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# Dr Edward Freis: A pioneer in evidence-based treatment of hypertension

Our understanding of the need for antihypertensive therapy owes much to the work of Edward Freis.

**ABSTRACT**

**Dr Edward Freis (1912–2005) was a pioneer in answering the question of whether hypertension should be treated. Freis contributed to the development of evidence-based medicine by conducting the first double-blind RCT comparing the effectiveness of single agents vs combination therapies in hypertension from 1964–1969. Though the study did not have an immediate impact, over time its value was recognized and Freis continued his work, eventually publishing over 400 articles on hypertension treatment. He was instrumental in changing medical and public attitudes toward hypertension screening and management, and was a pioneer in public health and preventive medicine. Hypertensive medicine began its golden age of evidence-based medicine in the early 1990s. Currently there has been a shift in this treatment paradigm toward prevention. Prevention of end organ dysfunction is a relatively new concept. Our treatment focus has shifted to include those patients with asymptomatic cardiovascular risk factors such as hypertension. The current recommendations of the Canadian Hypertension Education Program are to control blood pressure in diabetic patients; ensure all adults have regular blood pressure assessments; conduct overall assessments of patients' CV risks; make lifestyle modifications the cornerstone of prevention and treatment; treat most patients to a target below 140/90; use combination therapies when necessary; and treat newly diagnosed hypertension in patients older than 80.**

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Preventive measures have played a major role in how patients are screened and treated for cardiovascular disease (CVD) over the last 30 years. Most of our previous clinical decisions focused on treating the effects of atherosclerosis: coronary artery disease, cerebral vascular disease, nephropathy, and peripheral vascular disease. Today our treatment focus has shifted to managing those patients with asymptomatic cardiovascular (CV) risk factors such as hypertension[1] in response to overwhelming evidence showing the CV benefits of antihypertensive therapy.[2] Clinical research has prompted a revolution in practice philosophy to include CV risk prevention. The randomized clinical trial (RCT) has been the catalyst for this change and has provided a scientific base for many modern treatment decisions.

We have Dr Edward Freis, a pioneer in the application of evidence-based medicine (EBM), to thank for making us more aware of the need for CV risk prevention. He completed the first double-blind RCT comparing the effectiveness of single agents and combination therapies in hypertension, and showed the benefit of antihypertensive treatments for prevent-

ing CV disease in patients with moderate to severe hypertension.[3] He also promoted patient screening and the use of antihypertensive medications for all patients with hypertension.

Born in Chicago in 1912, the youngest of four sons, Edward Freis began his academic career at the University of Arizona. He chose the drier climate in the hopes that it would help his asthma. He hoped to become an actor and took time off from university to study at the Pasadena Playhouse. Freis soon decided he was not tall enough to succeed in show business and returned to Arizona where he received his bachelor of science in 1936. Four years later he received a medical degree from Columbia University. Following his internship and residency at Massachusetts Memorial Hospital, Freis joined the United States Army Air Forces (now known as the US Air Force) and served as chief of the laboratory service at the Lincoln Air Force Base in Lincoln, Nebraska. After the war, Freis began a cardiology residency at Evans Memorial Hospital in Boston. He followed this with a research fellowship focusing on hemodynamics and pharmacotherapy for hypertension.

In 1949 Freis was appointed assistant chief of the medical service at the Veterans Administration (VA) hospital in Washington, DC, with a joint appointment as adjunct clinical professor at Georgetown University School of Medicine. From 1950 to 1960 he served as chief of the Hypertension Clinic at Georgetown University.

In the 1950s hypertension management was vastly different from what it is today. Treatment was confined to patients with malignant hypertension, who were hospitalized, treated with intravenous medications, and often discharged home on salt restriction and dietary management. It was only after the launch of chlorothiazide that outpatient hypertension management began. In 1952 the VA conducted an RCT looking at the efficacy of antifungal medications in tuberculosis. Dr Freis and his colleagues used this study as a model for the first RCT in hypertension using chlorothiazide versus placebo.[4]

Photo courtesy of the Albert and Mary Lasker Foundation.

*Dr Edward Freis completed the first double-blind RCT comparing the effectiveness of single agents and combination therapies in hypertension*.

The study ran from 1964 to 1969 and was the first double-blind placebo-controlled multicentre trial done in the United States. The study was done at 17 VA medical centres and involved 523 patients. It was the first study of its kind to demonstrate that the treatment of hypertension reduced the incidence of major hypertensive complications. The treatment group showed a 50% reduction in the incidence of stroke, congestive heart failure, and progressive nephropathy. However, the VA study failed to demonstrate a treatment benefit for prevention of myocardial infarction and sudden cardiac death.[5]

The VA study results were published in 1970 to little fanfare. The medical community had yet to appreciate the impact of EBM in the areas of preventive medicine and public

health. But Mary Lasker, a philanthropist and health policy advocate, was not a member of the medical community, and she believed that the VA study revealed a major public health problem that should and could be addressed. She asked the then secretary of health, Elliot Richardson, to establish a hypertension education program to alert physicians and the general public to the significance of hypertension. With the support of Freis's scientific proof and Mary Lasker's political and financial influence, the National High Blood Pressure Education Program was launched in 1972. It was the first program of its kind to unite the scientific community and public health policymakers who together focused on the idea that CVD was preventable and something patients should be screened for.[6] The program was the first of many initiatives that today encourage a partnership between patient and physician in the screening and treatment of preventable diseases.

Dr Edward Freis was given the Lasker Award for clinical research in 1971 for his leadership in the VA study. At the time, Lasker Award recipients were considered to be Nobel Prize hopefuls. For the next decade Freis continued to direct cooperative studies on hypertension, to advocate for antihypertensive treatment in all patients, and to become recognized as one of the world's foremost authorities in the area of hypertension medicine. In 1977 he was honored by the American College of Physicians with the James D. Bruce Award in preventive medicine. In 1979 Freis coauthored *The High Blood Pressure Book*, *A Guide for Patients and Their Families*.[7] The publication proved Freis to be a "patient's physician," able to contribute to publications for his colleagues in the scientific community and able to create reference material for the patients who would directly benefit from his research.

Dr Freis published over 400 articles on hypertension treatment during his career and was instrumental in changing medical and public attitudes toward the screening and management of hypertension. He received awards from the most respected CV centres in North America, including the American Society of Hypertension, the American College of Physicians, and the American Heart Association. On his 90th birthday he played Chopin on the piano and recited Hamlet from memory. He died at the age of 92 on 1 February 2005 in Washington, DC, of multiorgan failure—ironically as a result of the hypertension he had diagnosed in himself 40 years earlier.

## Freis's Canadian legacy

EBM, preventive medicine, and patient education have been the cornerstones of hypertension management in Canada. In 1977 a national committee sponsored by Health and Welfare Canada met to review the evidence for the usefulness of pharmacotherapy and a stepped-care approach to the treatment of hypertension. The VA study and other RCTs undertaken by Dr Edward Freis provided a small body of evidence used to form the first Canadian guidelines. In 1979 the Canadian Hypertension Society (CHS) was established to act as the professional voice for hypertension treatment in Canada and to promote research and teaching in the disease.[8] The CHS produced several guidelines throughout the 1980s. The development of these recommendations was primarily funded by national and provincial grants and used a panel consensus approach. Over the next decade it was agreed that for any guidelines to be successful, they had to be current, based on evidence, and from a credible, national source. In 2000 the Canadian Hypertension Education Program (CHEP) was established as an offshoot of CHS in order to promote standards of clinical care for the treatment of hypertension. Almost a decade later CHEP is most widely known for its establishment of annual evidence-based guidelines on the diagnosis and management of hypertension.

## Management of hypertension in 2009

Hypertension management in Canada has evolved and improved as a result of the guidelines inspired by the work of Dr Freis. The release of the CHEP recommendations for 2009 marked a decade of Canadian evidence-based approaches to hypertension management. The current guidelines reflect the need to target specific populations for screening, treatment, and adherence.[9] The key points ("red flags") of CHEP 2009 are as follows.

**Ensure blood pressure in diabetic patients is below 130/80 mm Hg.** The latest CHEP guidelines emphasize the need to improve control of hypertension in people with diabetes. Sixty-five percent of diabetic deaths can be attributed to the CV complications.[10-18] Several large-scale RCTs have confirmed the morbidity and mortality benefits of blood pressure reduction in this high-risk population. In 2008 data from ACCORD and ADVANCE confirmed that intensive reduction in blood pressure (below 130/80 mm Hg) in people with diabetes leads to significant reductions in overall mortality rate and CV events.[18,19] Furthermore, the ADVANCE trial showed an additional CV mortality benefit when two agents were used as initial therapy in diabetic patients with blood pressure above 150/90 mm Hg.[18]

The CHEP 2009 guidelines now recommend initial therapy with two antihypertensive drugs for people

with diabetes and blood pressure above 150/90 mm Hg. The use of ACE inhibitors and angiotensin receptor blockers (ARBs) as first-line therapy in diabetes is again a reflection of the last decade's evidence.[20,21]

**All Canadian adults need to have blood pressure assessed at all appropriate clinical visits.** CHEP 2009 emphasizes that 90% of Canadians will develop hypertension in their lifetimes.[22] At a time when antihypertensive treatment is so available and so varied, screening and diagnosis remain the key to adequate care.

**Table.** Lifestyle modification and impact on blood pressure.

| Intervention | Comments | Reduction in systolic blood pressure |
|---|---|---|
| Diet | Adopting a Dietary Approach to Stop Hypertension (DASH): A diet rich in fibre, fruits, and vegetables and low in fat and salt. | 8–14 mm Hg |
| Weight loss | Losing as little as 4 kg or maintaining a BMI between 20–29 kg/m.$^2$ | 3–20 mm Hg depending on amount of weight lost |
| Regular exercise | Undertaking 30–60 minutes of moderate intensity dynamic exercise 4–7 days per week in addition to daily activities. | 4–9 mm Hg |
| Restricting sodium | Limiting total sodium consumption to less than 2 g per day. | 2–8 mm Hg |
| Reducing alcohol consumption | Consuming <2 standard drinks per day and <14 per week for men and 9 per week for women. | 2–4 mm Hg |

**Optimum management of BP requires assessment of overall CV risk.** Ninety percent of all patients with hypertension will have another risk factor for CVD.[23] The paradigm of antihypertensive management should therefore shift to one of CV risk management, making the diagnosis of hypertension in any patient the start of CV risk reduction in general. Risk calculators such as the Framingham and Reynolds risk scores have proven to be useful tools for assessing global CV risk and should be used to guide patients' therapy.[24,25]

**Lifestyle modifications are effective in preventing hypertension, treating hypertension, and reducing CV risk.** Although lifestyle modification remains the most difficult treatment to enforce with patients, it is still the most effective way to prevent hypertension. The benefits of a healthy diet, regular exercise, and weight loss have been proven in a variety of trials to confer significant benefit on the treatment and management of hypertension (**Table**).[26-34]

**Treat to target.** Blood pressure should be lowered to below 140/90 mm Hg in most patients. The CHEP 2009 guidelines recommend a target below 130/80 mm Hg in patients with diabetes and those with chronic renal failure.

**Combinations of therapies (both lifestyle and drug) are generally necessary to achieve target blood pressures.** A variety of trials have confirmed the need for combination therapy to manage hypertension. The more recent CHEP guidelines have advocated the use of combination therapy as initial therapy in patients with blood pressure above 160/100 mm Hg. Based on the newest ONTARGET data, CHEP 2009 now specifically recommends that an ACE inhibitor not be combined with an ARB in people with uncomplicated hypertension, diabetes (without micro- or macroalbuminuria), chronic kidney disease (without micro- or overt proteinuria), or ischemic heart disease (without heart failure).[35]

**Treat newly diagnosed hypertension in patients older than 80.** Prior to October 2008, controversy surrounded the use of antihypertensive medications in patients older than 80 who were newly diagnosed with hypertension. Meta-analysis data in fact suggested cautionary use of pharmacotherapy in this patient population. The Hypertension in the Very Elderly Trial (HYVET), which showed an absolute reduction in the primary endpoint of fatal and nonfatal stroke of 18% in octogenerians treated with indapamide (with possible addition of perindopril) over placebo,[36] has now settled the argument of whether to treat newly diagnosed hypertension in patients over the age of 80. The CHEP 2009 guidelines echo this with the recommendation to initiate diuretics in these patients. Dr Edward Freis would be pleased indeed.

## The future

Hypertension medicine has enjoyed a golden age from the early 1990s to the present day. From the outset Dr Edward Freis helped answer the question, Should hypertension be treated? Over the last two decades, the great debate in hypertension medicine has shifted away from *whether* to treat this disease. Now researchers and physicians are trying to determine exactly *how* to treat.

The current CHEP 2009 guidelines advocate a target blood pressure in patients without compelling indications to be below 140/90 mm Hg. The

initial choice of medication is based on evidence from the trials published in the last decade. There is overwhelming data supporting the use of ACE inhibitors and ARBs as one of the possible first-line choices. In a tribute to Freis's work, ALLHAT showed the superiority of thiazide diuretics.[37] Long-acting calcium channel blockers also show benefit and as such are included among the choices for first-line therapy.[38] Beta blockers are no longer recommended as first-line therapy for uncomplicated hypertension in patients over the age of 60 based on recent data.[39]

The scientific community has spent the last two decades determining the best method for treating the most common disease in North America. Through these years the evidence has shaped our appreciation for this disease and its management. The future of hypertension medicine lies not in the development of newer agents to treat this disease. Nor does it lie in the evidence-based pursuit of the "best drug" for the management of high blood pressure. The future lies in the prevention of this disease. The CHEP 2009 guidelines strongly advocate the screening of patients for hypertension and the use of lifestyle modification both in the treatment and prevention of disease. It cannot be denied that prevention of hypertension is an ambitious and perhaps unrealistic pursuit. Whether it can be achieved in a scientific laboratory or through a community's pursuit of lifestyle modification remains to be seen.

## A final word

At the time of his death, Dr Freis was working on a second book about hypertension for a popular audience. His career was a true marriage of clinical and academic medicine. He treated hundreds of thousands of patients with the help of EBM, a medical approach he also contributed to by completing clinical trials. His publications spanned the clinical, basic science, and popular medical databases, yet he also made significant contributions to public health and patient education.

Freis changed the way we deliver care. He gave us the scientific evidence to support preventive medicine and was a driving force behind the public programs that allow such information to be adopted by and disseminated to the public. Dr Edward Freis's legacy is both the breadth of his scientific publications about medicine for hypertension and the impact this body of work has had on the public health movement in North America and on disease prevention worldwide.

**Competing interests**

None declared.

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