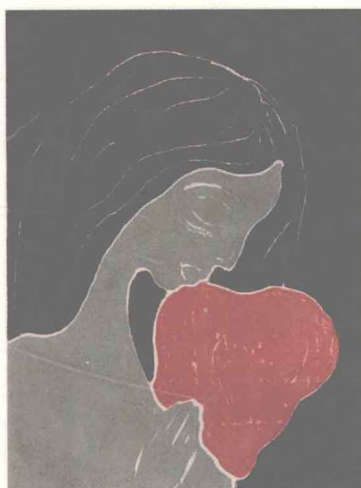


# Hypertension *in* Postmenopausal Women



edited by

Franz H. Messerli

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Hypertension  
*in*  
Postmenopausal  
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## PREFACE

In 1955, Sir Geroge Pickering, after having reviewed the data on morbidity and mortality in men and women with essential hypertension, concluded that “for any given level of arterial pressure, women fare better than men.” Ever since then, it has remained a textbook opinion that hypertension is a less severe risk factor in the female than in the male population. As a consequence, women were very often treated with benign neglect, not only when they had hypertension but also when they suffered from other cardiovascular diseases.

As is outlined in *Hypertension in Postmenopausal Women*, a variety of recent studies have documented that, particularly after the menopause, the risk of hypertensive women suffering from heart attack, sudden cardiac death, stroke, and other cardiovascular morbidity and mortality is as high as or even exceeds that of hypertensive men. The menopause not only increases the prevalence of hypertension, but also exponentially accelerates the development of other cardiovascular risk factors such as insulin resistance, dyslipoproteinemia, and obesity. In concert, these cardiovascular risk factors exert a powerful impact on life

expectancy in the postmenopausal female population. The present monograph serves to inform the practicing physician of the specific problems related to hypertension and other cardiovascular disorders in the menopause and to familiarize the reader with the epidemiology, pathophysiology, clinical findings, and therapeutic options in hypertensive women after the menopause. Although hormone replacement therapy has been shown to diminish the overall risk of cardiovascular morbidity and mortality, much remains to be learned about preventive aspects as well as the safety and efficacy of cardiovascular drug therapy in this special situation. It is hoped that *Hypertension in Postmenopausal Women* will be a practical and useful resource for helping the practicing physician to deal with this exceedingly common entity.

I would like to acknowledge the help of the Alton Ochsner Medical Foundation Medical Editing Department, under the direction of Marion Stafford, in the completion of this project. It has been a pleasure for me to work with Marcel Dekker, Inc., especially Sandra Beberman, Assistant Vice President, Medical Division.

**Franz H. Messerli**

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## Overview

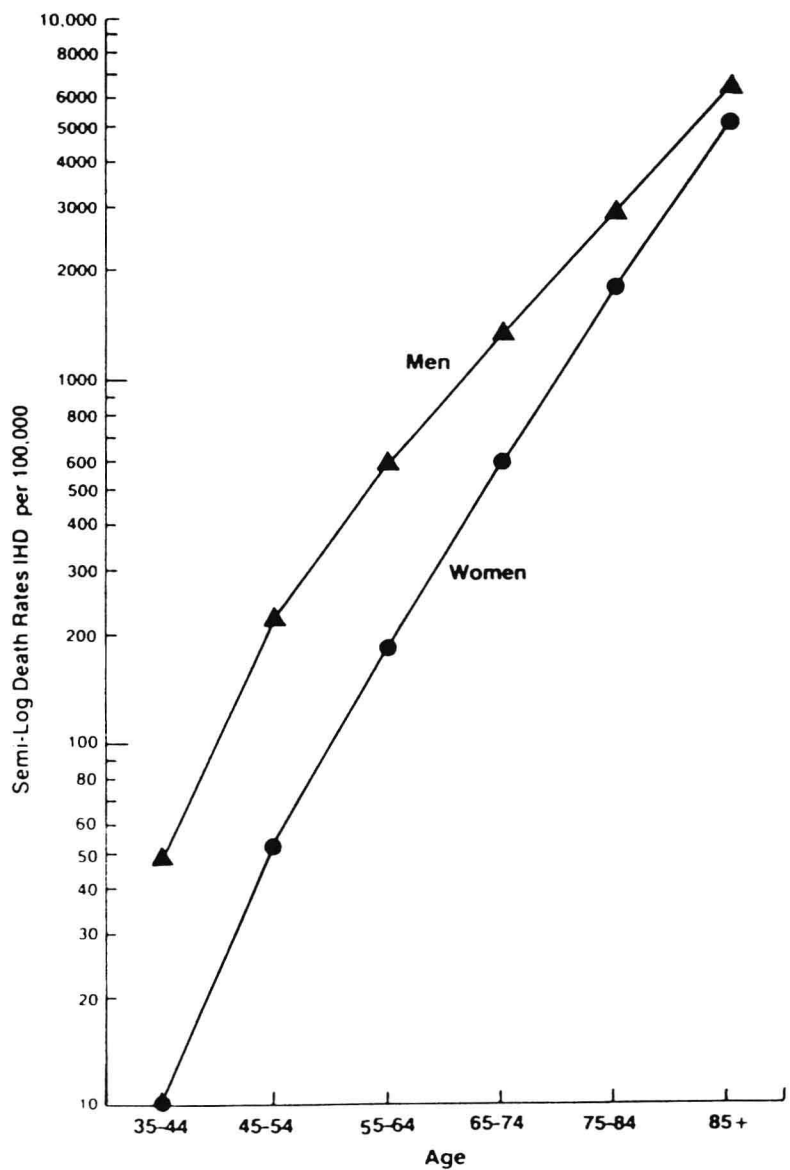
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### I. INTRODUCTION

Coronary heart disease is the leading cause of mortality in women (1). Although it has been regarded as a disease that mainly afflicts men, it accounts for about 250,000 deaths annually in women in the United States and 76,000 in the United Kingdom, figures that are only slightly less than those for men from this cause.

The cardiovascular health of women has received little attention (2–4). The focus of research, of campaigns to reduce cardiovascular disease, and of major trials of primary and secondary prevention of coronary artery disease have been either



**Figure 1** Death rates from ischemic heart disease among men and women aged 35 to 85+ years: United States, 1980 (rates per 100,000). (Data from the Natural Center for Health Statistics, U.S. Department of Health and Human Services.)

exclusively in males or with only minor recruitment of women, largely because of an upper-age cutoff and relatively few women in the age group studied (5).

Although cardiovascular deaths have been falling in the United States since the late 1960s and the past 10 years have seen the cardiac death rate fall by 25% in men in the United Kingdom, it has fallen by only 17% in women (6). While men in their fourth decade have five times the mortality of women from coronary heart disease, women start to catch up at an increasing rate after the menopause, reaching parity in old age (7,8) with men (Figure 1). The greater number of women compared with men living into old age with hypertension and coronary artery disease accounts for the closeness of the overall mortality figures.

## II. RISK FACTORS AND CLINICAL FINDINGS

Most of the morbidity, disability, health care costs, and mortality occur in women after the menopause, but coronary artery disease, once almost nonexistent in younger women (except in severe familial hypercholesterolemia), is increasing and myocardial infarction is no longer uncommon. Younger women are smoking more, they are using oral contraceptives, and, believing that they are not at risk, they eat more saturated fats than men. They have also adopted an increasingly sedentary lifestyle from doing office jobs rather than housework. It has been suggested that coronary heart disease rates in younger women are moving closer to those in men because, as women adopt a lifestyle that is similar to men's, their advantage may be disappearing. In the 1950s twice as many men as women smoked. In the United Kingdom the figures are now similar. Death rates for British women are among the highest in the world—in Glasgow they are the highest (5).

Hypertension is a major risk factor for premature death and disability from stroke and heart failure, and it is the most frequent cause of end-stage renal failure. Hypertension is common in women, especially as they grow older, but since epidemiological studies have shown that women tolerate high blood pressure better, live longer, and have fewer complications than men with

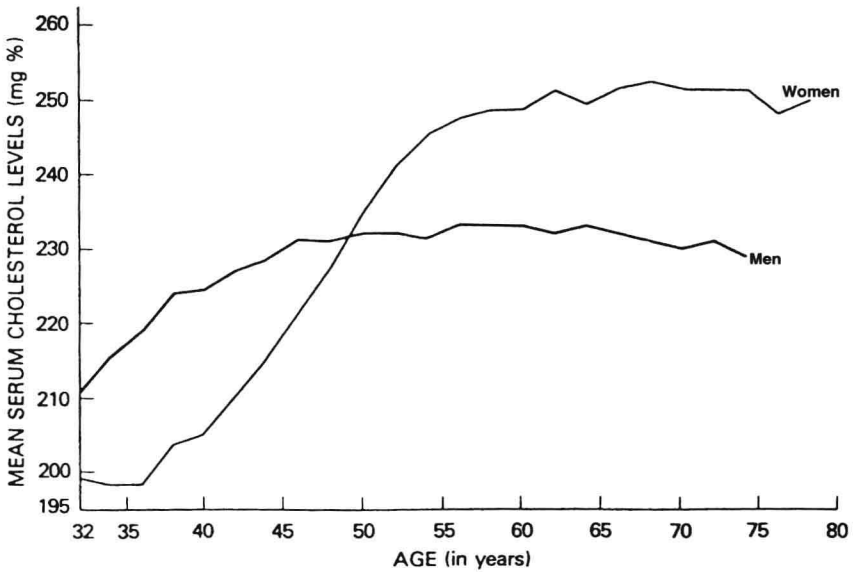
similar blood pressure levels, raised blood pressure in women has far too long been regarded as relatively benign.

A report published in London by the National Forum for Coronary Heart Disease Prevention has called for a national education campaign in the United Kingdom to increase awareness of the risks of heart disease in women (6).

Three large nationwide surveys carried out in the United States between 1960 and 1980 showed that up to 22% of the total population had a blood pressure equal to or greater than 160/95 mm Hg (9). The prevalence increased progressively with age and was higher in blacks than in whites and in men than in women except in older women. Younger black women have a higher prevalence of hypertension than white women, catching up with black men by the menopause, and have a higher cardiovascular mortality in their younger years than white women.

It is now well recognized that left ventricular hypertrophy is not a benign adaptive response to hypertension but a major risk factor for sudden death and heart failure. A complex interplay of many genetic factors (most still to be worked out) contribute not only to the development of hypertension but also to hypertrophy. This occurs not only in the myocardium but also in the smooth muscle of the systemic resistance vessels. Polymorphisms of the angiotensin converting enzyme (ACE) gene may contribute to the risk of myocardial infarction as well as to a fatal outcome from it (10). Clustering of risk factors for cardiovascular disease determines that hypertensives also have a higher prevalence of insulin resistance, non-insulin-dependent diabetes, hyperlipidemia, and abdominal obesity—a metabolic syndrome that is important in women as well as in men (11).

The increase in prevalence of coronary heart disease after the menopause—previously thought to be only an effect of aging—is also attributable to loss of estrogens, with associated adverse changes both in lipid levels and in vascular resistance. Data from the Framingham heart study showed that total cholesterol levels in women are lower than those in men up to the age of about 50, but that, while male cholesterol levels subsequently remain about the same, cholesterol levels in women start to rise from the age of about 40, exceeding those in men by the age of 50



**Figure 2** Average age trends in serum cholesterol levels. (U.S. National Data from the Framingham Study.)

and thereafter (7) (Figure 2). Low-density-lipoprotein levels rise after the menopause, with little change in total high-density lipoprotein (except for a fall in major protective HDL-2 component of cholesterol). Thus, the favorable ratio of high- to low-density lipoprotein present in younger women deteriorates after the menopause, as it does in women who have undergone oophorectomy or premature menopause, both of which are well known to increase the risk of coronary heart disease. Recent studies have shown evidence of estrogen receptors in the smooth muscle of coronary arteries whose expression was most evident in premenopausal subjects without coronary artery disease (12). Hormone replacement therapy changes the lipid profile back to resemble that seen before the menopause, lowers blood pressure, is antithrombotic, and reduces the incidence of myocardial infarction. Administration of estradiol-17- $\beta$  may even be a useful adjunct in the treatment of angina in postmenopausal women



with coronary disease, possibly through a coronary vasodilator and calcium antagonist effect (13).

Loss of estrogens may also contribute to a rise in blood pressure and to the increase in cardiovascular events, stroke, and myocardial infarction after the menopause. In contrast, synthetic estrogens given in nonphysiological dosage for oral contraception increase cardiovascular risk by elevating triglycerides, blood pressure, and plasma insulin and raising the hemostatic profile through an increase in coagulation factors. The synthetic progestogens are androgenic and may compound the risk. The adverse effects of oral contraceptives containing synthetic estrogens and progestogens may be enhanced and the risks increased in women over the age of 35, particularly if they smoke and are overweight. The fact that it takes more than 20 years for the fatality rate from coronary heart disease in women to reach that of men of the same age may be because of the slow natural history of atherogenesis, but oral contraceptive use—often for more than 20 years—may be contributing to the trend for women's cardiovascular mortality figures to be catching up with men's.

In the past, medical interest has focused on the reasons for the differential risks of cardiovascular disease between men and women rather than on attempting to reduce the prevalence of such disease in women. The big primary prevention trials, which excluded women, have resulted in a shortage of information on risk factors in women and on mortality differences between women from different nations and different cultural and ethnic groups (14). We know that a Spanish or Japanese woman of 70 can look forward to the probability of living until almost 90 whereas a Scottish woman of the same age may not anticipate reaching even 80.

### **III. DIAGNOSIS AND TREATMENT OF CORONARY HEART DISEASE**

Important gender differences exist in the clinical presentation of coronary heart disease but account only in part for major differ-