Adel E. Berbari
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Special Issues in Hypertension

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Preface

Hypertension, i.e. the single major cause of cardiovascular morbidity and mortality worldwide, has been addressed by a large number of books and monographs which have dealt with this topic in all its multifold epidemiological, diagnostic and therapeutic aspects. The aim of this book, however, is not to add another systematic review to those already available. It is rather to provide a cutting edge on key basic and clinical issues on high blood pressure and its related cardiovascular disorders, which are of greater current interest and sometimes controversial interpretation, either because of conflicting data or because hypotheses, rather than data, are available.

Some of the topics included in the book are well known to students of hypertension, also because they have a prominent place in the scientific programme of all major meetings: the risk involved in high normal blood pressure and the evidence in favour or against extending treatment; to this "prehypertension" condition; whether white coat hypertension is clinically innocent or it carries a higher than normal risk that deserves a close follow-up and treatment; how to identify, within the normotensive population, those with ambulatory or home BP elevations who should be treated; how often hypertensive patients should be assessed for their asymptomatic organ damage, and whether the treatment-induced changes in the damage allow physicians to better appreciate the achieved cardiovascular protection; how to score new effects of antihypertensive treatment that can differ between drug classes such as short-term (within 24 h) and visit-to-visit blood pressure variability; which is our knowledge of the epidemiology and the treatment-dependent benefits of conditions frequently seen in hypertension, such as obstructive sleep apnea, cognitive impairment and dementia, hypertension of the very elderly, and hypertension associated with diabetes or dyslipidemia; how can we deal with the challenge of reducing the high residual risk exhibited by even apparently well treated hypertensive patients and whether this can be obtained by lower blood pressure targets or earlier initiation of treatment.

The above few examples give the reader an idea of the range and scope of the topics included in this book, which in addition deals with problems perhaps less controversial but nevertheless of practical importance, such as hypertension in post menopausal women, the difficult coexistence of antihypertensive treatment with drugs to be given for inflammatory disorders and pain, the sexual dysfunction

accompanying treatment (and leading to treatment discontinuation) and, a topic virtually unaddressed before, the effect of Ramadan fasting on blood pressure control.

We hope this will increase general and specific knowledge of the pathophysiology and clinical aspects of hypertension, and also stimulate not only curiosity but also a critical attitude on issues on which much future research and confrontation of ideas is needed.

We express our deep gratitude and warm appreciation to the experts who kindly contributed to the various chapters of this book.

Beirut and Milan, December 2012

Adel E. Berbari
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Part I

1 Prehypertension: Definitions, Clinical Significance and Therapeutic Approaches—To Treat or not to Treat?

Stevo Julius and Carlos A. Feldstein

1.1 Introduction

In 1939, Robinson and Brucer examined longitudinal data from 11,383 life insurance records [1] and reported that in the group with an initial blood pressure (BP) below 120/80 mmHg, BP did not increase with aging. However, BP did increase with age and mortality rates were higher in the *prehypertension* (120–139/80–89 mmHg) and *hypertension* (140/90 mmHg or higher) groups. The data in this seminal paper were undisputable, but the term *prehypertension* did not take root.

About 60 years ago, the first appearance of effective antihypertensive agents generated a renewed interest in BP classification. All first-generation antihypertensive drugs caused serious side effects and it was important to select for treatment patients with reproducible, *sustained*, hypertension. In contrast, patients with occasionally elevated BP values were classified as having *labile* hypertension. This proved to be a semantic mishap, as it implied that patients with labile hypertension have excessive BP variability. In a review of papers published prior to 1971 [2], we found no solid evidence for increased BP variability and reactivity in labile hypertension and proposed to replace *labile* by the term *borderline* hypertension.

In the USA, the term *high-normal blood pressure* (HNBP) first appeared at the fifth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 5). In this and in the sixth [3] JNC report (JNC 6), the BP range for HNBP was set at a value of 130–139/85–89 mmHg. The World Health Organization (WHO), the International Society of Hypertension [4], and the

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European Society of Hypertension (ESH) guidelines [5] also use the term HNBP and define it as in JNC 6. Obviously, world opinion leaders preferred not to use the word *hypertension* for people with HNBP. Indeed, the semantic difference between *high-normal* blood pressure and *borderline* hypertension is huge; the former is a variant of normalcy, whereas the latter refers to a subform of the disease of hypertension. Particularly worrisome was the likelihood that the term *hypertension* may decrease an individual's chances to obtain health insurance or to secure employment.

Against this background, it came as quite a surprise that the 2003 JNC 7 report [6] reintroduced the term *prehypertension* for people with marginal BP elevation and widened the prehypertension range to 120–139/80–89 mmHg. This range is so wide that it becomes meaningless. In 347,978 middle-aged men screened for the Multiple Risk Factor Intervention Trial (MRFIT) [7], only 18.2 % had normal BP. The rest had either prehypertension (46.7 %), stage 1 hypertension (25.9 %), or other stages of hypertension (9.2 %). Using the new prehypertension definition, physicians would be obliged to manage the BP in 80 % of all patients. Worldwide, practitioners are urged to be cost-effective and see more patients. Under such circumstances, clinicians are likely to focus on patients with *serious* hypertension and neglect the sea of people with prehypertension. Based on the National Health and Nutrition Examination Survey (NHANES) of a representative sample of the USA population, we calculated [8] that approximately 83 million US people have prehypertension as defined by the JNC 7. If the selection is narrowed down to a HNBP range of 130–139/80–89 mmHg, the number of people with a *hypertension problem* decreases to 31 million. However, as it is the case with other *pre* conditions (precancer, prediabetes), the term *prehypertension* is appealing and is often used. Consequently, we proposed that the group within the HNBP range be alternatively named as *stage 2 prehypertension* and argued that the BP in this group should be diligently managed.

Since nomenclature changes frequently, this chapter focuses on studies of HNBP as defined by the JNC 6, the ESH, and the WHO guidelines and uses the term *prehypertension* for studies that investigated marginal BP elevations but did not abide by the HNBP definition.

1.2 The Public Health Impact of High-Normal Blood Pressure

In a number of longitudinal studies, the group with HNBP [8] was 2–3 times more likely to develop hypertension than normotensive individuals. In the placebo group of the Trial of Preventing Hypertension (TROPHY) [9], 52 % of subjects with HNBP developed hypertension over a period of 4 years. Whereas the frequent transition of prehypertension to stage 1 hypertension increases the cardiovascular (CV) risk, there is evidence that HNBP per se is also deleterious. In six longitudinal studies [8], data were adjusted for progression to hypertension and compared to the normotensive population. The hazard ratio of a CV event in 10 years in the HNBP group ranged from 1.42 to 2.33.

To further assess the public health impact of HNBP in this review, we used the cumulative incidence, spanning 15 years, of CV events in 347,978 men aged 35–57 years screened for the MRFIT trial [7]. The prevalence of HNBP in this population was 22 % and the cumulative incidence of deaths from coronary heart disease (CHD) and strokes was 2.9 %. We adjusted [8] the prevalence of HNBP and the incidence of events for age and gender to extrapolate the 15-year cumulative incidence of events to the total adult (35 years or older) USA population. According to our rather conservative projection, at least 2,000,000 persons with HNBP may have died from CHD or stroke over a period of 15 years.

The increasing use of out-of-office BP measurements introduced a new element in the field of prehypertension. These measurements invariably detect subgroups with *white coat* (high in office/normal at home) and *masked* (high at home/normal in the clinic) hypertension. In the population-based Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study [10], 14.5 % had masked hypertension with ambulatory blood pressure (ABP) and 15.5 % by home BP monitoring. In a further analysis of that study [11], after 12 years of follow-up, the total and CV deaths increased in a stepwise fashion from normotension to white coat, masked, and sustained hypertension. This pattern was detected both with ABP and home BP measurements. In a recent meta-analysis of eight studies with a follow-up ranging from 3.2 to 12.8 years [12], the odds ratio of CV events in the masked hypertension compared to normotensive group was 2.09.

The widely used ABP and home BP monitoring are bound to detect more cases of white coat and masked hypertension. Since in such patients the risk of total and CV mortality is increased, it is likely that physicians will manage masked hypertension in the same manner as they manage HNBP. This, in turn, will further expand the number of patients with prehypertension.

1.3 Association of Prehypertension with Other Cardiovascular Risk Factors

Most guidelines take note of the association of prehypertension with other CV risk factors and, based on the presence of these predictors, recommend different levels of therapeutic vigilance. In the study of a representative section of the middle-aged inhabitants of Tecumseh, Michigan [13], 822 subjects were normotensive and 124 were prehypertensive. The prehypertension group had significantly higher than normal percentage of obesity, thicker skinfolds, and increased waist-to-hip ratio. Furthermore, cholesterol, glucose, insulin, and triglyceride levels were significantly higher in the prehypertension group whereas high-density lipoprotein (HDL) levels were significantly lower. The resting heart rate, a recognized coronary risk factor [14], and hematocrit [15], another known CV risk factor, were increased in the Tecumseh prehypertension group [16]. When we grouped the total study population in tertiles of hematocrit levels, the clinic, home, and work BP values increased significantly in a stepwise fashion from low to medium to high hematocrit brackets. Furthermore the

cholesterol, glucose, insulin, and triglycerides levels and the percentage of overweight persons were significantly elevated in the highest hematocrit group.

The close association of HNBP with CV risk factors was again demonstrated in patients with HNBP enrolled in the TROPHY trial [9]. When all anthropometric (overweight or obese), hemodynamic (BP, tachycardia), metabolic (dyslipidemia), and rheological (hematocrit) risk factors were considered, 96 % of TROPHY participants had at least one, 81 % had two or more, and 13 % had five or more additional risk factors [17]. Consequently assessment and management of CV risk factors must become an integral part of the clinical approach to prehypertension.

1.4 Natural History of Marginal Blood Pressure Elevation

In clinical practice, HNBP is usually detected in the third or fourth decade of a patient's life. However, adults with prehypertension have higher than normal BP already as children and young adults. This *tracking phenomenon* has been verified in a systematic meta-regression analysis of 50 cohort studies [18]. In the Tecumseh study, we used records of earlier medical exams [13] to reconstruct previous BP trends in subjects who, at 32 years of age, were normotensive or prehypertensive. Adult subjects with prehypertension had significantly elevated BP levels already at 6 and 21 years of age. There was little or no BP increase between the ages of 6 and 21. However, this pattern dramatically changed from 21 to 31 years of age. In the third decade of life, the average BP increased in both cohorts but the increase in the prehypertension group was nearly three times as steep as in normotensive subjects (Fig. 1.1).

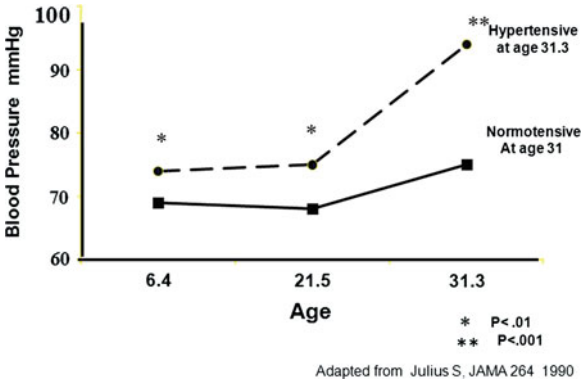

Fig. 1.1 Diastolic blood pressure (BP) trends in the Tecumseh, Michigan study. Participants were classified as normotensive ($N = 563$) of prehypertension ($N = 78$) at the average age of 32 years. BP levels at a younger age were retrieved from previous Tecumseh health exams

The nonlinearity of the BP increase was also demonstrated in 26,980 teenagers recruited to the Israeli army and followed over an average period of 14 years [19]. In men the relative risk of developing hypertension was 51 % and in women 48 % higher in the baseline HNBP group than in the normotensive groups. At the beginning of the follow-up, the difference in cumulative incidence of new onset hypertension was only slightly higher in the baseline HNBP. However, as time