present the results of the VA Cooperative Study at any medical meeting before they had been published so that credit would not...
focus on any single individual and also to make sure that all of the relevant data would be immediately available for study by the scientific community.

**Reaction to the Veterans Administration Trial**

When the results of the treatment of mild-to-moderate hypertension were published in 1970,\(^6\) I called a press conference that generated little interest among the media in most areas of the country. An Associated Press dispatch was published in abbreviated form in the inside pages of some newspapers around the country. Television coverage was limited to a brief remark by Walter Cronkite. Physicians also were at first singularly unimpressed or unaware. Interest increased with the publicity attending my receipt of the Lasker Award in 1971. However, the event that made hypertension and its treatment a household word was the establishment of the High Blood Pressure Education Program by Elliot Richardson, who was then Chief of Health, Education, and Welfare. Richardson's interest was aroused by Mary Lasker, who came to him armed with reprints from our VA Study publications. Richardson's father was a physician who had hypertension and died of a stroke, which may have helped influence his reaction to Mrs. Lasker's arguments. The resulting highly successful media promotion, aimed mostly at the public, also owes much to Dr. Theodore Cooper who, as director of the National Heart, Lung, and Blood Institute, proceeded vigorously to carry out the program.

**Veterans Administration Trial Compared With Later Trials**

How well have the results of the VA Cooperative Study withstood the test of time? The results agree well with most of the later and much larger trials, especially with regard to prevention of stroke.\(^5^78\) Because the VA trial included more severe hypertension than later trials, the findings indicated protection against myocardial infarction, which contradicted our results and also those of most other trials.

The VA investigators recognized that the size of the trial was not large enough to draw valid conclusions regarding the effectiveness of treatment in patients with mild (diastolic blood pressure 90–104 mm Hg) hypertension. Because the incidence of morbidity events is so small in mild hypertension, large numbers are required to detect a reliable difference between treatment and placebo groups. Therefore, we concluded that our study demonstrated that treatment was effective in moderate and moderately severe hypertension but that larger scale studies were required to settle the question in mild hypertension. This important question, however, still remains controversial for the patients with diastolic pressures in the range of 90–94 mm Hg.\(^11\)

The VA Cooperative Study will be remembered for changing the management of hypertension. It altered the emphasis from secondary forms of hypertension, which while still important, applied only to a small percentage of the hypertension population. It convinced physicians that the numerically much more prevalent essential or primary hypertension could be benefited by antihypertensive drug treatment. Our study demonstrated that by controlling the blood pressure, we could prevent most of the complications of the disorder, and equally important, its progression to a more severe state could be arrested.

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E D Freis

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