High blood pressure at old age : The Leiden 85 plus study

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Chapter 1

Introduction

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The last decades have shown an increasing interest in treatment of high blood pressure. Copious amounts of data have been published on the mortality and morbidity risks of high blood pressure. [1] Overall these data have resulted in an increasing awareness of the deleterious effects of only modest elevation of blood pressure on morbidity and mortality. Moreover, treatment of high blood pressure resulted in substantial benefits in terms of reduced morbidity and mortality. [2-6] This has resulted in official guidelines about treatment for hypertension that have become stricter with every decade. However, most of the evidence has been generated from middle-aged people. Only a few trials have included people of 80 year and older. [7-9] Looking at the results in detail within that age group the evidence is not robust. Given the increasing lifespan worldwide, physicians are confronted with many elderly patients over eighty. Hence, there is an increasing urge to generate more knowledge in regard to the effects of high blood pressure in the elderly.

Even in ancient times, high blood pressure has been recognized as a potential health threat. In the Yellow Emperor's Classics of Internal Medicine, the following answers were given to the plain questions of the emperor of China, 2600 B.C [10]:

> "The blood current flows continuously in a circle and never stops."
>
> "When the heart pulse beats vigorously and the strokes markedly prolonged, the corresponding illness makes the patient unable to speak."
>
> "If too much salt is used in food, the pulse hardens."

More than 4000 years elapsed before William Harvey in 1628 proved the circulation of the blood; still later the sequence of hypertension, cerebral haemorrhage, and aphasia was recognized. [11] A hundred years later, Stephen Hales managed to measure systolic arterial blood pressure and the effect of haemorrhage on arterial blood pressure. [12] He also determined that the capillary arteries were the site of the chief peripheral resistance. The latter observation remains a basic concept in modern human physiology. In the early nineteenth century it became possible to measure blood pressure with a mercury manometer; it was used until 1896 when Scipione Riva-Rocci of Turin designed the first clinically acceptable sphygmomanometer. [13] In 1905 Korotkoff reported the now standard clinical procedure on the auscultatory method of determining systolic and diastolic blood pressure. [14]

At the beginning of the twentieth century there were three schools of thought with reference to the pathogenesis of hypertension. [15] First, the school of Bright that believed that essential hypertension was due to renal disease. [16] In 1827 Bright associated hardness and fullness of the pulse with albuminuria, edema and hypertrophy of the left ventricle with contracted kidneys. Thus, Bright introduced the concept of renal disease at the base of cardiovascular disease. Second, the school of Gull and Sutton believed that primary generalized arteriocapillary fibrosis caused contracted kidneys and left ventricular hypertrophy causing hypertension. [17] Hence regarding hypertension as the result of widespread vascular disease. Third, the school of Huchard and Allbutt making the statement that hypertension could occur without renal disease. [18,19] Years before, Mahomed had already published his clinical observation showing that high arterial blood pressure could exist without albuminuria. [20] Due to his untimely death, it wasn't until Huchard and Allbutt's finding that it was more widely established that arteriosclerosis and hypertension were independently associated diseases. These concepts were evaluated further in the early thirties of the 20th century mainly after Goldblatt could make dogs hypertensive after constricting their renal arteries. [21] In 1940, this resulted in the discovery of renin and finally in the discovery of the renin-angiotensin system. Nowadays many forms of secondary hypertension have been acknowledged, but the most frequent diagnosis remains essential hypertension. Though the pharmacological treatment has expanded explosively, still no definite pathophysiological process has been recognized as the sole determinant of essential hypertension.

Although high blood pressure was known to have deleterious effects on health, the ultimate prognosis was considered to be different according to the underlying cause of hypertension. For example, in 1953 the arteriosclerotic form of hypertension in the elderly associated with arteriosclerosis of the large vessels, e.g. resulting in a wide pulse pressure, was supposed to have a benign prognosis. [22] Presently this is recognized as a common, but by no means, benign form of hypertension and referred to as isolated systolic hypertension. [23] Up to the late seventies of the 20th century only diastolic blood pressure was considered to be detrimental and was used to classify subjects who suffer from hypertension. [24] Later on, systolic blood pressure became recognized as an even stronger predictor of morbidity and mortality than diastolic blood pressure. Presently, goal levels of systolic blood

pressure should be attained lower than 140 mmHg and for individuals with renal disease and diabetes even lower than 130 mmHg, irrespective of age. [23]

According to the recent guidelines, hypertension has a very high prevalence amongst elderly. [23] In the Framingham study one could discern the average diastolic and systolic blood pressure increased up to the sixth decade resulting in a prevalence of hypertension up to 40% at the age of sixty. [25,26] From that point on the systolic blood pressure continued to rise up to the eighth decade, however the diastolic blood pressure started to decline.

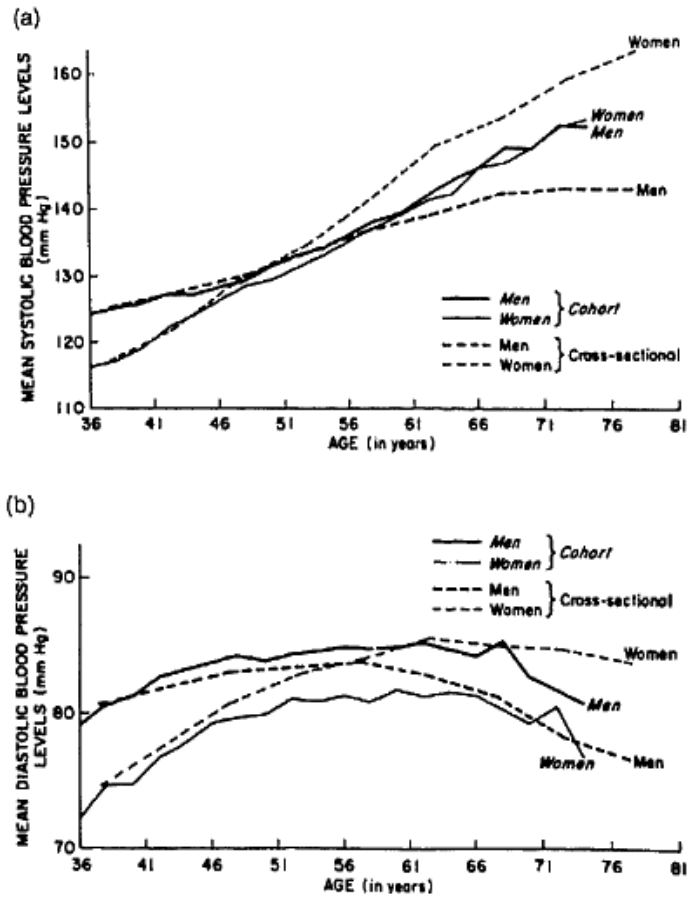

Figure 1. Average age trends in (a) systolic and (b) diastolic blood pressure levels for men and women based on cross-sectional (dotted lines) and longitudinal (cohort, unbroken lines) data on participants in the Framingham Study. [26]

In another report the prevalence of hypertension reached 60% in persons aged 85 and over. [27] Given this high prevalence, many are reluctant in accepting the strict criteria for high blood pressure at middle age for people at old age, as most of the population eventually will fulfil these criteria.

It is argued that a high blood pressure at old age might have a different effect on health compared to same levels of blood pressure in the middle aged. This has been proven for other cardiovascular risk factors also. For example in persons aged 85 years and older total cholesterol levels were no longer related to mortality. [28] Additionally observational data have shown that high blood pressure in elderly persons; above 80 years is no longer a risk factor for mortality. [27, 29, 30] Placebo-controlled clinical trials are not conclusive. Few subjects older than 80 years are included in these studies [2-6, 8]. An open-randomised trial has been published with patients exclusively over eighty years old. [7] In the treated group there was a non-significant increase in mortality that completely nullified the significant reduction in strokes. In contrast, the HYVET study, a placebo controlled double blind trial in persons aged 80 years and older, was prematurely stopped after safety analysis showed excess mortality in the placebo group. [9]

The differences in outcome between the observational and interventional studies at old age versus younger age are difficult to understand. In younger subjects the observational studies are in line with the intervention studies. A high blood pressure is related with greater mortality/morbidity and lowering high blood pressure reduces the mortality/morbidity. It is counterintuitive that high blood pressure at old age suddenly appeared not to be a risk factor; even more, that treatment of high blood pressure at old age may prove harmful. Possibly the elderly, as a group, are not so heterogeneous compared to the middle aged people. Treatment of high blood pressure in more diseased elderly might have more harmful effects compared to treatment in less diseased elderly. In younger age groups who are more vascular diseased, it has been reported that treatment for high blood pressure resulting in low diastolic blood pressure might give excess morbidity and mortality as well. [31, 32] In this thesis we have explored the predictive value of blood pressure and the possible underlying mechanism for the above-mentioned contradictory findings. This thesis consists of a general

introduction, a prognosis part, an etiological insight part, a general discussion and a summary.

Prognosis:

Is high blood pressure at older age associated with adverse outcomes, including cardiovascular mortality, renal failure and cognitive decline?

Etiological insights:

What is the association between blood pressure and cardiac function at older age?

We have used data of the Leiden 85-plus Study and the Rotterdam Study. The Leiden 85-plus Study was a prospective population-based study of all 85 years old inhabitants of Leiden, The Netherlands.[33] Between September 1997 and September 1999 all 705 members of the 1912 to 1914-birth cohort in the city of Leiden were asked to participate in this study in the month after their 85th birthday. There were no selection criteria related to health or demographic characteristics. At baseline, 85 year old participants were visited at their place of residence. During these visits blood pressure was measured twice, an electrocardiogram recorded, a face-to-face interview taken and performance tests were conducted. The participants were annually visited up to age 90 years old. At this age, a sample was invited to the study-centre for an echocardiographic examination. The collected data provided unique opportunities to examine population wise the effects of blood pressure at old age.

The Rotterdam Study is a large, prospective, population-based cohort study conducted in all inhabitants aged 55 and older of Ommoord, a district of Rotterdam, The Netherlands. [34] Of 10,275 eligible subjects, 7,983 (77.7%) participated in the baseline examinations between 1990 and 1993 (mean age 71.2±25.2, range 55–106). All participants were interviewed at home and visited the research centre for further examinations. At the fourth survey (2002–2004), cognitive function was extensively assessed using a dedicated neuropsychological test battery.

In the first part three studies on prognosis of blood pressure are presented. Chapter two presents the association between blood pressure at age 85 years and mortality in the following 5 years. Chapter three presents the association between

blood pressure and creatinine clearance at the age of 85 years up to the age of 90 years. Chapter four describes the association between blood pressure and cognitive function over time. In the second part, three etiological oriented studies are presented. Chapter five describes the prevalence of cardiac valve dysfunction in participants aged 90 years. Chapter six describes the association between blood pressure and cardiac function at the age of 90 years. Chapter seven studies the possible connection between the autonomous nervous system and mortality in subjects 85 years and older. The eighth chapter contains a general discussion of the preceding studies chapters and their possible implications for care of older people with high blood pressure. The ninth chapter reveals the summary in English and Dutch.

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