Essential hypertension

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Essential hypertension can be defined as a rise in blood pressure of unknown cause that increases risk for cerebral, cardiac, and renal events. In industrialised countries, the risk of becoming hypertensive (blood pressure >140/90 mm Hg) during a lifetime exceeds 90%. Essential hypertension usually clusters with other cardiovascular risk factors such as ageing, being overweight, insulin resistance, diabetes, and hyperlipidaemia. Subtle target-organ damage such as left-ventricular hypertrophy, microalbuminuria, and cognitive dysfunction takes place early in the course of hypertensive cardiovascular disease, although catastrophic events such as stroke, heart attack, renal failure, and dementia usually happen after long periods of uncontrolled hypertension only. All antihypertensive drugs lower blood pressure (by definition) and this decline is the best determinant of cardiovascular risk reduction. However, differences between drugs exist with respect to reduction of target-organ disease and prevention of major cardiovascular events. Most hypertensive patients need two or more drugs for blood-pressure control and concomitant statin treatment for risk factor reduction. Despite the availability of effective and safe antihypertensive drugs, hypertension and its concomitant risk factors remain uncontrolled in most patients.

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Introduction

> "The treatment of the hypertension itself is a difficult and almost hopeless task in the present state of our knowledge and in fact, for ought we know the hypertension may be an important compensatory mechanism which should not be tampered with even if it were certain that we could control it."[1]

With these words in 1931, Paul Dudley White described what is nowadays regarded as a common misconception about the clinical significance of essential hypertension: namely, that the increase in blood pressure was essential (or compensatory) to guarantee adequate perfusion of the target organs. Regrettably, this misconception lingered in published work (and in many doctors' minds) until a few years ago, despite the results of the Veterans' Administration studies[2,3] attesting to the benefits of antihypertensive treatment. Since then, findings of many trials have shown unequivocally that lowering blood pressure reduces cardiovascular morbidity and mortality for hypertension of all degrees of severity and even in high-risk normotensive individuals.

As of July 1, 2007, a Medline search with the term "essential hypertension" retrieved a total of 22 376 articles, of which 3430 were reviews. Rather than attempting to review this work, we will focus here on a few key and emerging issues that we think are of interest to clinicians dealing with hypertensive cardiovascular disease.

Search strategy and selection criteria

We scanned the leading journals that publish basic and clinical research in the area of hypertensive cardiovascular disease and searched Medline. The main terms we used were: "essential hypertension", "cardiovascular disease", "lifestyle modification", and "antihypertensive drug therapy". Additionally, the thoughts and input of our collaborators and colleagues and the reviewers of this Seminar were also considered.

Ambulatory versus casual blood-pressure measurements

Diagnosis and treatment of hypertension hinges on correct measurement of blood pressure (panel 1). However, this seemingly simple procedure poses many pitfalls and—apart from the introduction of 24-h ambulatory blood-pressure measurement and automated self measurement—has progressed little beyond the procedure that Korotkoff introduced 100 years ago.[4] As Kaplan noted: "The measurement of [blood pressure] is likely the clinical procedure of greatest importance that is performed in the sloppiest manner."[5]

Diagnosis of hypertension should be based ideally on several blood-pressure measurements taken on separate days, as stated in guidelines.[6] For this purpose, the mercury sphygmomanometer has an unsurpassed accuracy,[7] but it has been substituted by aneroid and auscultatory or oscillometric semiautomatic devices. Aneroid manometers must be serviced and recalibrated periodically. The reliability of wrist blood-pressure measurements with oscillatory devices is limited.[8,9] Home blood-pressure measurement permits identification of so-called white-coat hypertension (see next section) correlates better than blood-pressure values measured in the doctor's office with target-organ damage,[10] and could enhance patients' adherence to drugs.

White-coat hypertension and masked hypertension

Because the correlation between 24-h ambulatory blood-pressure measurements and those taken in the doctor's office is moderate, the diagnosis of hypertension can be missed by office blood-pressure measurements in some patients who are truly hypertensive (masked hypertension). Conversely, blood pressure can be raised

***Panel 1:* Points to consider for blood-pressure measurement in the doctor's office**

- The patient should sit for several minutes in a quiet room before blood-pressure measurements are taken. Pain, stress, full urinary bladder, a recent meal, and talking or active listening during measurement affect blood pressure
- Take at least two measurements spaced by 1–2 min and additional measurements if the first two are quite different
- Using a bladder that is too narrow yields false high readings. Instead of the standard bladder (12–13 cm long, 35 cm wide) use an appropriate bladder in patients with increased midarm circumference
- Use phase I (first tapping sound) and V (disappearance) Korotkoff sounds to identify systolic and diastolic blood-pressure values, respectively
- Do not deflate the cuff too rapidly, otherwise individual Korotkoff sounds are missed and too low a value is measured; start with a deflation rate of 2 mm/s
- Measure the heart rate by palpation and watch out for arrhythmia, which mandates repeated blood-pressure measurements
- At the first visit, measure blood pressure in both arms and take the higher value as the reference; measure blood pressure at 1 and 5 min after standing upright if the patient has a disorder that frequently causes orthostatic hypotension

in the doctor's office but not on ambulatory blood-pressure monitoring or at home—a situation known as white-coat hypertension. Risk of patients having white-coat hypertension was noted to be somewhat higher than in normotensive individuals but distinctly lower than in people with sustained hypertension.[11–15] By contrast, masked hypertension is a less well known (but not necessarily a less frequent) entity with a more serious prognosis than white-coat hypertension. It was noted in as many as a third of the hypertensive population.[16,17] In participants of the PAMELA study,[18] those with masked hypertension had a higher prevalence of echocardiographic left-ventricular hypertrophy than did normotensive individuals. Inappropriate target-organ disease (for office blood-pressure levels) should trigger suspicion of masked hypertension and motivate doctors to undertake 24-h ambulatory blood-pressure monitoring in a patient. Upper limits for optimum, normal, and hypertensive blood-pressure levels have been redefined (table).[19] Importantly, rises in blood pressure in the doctor's office, at home, and while ambulatory seem to have an additive effect on cardiovascular risk.[20]

	24 h	Daytime	Night-time
Hypertensive above	130/80	140/85	120/70
Normal below	125/75	130/85	110/70
Optimum below	115/75	120/80	100/65

Data are mm Hg. Reprinted from reference 19, with permission.

***Table:* Diagnostic thresholds for ambulatory blood-pressure measurements**

Compared with white-coat hypertension, masked hypertension needs to be looked for and there are few clinical hints to its presence. Because most patients take their medication for hypertension in the morning, blood-pressure values in the doctor's office usually are normal but can be raised at the end of the dosing interval (ie, during early morning hours). Many patients are still prescribed once-a-day atenolol—a drug that does not reduce heart attack or strokes. Atenolol's inefficiency might be related to inappropriate duration of action, its pseudo-antihypertensive effect, or both (see next section). For many clinicians, masked hypertension has unfortunately become a blind spot in antihypertensive treatment.[21]

With respect to the therapeutic approach, we should remember that white-coat hypertension can only be over-treated; therefore, a conservative approach to treatment is justified. Conversely, masked hypertension has a more serious prognosis than white-coat hypertension and can only be under-treated; it deserves, therefore, an aggressive diagnostic and therapeutic approach.

Aortic versus brachial blood pressure

Since the pulse wave is amplified in transit from the heart to the brachial artery, central aortic systolic pressure is usually lower than brachial pressure.[22] The magnitude of amplification is greatest in people with healthy compliant arteries and diminishes with age. Systolic pressure within the aorta is a composite of two items: 1) the outgoing pressure wave, generated by ventricular contraction; and 2) pressure wave reflection from periphery. The reflected wave should ideally return towards the heart during diastole to augment diastolic filling. If it returns earlier during the cardiac cycle it amplifies the outgoing pressure wave and leads to an increase in central aortic pressure. The timing and magnitude of pressure-wave reflection is affected by several factors, including: the stiffness of the aorta; the distance of reflection sites from the heart; and heart rate.

As a result, brachial pressure can be an imperfect surrogate for central aortic pressure, particularly when drug treatments differentially affect central aortic haemodynamics, wave reflection, heart rate, or a combination.[23] Findings of the CAFE study, in which pulse-wave analysis was used to derive central aortic pressures, showed that β blocker-based treatment was significantly less effective than a calcium-channel blocker-based regimen at lowering aortic systolic pressure and pulse pressure, despite identical brachial

pressures in both treatment arms.[24] This pseudo-antihypertensive effect could account for why β blocker-based strategies are less effective than alternative treatments at regressing end-organ damage and in prevention of stroke.[24–27] Whether central aortic pressure is a better predictor of outcome than conventional brachial blood pressure remains to be established.

Hypertension as a gateway to cardiovascular risk management

Although measurement of blood pressure is a simple procedure to identify a risk phenotype of cardiovascular disease, treatment of raised blood pressure alone is insufficient to optimally reduce the associated cardiovascular disease risk, and formal cardiovascular disease risk estimation has been recommended. Risk calculations based on the Framingham cohort used in the USA and the UK[28,29] can overestimate risk in European populations by about 7% and by a larger proportion in Asia. The European Society of Cardiology has recommended use of the SCORE risk calculator.[30] Pragmatism in risk assessment is important, and available risk calculators are based on conventional risk markers that can be recorded in a basic clinical setting—ie, systolic blood pressure, age, sex, cholesterol concentration, presence of diabetes, smoking history, and presence or absence of structural damage. Findings of the INTERHEART study suggested that more than 90% of population-attributable risk for acute myocardial infarction can be accounted for by these risk factors.[31] Use of more elaborate risk assessment by a series of biomarkers adds little to the aforementioned conventional methods of cardiovascular disease risk estimation.[32]

One of the most relevant criticisms of cardiovascular disease risk estimation is that it is based on limited time projections—eg, 10-year absolute risk estimations—that strongly favour treatment of the elderly population versus young people because age is a powerful determinant of short-term risk. Additional factors contributing to and amplifying risk are diabetes[30,33] and renal malfunction, as indicated by a low estimated glomerular filtration rate[34,35] and microalbuminuria or proteinuria.[36] For both microalbuminuria and proteinuria, the conventional cutoff points are arbitrary, particularly for albuminuria.[37] Equally random is that a serum creatinine concentration of 107–133 μmol/L is a sign of target-organ damage and an amount greater than 133 μmol/L indicates renal disease. Assessment of renal malfunction was enhanced by estimation of the glomerular filtration rate, taking into account age, sex, and body-mass index.[38] Cardiac abnormalities by electrocardiography[39] or echocardiography[40] are correlated to outcome. Figure 1 outlines progression of the natural history of hypertensive cardiovascular disease. In a study of the natural history of (untreated) hypertension in control groups, wide variability of the absolute risk of stroke and heart attack was noted (figure 2), but the relation between number of events prevented and absolute risk was near-linear for both coronary heart disease and stroke.[41]

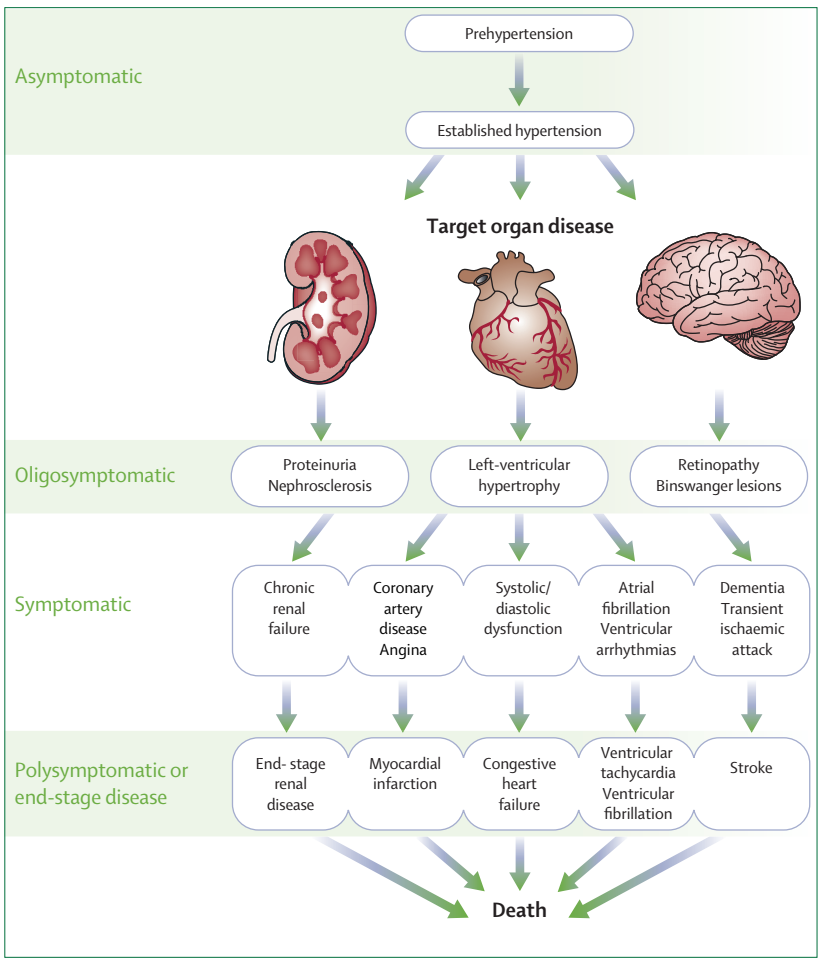

Figure 1: **Range of hypertensive cardiovascular disease from prehypertension to target-organ damage and end-stage disease**

Cardiovascular disease risk thresholds for intervention currently define high-risk patients as having a 10-year Framingham-derived cardiovascular disease risk of 20% or more. The typical hypertensive man aged 55 years or older will have this level of risk. This threshold takes account of current evidence and economics, and lower thresholds for intervention would also be cost effective with existing criteria for cost-benefit analyses.[32] Of note, formal cardiovascular disease risk estimation is not necessary for patients with hypertension and cardiovascular disease, diabetes, or overt end-organ damage. These patients are at sufficient risk of cardiovascular disease to benefit from multifactorial risk-factor intervention.

The prothrombotic paradox

Hypertension by definition is a haemodynamic disorder and, as such, exposes the arterial tree to increased pulsatile stress. Paradoxically, however, most major complications of longstanding hypertension (ie, heart

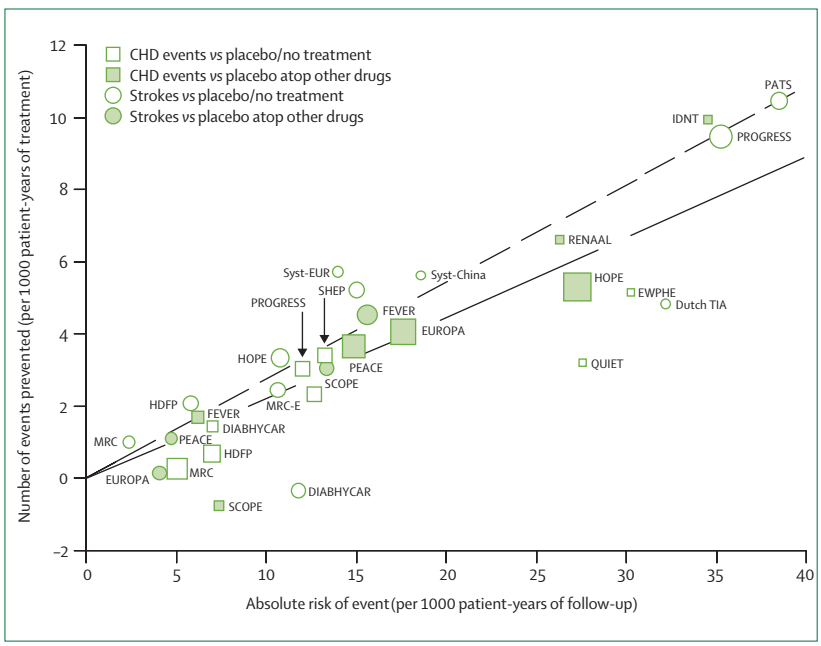

Figure 2: **Correlation between absolute risk of coronary heart disease or stroke event in selected clinical trials and number of events prevented per 1000 patient-years of treatment**

Relation between absolute risk and event prevented is steeper for stroke than for coronary heart disease, possibly because stroke is more dependent on blood pressure. Unweighted correlation coefficients were: r=0·89, p<0·0001 for stroke (dashed line), and r=0·87, p<0·0001 for coronary heart disease (solid line). Only trials in which 100 or more events were reported are included. Symbols are drawn encompassing an area proportional to the number of events in every trial. DIABHYCAR=DIABetes and HYpertension Cardiovascular events with Ramipril. Dutch TIA=Dutch Transient Ischemic Attack trial. EUROPA=EUropean Reduction Of cardiac events with Perindopril in stable coronary Artery disease. EWPHE=European Working Party on Hypertension in the Elderly. FEVER=Felodipine EVEnts Reduction trial. HDFP=Hypertension Detection and Follow-up Program. HOPE=Heart Outcomes Prevention Evaluation. IDNT=Irbesartan Diabetes Nephropathy Trial. MRC=Medical Research Council Trial (in mild hypertension). MRC-E=Medical Research Council Trial in Older Patients. PATS=Post-stroke Antihypertensive Treatment Study. PEACE=Prevention of Events with Angiotensin-Converting Enzyme inhibition. PROGRESS=Perindopril pROtection aGainst REcurrent Stroke Study. QUIET=QUinapril Ischemic Events Trial. RENAAL=Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan trial. SCOPE=Study on COgnition and Prognosis in the Elderly. SHEP=Systolic Hypertension in the Elderly Program. Syst-China=Systolic hypertension in China trial. Syst-EUR=Systolic hypertension in Europe trial.[41]

attack and strokes) are thrombotic rather than haemorrhagic, referred to as the so-called thrombotic paradox of hypertension. Virchow suggested three components facilitating thrombus formation: 1) damage to the vessel wall; 2) hypercoagulability; and 3) abnormal blood flow. For thromboembolic events to take place, all the components of Virchow's triad must be fulfilled.[42] In hypertensive individuals, abnormalities in blood flow have been well recognised. Hypertension has also been associated with endothelial damage or dysfunction[43] and a hypercoagulable state.[42] This prothrombotic state could be the result of chronic low-grade inflammation. Chronic shear stress can lead to remodelling of the vascular endothelium, turning it from an anticoagulant into a procoagulant surface.

The mechanisms leading to endothelial dysfunction are multifactorial and include decreased activity of vasodilator agents[44–46] and increased activity (or sensitivity) to vasoconstrictor agents.[45–47] Overall, fibrinolytic activity is ascertained by the balance between tissue plasminogen activator and plasminogen activator inhibitor type 1 (SERPINE1). With respect to endothelial function, enhanced activity of the renin-angiotensin system and kallikrein-kinin system has opposite effects, resulting in vasoconstriction and vasodilation, respectively.[48] By contrast, with respect to coagulation, increased activity of the renin-angiotensin system and the kallikrein-kinin system has a negative effect, resulting in a hypercoagulable state.[48] Thus, hypertension not only confers a hypercoagulable state (vulnerable blood) but also gives rise to left-ventricular hypertrophy, ventricular and atrial arrhythmias, and impaired coronary reserves (vulnerable myocardium), thereby fulfilling all criteria for a vulnerable patient.[49]

In enhancing the coagulation-fibrinolysis balance, antihypertensive treatment can decrease the frequency of thrombotic events independent of blood pressure. Whether differences in antihypertensive drug classes[48,50,51] will translate into altered outcomes remains to be established.

Prehypertension and lifestyle interventions

The issue of prehypertension has stirred tempers to an extent that seems more suitable to medieval theologians than modern scientists.[52] Epidemiological evidence suggests a continuous relation between risk of cardiovascular disease and usual blood-pressure values of at least 115/75 mm Hg.[53] In the Framingham cohort, a stepwise increase in cardiovascular events was reported in individuals with high baseline blood pressure within the normotensive range.[54] Thus, in people without hypertension (blood pressure <140/90 mm Hg), blood-pressure levels parallel cardiovascular disease risk in the same way as hypertension.[55] Therefore, normotensive individuals with a host of risk factors could show higher overall risk than mildly hypertensive patients without risk factors. Furthermore, the absolute benefits of antihypertensive treatment for such normotensive people can be greater than for uncomplicated hypertensive patients.

Since individuals without hypertension still outnumber those with the disorder, the blood-pressure-related disease burden remains larger in the normotensive than the hypertensive population.[55] Irrespective of the level of hypertension, lowering of blood pressure is always preferable by non-pharmacological means, such as a low salt diet, weight loss, exercise, and alcohol restriction. Indeed, a small but significant fall in blood pressure was noted in meta-analyses of these interventions (figure 3).[56–59] However, patients' adherence to lifestyle interventions is notoriously poor; therefore, antihypertensive treatment might have to be considered even in some normotensive individuals. Since the benefits in this population are fairly small, such an approach needs documents of long-term safety. Thus, drugs with metabolic side-effects, such as β blockers and diuretics, are not suitable to be used in prehypertensive patients. Also, angiotensin-converting-enzyme inhibitors should probably be avoided

because of risk for angio-oedema. The only two drug classes that presently fulfil safety requirements are angiotensin-receptor blockers and some calcium-channel blockers. Indeed, in two studies (TROPHY and PHARAO), treatment of prehypertensive patients with renin-angiotensin system blockers delayed the onset of stage I hypertension and prolonged the hypertension-free period.[60,61] We certainly are not advocating treatment of all prehypertensive patients, which could be up to 45 million in the USA alone. However, in those with high-normal blood pressure and diabetes, or a history of cerebrovascular or coronary disease, evidence suggests that antihypertensive drugs are beneficial. Clearly, the time has come to abandon the hypertension/normotension dichotomy and to focus on global risk reduction, either by antihypertensive drugs, lipid-lowering treatment, or their combination.

New-onset diabetes with antihypertensive treatment

Ever since the report of Colin Dollery's team more than 20 years ago,[62,63] diuretic treatment—particularly when combined with a β blocker—has been known to increase risk for new-onset diabetes. From 1980 to 2004, the prevalence of diabetes more than doubled in the USA, and almost 10% of people older than age 20 years have this disease.[64] Patients with hypertension are known to be at higher risk of developing new-onset diabetes than normotensive individuals. In the ALLHAT study, about 10% of all patients developed the disorder throughout the duration of the study.[65] However, the relative risk was 18% and 40% higher in the chlorthalidone arm than in the amlodipine and lisinopril arms, respectively.[66] In a network meta-analysis, Elliott and Meyer reported the odds ratio of new-onset diabetes to be 0·62 with angiotensin-receptor blockers, 0·67 with angiotensin-converting-enzyme inhibitors, 0·75 with placebo, 0·79 with calcium-channel blockers, and 0·9 with β blockers; diuretics were the reference.[67]

Admittedly, risk for new-onset diabetes associated with β blockers, diuretics, or both[68] seems to be small. Over a 4-year period, in ALLHAT, the absolute risk was 3·5% higher with chlorthalidone than with lisinopril,[65] and in ASCOT, risk was 2·5% higher in the atenolol arm than in the amlodipine arm.[69] However, since in the USA alone about 20 million patients are on thiazide diuretics and an almost equal number are on β blockers, this risk translates into 250 000 cases of new-onset diabetes associated with these so-called traditional antihypertensive drugs every year. This figure would indicate that about 20–25% of the 1 million cases of new-onset diabetes arising yearly in the USA could possibly be related to antihypertensive treatment—not an insignificant number.

An anonymous statement was published in the *BMJ* in 2003: "It can't get clearer. Diuretics—the least expensive and most effective agents—should be the first line treatment for almost everyone with hypertension, including patients with diabetes."[70] We beg to differ and think that in uncomplicated hypertension, diuretics and β blockers should no longer be considered for first-line treatment. The trade-off of lowering blood pressure at the expense of increasing risk for diabetes by up to 10% yearly is not acceptable. Not unexpectedly, Thomas Sydenham's dictum of primum non nocere also applies to first-line antihypertensive treatment.

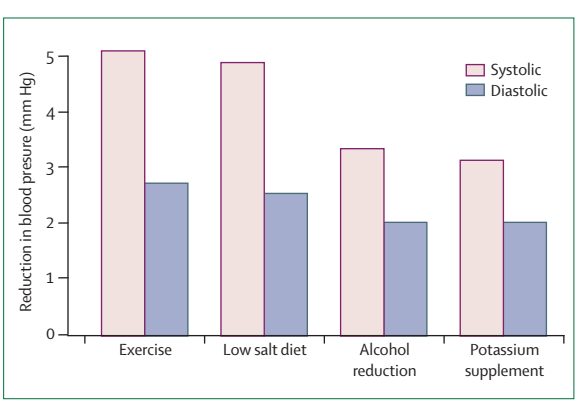

Figure 3: **Estimated decrease in blood pressure mediated by non-pharmacological intervention in hypertension[56–59]**

First-line antihypertensive treatment and concomitant risk factor reduction

The most important question to ask when selecting initial drug treatment is which class of drug will deliver the most effective blood-pressure lowering for this patient? This question is most relevant because blood-pressure lowering is the driver of benefit and initial reductions seem to be a determinant of early cardiovascular disease risk reduction and long-term quality of blood-pressure control.[71,72] The response to different classes of drugs is similar when compared head-to-head in heterogeneous populations. However, individual responses can differ strikingly. Some characteristics can help predict the initial response to drugs that lower blood pressure. Blood-pressure lowering in older patients (eg, those older than age 55 years) or those of black ethnic origin at any age will generally be greatest with thiazide-type diuretics or calcium-channel blockers.[65,71,72] In young people, who generally have a more active renin-angiotensin system than older individuals, blood pressure is lowered effectively with inhibitors of the renin-angiotensin system—eg, angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers.[73,74] Such stratification for selection of drug type has been adopted by some guidelines, emphasising that efficiency of blood-pressure control should drive initial drug selection.[75] For patients whose blood pressure is already 20 mm Hg or more above their goal, guidelines recommend initial treatment with a two-drug combination because monotherapy is likely to be insufficient.[76,77] If findings of an ongoing study[78] confirm safety and efficacy then initial treatment

with a combination of two drugs is likely to become common practice.

High-risk patients with hypertension should not only undergo optimum blood-pressure control (with two drugs) but also receive a statin and low-dose aspirin.[29,30] This strategy would halve deaths from cardiovascular disease in high-risk patients at a cost of less than US$1000 per quality-adjusted life-year gained.[32] Traditional thinking about cardiovascular disease risk factors as individual entities has, unfortunately, impeded this idea of combined risk factor intervention.

The complicated and refractory hypertensive patient

Refractory (or resistant) hypertension is defined as blood pressure that is persistently higher than target—ie, 140/90 mm Hg for most hypertensive patients and 130/80 mm Hg for individuals with diabetes or renal disease—despite prescription of three different antihypertensive drug classes, including a diuretic. Refractory hypertension is seen frequently. Even in most controlled trials the mean achieved blood pressure failed to reach targets.[79] Poor blood-pressure control in primary care,[80] particularly in elderly people,[81] is not surprising but, nevertheless, disquieting because of the high associated cardiovascular risk.[82,83] Two categories of refractory hypertension can be distinguished: 1) true resistance; and 2) apparent resistance.[84]

True resistance

Panel 2 summarises factors that can lead to true resistant hypertension. Most patients in this category can be treated by omitting relevant drugs and altering the antihypertensive drug regimen. In a few individuals, secondary causes of hypertension can be noted.

One major step forward in management of patients with true resistance has been recognition that inappropriate aldosterone concentrations (raised aldosterone/renin ratio) arise in up to 20% of people,[85–87] including hypertensive emergencies.[88] Although patients are frequently normokalaemic,[89] only a few have surgically correctable adenoma.[90] Irrespective of whether or not an adenoma is present, aldosterone antagonists provide relevant additional blood-pressure reduction[85,87,91,92] independent of aldosterone concentrations. Hyperkalaemia is rare,[85] at least as long as renal function is not impaired.

Apparent resistance

A typical cause of faulty blood-pressure measurement is use of a cuff that is too small relative to the circumference of the arm, particularly in obese individuals. The blood-pressure value taken in the doctor's office might also be raised if the patient smoked or had coffee before their appointment. A less frequent occurrence is malfunction of the measuring device used by the patient.

***Panel 2:* True resistant hypertension**

Volume overload

- Excessive dietary sodium intake
- Compensatory response to vasodilatory antihypertensive drugs
- Insufficient diuretic treatment
- Reduced renal function
- Hyperaldosteronism

Contraindicated drugs or exogenous substances

- Non-steroidal anti-inflammatory drugs, COX2 inhibitors
- Sympathicomimetics (nasal drops, appetite suppressants)
- Cocaine
- Oral contraceptives
- Glucocorticoids
- Mineralocorticoids
- Liquorice
- Herbal drugs (ginseng, yohimbin)
- Drugs (eg, erythropoietin, cyclosporin, tacrolimus)
- Different types of drugs can also affect pharmacokinetics and cause rapid inactivation of antihypertensive drugs

Associated condition

- Smoking
- Obesity (visceral obesity)
- Metabolic syndrome or type 2 diabetes
- Excess alcohol intake
- Anxiety-induced hyperventilation or panic attacks
- Pain

A rare cause is so-called pseudohypertension as a result of stiff or calcified brachial arteries, which should be suspected if either measured blood-pressure values are inappropriate for target-organ damage or antihypertensive drugs provoke symptoms of hypotension despite persistent raised blood pressure. Non-specific but helpful is Osler's manoeuvre—ie, a palpable radial artery when the brachial artery is occluded.[93]

Another common cause of apparent refractory hypertension is an inadequate drug regimen—ie, insufficient dosing, selection of inadequate combinations of drugs, and choice of antihypertensive agents with insufficient duration of action. The solution is long-acting well-tolerated drugs or drug combinations, including a diuretic, taken once a day.[94] Arguably the most frequent cause of apparent resistant hypertension is non-adherence to treatment.

Non-adherence to treatment

> "I've also been treating the high cholesterol and then I stopped the medicine because I got my cholesterol down low. And, I had in the past, a little [blood pressure] problem, which I treated and then I got it down..."
>
> *(Former US President Clinton, awaiting coronary bypass surgery, calls into Larry King Live from his hospital bed; posted Friday, Sept 3, 2004, 23:31 h EST).*

Unfortunately, the contention among patients that once a target is achieved (ie, cholesterol and blood pressure are down) medication can be stopped remains too common. Many physicians assume that educated patients do not need to be told why medicine for chronic cardiovascualr diseases such as hyperlipidaemia and hypertension has to be continued for life is not necessarily related to degree of education. The issue of adherence is an anathema for most doctors. However, non-adherence to a drug regimen can account for treatment failures in nearly half of hypertensive patients.[93] WHO has estimated that 50–70% of patients do not take their antihypertensive drugs as prescribed and has identified poor adherence as the most important cause of uncontrolled hypertension.[95] Non-adherence to drug regimens has been called "America's other drug problem".[96] As a rule, the patient who most needs antihypertensive treatment is usually least compliant. Fixed drug combinations are increasingly useful for improvement of compliance because they reduce the pill burden.[97] Of note, advanced therapeutic wisdom is utterly useless if the patient is unable or unwilling to follow the prescription.

J-curve

For more than two decades, published work in the area of hypertension has been haunted by findings of a paradoxical increase in cardiovascular events with low blood pressure (J-curve). In a meta-analysis, Farnett and colleagues recorded a consistent J-shaped relation between cardiac events and diastolic pressure, whereas no J-shape association was seen between stroke and blood pressure.[98] By contrast with other organs, the heart is perfused mostly during diastole and, therefore, is more vulnerable to diastolic pressure reduction. If a J-curve did exist in the physiological blood-pressure range, it should be most evident in patients with compromised coronary perfusion—ie, in those with coronary artery disease. In the INVEST study, in which all 22 000 participants had coronary artery disease and hypertension, risk for the primary outcome of all-cause death and myocardial infarction but not of stroke rose progressively with low diastolic blood-pressure values.[99] Below a diastolic pressure of 70 mm Hg, the odds of the primary outcome doubled, and at pressures less than 60 mm Hg, they quadrupled. Similar relations between diastolic pressure and coronary events were reported in patients with coronary artery disease in the HOT study,[100] the ACTION study,[101] and in an analysis of the Syst-Eur trial.[102] Of note, the nadir of 119/84 mm Hg in the INVEST study was steep for diastolic but very shallow for systolic pressure. These data, although not detracting from aggressive management of systolic pressure, suggest caution with excessive lowering of diastolic pressure in individuals with coronary artery disease. Thus, the clinician might have to face the dilemma that lowering risk for a cerebrovascular event could concomitantly increase risk for a coronary event in a susceptible patient.

Surrogate endpoint versus hard endpoint—beyond blood pressure

By definition, all antihypertensive drugs lower blood pressure. Distinct differences between various antihypertensive drugs have been reported with respect to systemic and regional haemodynamics, fluid volume state, sympathetic nervous system, renin-angiotensin system, electrolytes, metabolic findings such as insulin resistance, lipids, uric acid, and fibrinolytic action, and adverse effects. It would be surprising if some of these differences did not translate into differences in outcome. Indeed, the thiazides for any given fall in blood pressure seem to provide a better reduction in strokes and heart attacks than do β blockers as a class.[25] The relative ineffectiveness of the β blockers has been known ever since the MRC studies were undertaken,[103,104] but the information only surfaced because of the findings of several meta-analyses.[25,104–106] It could be attributable to many factors such as haemodynamic incompatibility, pseudo-antihypertensive effectiveness (failure to lower central aortic pressure), and, in the case of atenolol, insufficient duration of action leaving night-time blood pressure untreated. Despite their ineffectiveness in uncomplicated hypertension, β blockers might remain useful in certain clinical situations (figure 4).

With respect to other antihypertensive drugs, interpretation of the findings of most large prospective trials is hampered by small but consistent differences in blood pressure between various treatment strategies. Meta-analyses have the drawback that they need to adjust for such differences, which again makes interpretation difficult. The drug class reported most consistently to reduce morbidity and mortality in hypertension remains thiazide diuretics; yet, these drugs increase plasma renin activity, angiotensin II concentrations, and uric acid, stimulate the sympathetic

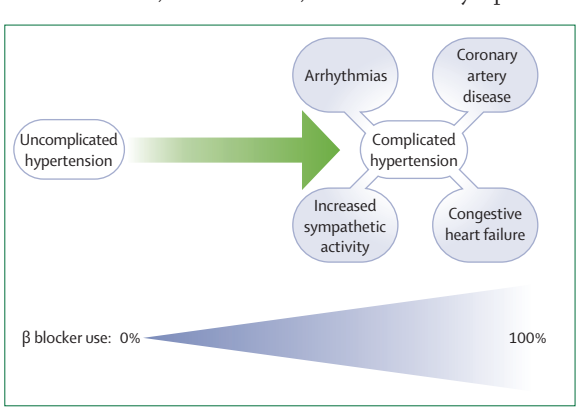

Figure 4: **Guidelines for β blocker use**
Patients with uncomplicated hypertension are not good candidates for β blockers. However, when hypertension is accompanied by coronary artery disease, congestive heart failure, increased sympathetic activity, and arrhythmia, such treatment could be beneficial.

nervous system, and accelerate insulin resistance, all of which have been identified as cardiovascular risk factors. Clearly, together with antihypertensive treatment, blood pressure remains the most powerful determinant of outcome.

Beyond blood pressure, some evidence suggests that coronary artery disease is best prevented by angiotensin-converting-enzyme inhibitors, calcium-channel blockers, and thiazide diuretics, stroke by angiotensin-receptor blockers, calcium-channel blockers, and diuretics, and congestive heart failure by diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers.[107–109] Conversely, these data would indicate that angiotensin-receptor blockers have little effectiveness for coronary artery disease, angiotensin-converting-enzyme inhibitors are not very effective for cerebrovascular disease, and calcium-channel blockers have reduced activity for congestive heart failure. However, since most of the evidence summarised above is based on findings of meta-analyses, we should be cautious to remember the bouillabaisse analogy of a meta-analysis: no matter how much fresh seafood is added, one rotten fish will make it stink.[110]

Stroke prevention and angiotensin II type 2 receptor

Some data have shown better stroke protection with thiazide diuretics, dihydropyridine calcium-channel blockers, and angiotensin-receptor inhibitors than with β blockers and angiotensin-converting-enzyme inhibitors.[111] This blood pressure-independent stroke protection could be mediated by increased angiotensin II concentrations stimulating the angiotensin II type 2 (AT2) receptor, as suggested by experimental findings.[112] Conceivably, activation of the AT2 receptor could facilitate recruitment of collateral vessels in the penumbra and enhance cerebral resistance to anoxia.[113] Indeed, activation of the AT2 receptor reduces focal cerebral ischaemia by induction of vasodilatation and reduction of oxidative stress.[114] Compared with thiazides and calcium-channel blockers, angiotensin-receptor blockers have the additional advantage of blocking the angiotensin II type 1 (AT1) receptor. The hypothesis of superiority of this class of drugs was tested in the MOSES study, in which eprosartan showed some benefits when compared with nitrendipine in patients with established cerebrovascular disease.[115] In a meta-analysis of more than 200 000 patients in 26 trials, we showed that antihypertensive drugs that raise angiotensin II concentrations are more cerebroprotective than are agents that reduce these levels.[116] These data, together with the experimental findings attesting to cerebroprotection by AT2-receptor stimulation, should be provocative enough to motivate investigators to undertake a randomised clinical trial on stroke prevention comparing an AT2 receptor-stimulating strategy (ie, angiotensin-receptor blocker-based treatment) against a regimen void of such stimulation (ie, an angiotensin-converting-enzyme inhibitor-based treatment).

Obesity and metabolic syndrome

Obesity is associated with a high prevalence of hypertension, and weight loss can reduce blood pressure.[117–119] Although body-mass index is sometimes used to define obesity, visceral adiposity seems to be more important in defining the relation between blood pressure and obesity.[120–124] Moreover, adiposity also increases the likelihood of coexisting metabolic syndrome in people with hypertension. The importance of this syndrome is that it identifies individuals at high risk of developing hypertension, diabetes, and premature cardiovascular disease.

In a study in which MRI was used to quantify adiposity in untreated hypertensive men, fat was seen to accumulate preferentially intra-abdominally and intrathoracically, and this visceral adiposity was related quantitatively to the height of blood pressure.[121] Importantly, the link between adiposity and blood pressure can be seen from early childhood and it is a key predictor of the likelihood of developing overt hypertension.[124] The frequent coexistence of visceral fat with other features of metabolic syndrome also accounts for the association between hypertension and increased risk for development of diabetes. The metabolic syndrome link underpins the need to view hypertension as more than just blood pressure in the context of cardiovascular disease risk management and it points to the importance of early lifestyle interventions as the foundation for prevention and treatment. Specific therapeutic interventions targeting visceral adiposity—such as cannabinoid 1-receptor blockers—will need to be investigated to confirm whether they provide outcome benefits beyond conventional treatment.

Dementia and cognitive dysfunction

Hypertension raises risk for dementia.[125,126] While this finding is not unexpected for vascular dementia, hypertension is also a risk factor for dementia of the Alzheimer's type. However, an increased risk has also been reported for chronic hypotension and, in some studies, a U-shaped curve was recorded between blood pressure and risk for dementia.[127,128] Conceivably, the common denominator accounting for this apparent discrepancy could be cerebral hypoperfusion.

Antihypertensive treatment could diminish risk for dementia, although not all antihypertensive drugs are equal in this respect. In the long-term follow-up of the Syst-Eur study, risk for dementia after 8 years of follow up was 55% lower in the active treatment (nitrendipine) arm compared with placebo.[129] By contrast, in the SHEP study, in a similar population, chlorthalidone had no effect on cognitive function. In SCOPE, no difference was noted in

mini-mental state examination score between people in the candesartan group and controls,[130] although in a substudy in elderly patients, some benefits could be seen.[131] Valsartan and losartan have been shown to enhance cognitive function compared with enalapril and atenolol, respectively, in two small studies.[132,133] In a substudy of PROGRESS, blood-pressure lowering with indapamide and perindopril reduced white-matter hyperintensity in patients with cerebrovascular disease.[134] Hanon and coworkers, in a cross-sectional study, noted improved cognitive function in elderly patients receiving antihypertensive drugs, particularly in those on calcium-channel blockers.[135] The mechanism by which this class of drugs decreased risk for dementia could be related to reduction of excess intracellular free calcium in neurons, which seems to happen in patients with dementia of the Alzheimer's type. Findings from the above studies, as compelling as they might be, are only hypotheses-generating, which, in view of the size of this problem, should be further investigated as a matter of urgency.

Hypertensive heart disease

Left-ventricular hypertrophy is a feature of hypertensive heart disease and predicts independently an adverse prognosis.[136,137] Coexistence of the electrocardiogram strain pattern of ST depression and T-wave inversion with evidence of left-ventricular hypertrophy worsens prognosis and increases risk for development of heart failure.[138,139] In a large study of blood-pressure lowering and regression of left-ventricular hypertrophy, lower on-treatment left-ventricular mass was associated with reductions in cardiovascular mortality and stroke, but not myocardial infarction.[140] Regression of left-ventricular hypertrophy on electrocardiography is also indicative of substantial clinical benefit and should be an important objective of treatment.[141]

Atrial fibrillation is an under-recognised complication of long-standing hypertension and increases likelihood of morbidity and mortality—at least doubling the risk for cardiovascular death or stroke.[142–144] The main factors predicting development of atrial fibrillation are: age, male sex, severity of hypertension, obesity, and presence of left-ventricular hypertrophy on electrocardiogram.[143,144] Some findings suggest that choice of blood pressure-lowering treatment could reduce risk of developing atrial fibrillation. Notably, treatment that inhibits the renin-angiotensin-aldosterone system[144] might be more likely to prevent new-onset atrial fibrillation than other antihypertensitive drug classes. The mechanism for this benefit is unclear but could be, at least in part, dependent on favourable structural regression of left-ventricular mass and a reduction in left atrial size.[145]

Long-term safety of antihypertensive treatment and carcinogenicity

Patients are exposed to antihypertensive treatment for decades; yet, long-term safety of these drugs is not well-reported. Most prospective randomised trials end after a few years without long-term follow up. This factor is of particular concern with respect to the possibility that risk for malignant disease could be affected by antihypertensive treatment. Hypertension by itself has been shown to increase risk for malignant disease,[146] which could be attributable to the fact that the two diseases share some risk factors, such as diabetes, obesity, alcohol consumption, and tobacco. In a meta-analysis of 47 119 patients, those with hypertension had a high rate of cancer mortality, with a pooled odds ratio (adjusted for age and smoking) of 1·23 (95% CI 1·11–1·36). A low-grade association was noted between rauwolfia derivatives and breast cancer, with an odds ratio of 1·25 (1·09–1·44).[147] Data for β blockers, calcium-channel blockers, and angiotensin-converting-enzyme inhibitors were too heterogeneous to allow firm conclusions. More noticeable, however, was an association between diuretics and renal-cell carcinoma, with a pooled odds ratio of 1·54 (1·4–1·68) in ten independent case-control studies and three cohort studies. This association between renal carcinoma and diuretic treatment remains of concern since the renal tubular cell—ie, the cell from which renal-cell carcinoma originates—is also the main target of the diuretic's pharmacological effect.[148] Conceivably, long-term chemical exposure of this cell by thiazides might have a low-grade carcinogenic effect.

Obviously, the issue of malignant disease associated with hypertension and its treatment is complex and hasty conclusions should be avoided. Prospective studies with all cardiovascular drugs should carefully monitor risk for malignant disease.

Lessons from clinical trials

Important lessons from some of the latest clinical trials have been reviewed[149,150] and are outlined below. First, blood pressure is the key driver of benefit from blood pressure-lowering drugs. Second, drugs that deliver less effective blood-pressure control have never produced a superior clinical outcome in clinical trials of blood pressure-lowering drugs. Third, the choice of initial treatment defines the initial blood-pressure response to treatment and the longer term quality of blood-pressure control, usually requiring fewer add-on drugs. Fourth, people with treated hypertension remain at higher risk of cardiovascular disease than those without hypertension, attributable in part to the common aggregation of other risk factors for cardiovascular disease. Fifth, people with hypertension should undergo formal estimation of their global risk, and if their risk is high, they should be offered treatment with statins and low-dose aspirin to further reduce their cardiovascular disease risk. Finally, treatment of blood pressure at the prehypertensive stage might prevent development of severe hypertension, target-organ damage, and diminish risk for dementia.

Conclusion

In 1951, in the fourth edition of his book *Heart disease*, White amended the sentence that we used as an introduction to this Seminar to: "The treatment of the hypertension itself continues to be a difficult task in the present state of our knowledge, but important studies in progress offer much hope for the future."[151] As can be seen from our Seminar, this statement is as true today as it was half a century ago.

Conflict of interest statement

FHM is on the speaker's list for and has received honoraria from the following organisations: Abbott, GSK, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, Forest, Sankyo, and Sanofi. BW has received grant support for investigator-led research (Pfizer and Merck); honoraria for presentations at scientific meetings (Pfizer and Merck); and consultancy (Pfizer, Merck, and Novartis). ER has received honoraria for presentations at scientific meetings (Boehringer, Abbott, Aventis) and for consultancy (Boehringer).

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