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ORIGINAL ARTICLE

The new concept of total cardiovascular risk management

Il nuovo concetto del trattamento del rischio cardiovascolare totale

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KEYWORDS

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Summary

Introduction: Cardiovascular risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus, often cluster together and can also be seen with other pathophysiological conditions that greatly increase an individual's risk for cardiovascular morbidity and death.

Aim of the study: This article emphasizes the importance of assessing and managing the total cardiovascular risk in an individual patient.

Materials and methods: Suggestions and recommendations from the most current hypertension management guidelines have been integrated with results from the major clinical trials published in the last decade.

Results: Based on a review of the epidemiological data on cardiovascular disease, this paper expands the concept of stratification of hypertensive patients according to the approximate added risk of major cardiovascular events in the next 10 years and stresses the importance of subclinical target-organ damage.

Conclusions: Although common in clinical practice, high-risk patients are often undiagnosed. Intensive hypertensive therapy is recommended for high-risk patients, and this treatment strategy will require combination therapy to control or reverse subclinical organ damage and prevent the progression of cardiovascular risk in subjects at low risk or medium risk.

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Introduction

Throughout the world, the prevalence of cardiovascular risk factors has been steadily increasing. Modifiable risk factors for cardiovascular disease (CVD), which include hypertension, smoking, abdominal obesity, high levels of cholesterol and diabetes, are the major contributors to cardiovascular morbidity and mortality [1,2]. A recent *World Health Organization* (WHO) report indicated that hypertension affected 972 million people worldwide in 2000; this number is predicted to increase by roughly 60% to 1.56 billion people by 2025 [3]. Furthermore, hypertension is the leading cause of global mortality [4]. It has been established that CV risk factors show a continuous association with overall cardiovascular risk, with no minimum threshold for disease [5,6]. Additionally, risk factors rarely occur in isolation. Instead, they tend to cluster, acting synergistically to increase an individual's total risk of CVD, from 4-fold with 1 risk factor to 60-fold in the presence of 5 risk factors [7]. Major clinical trials clearly show that reducing an elevated blood pressure (BP) is associated with a reduced risk of cardiovascular events, regardless of the antihypertensive agent used. Given these findings, the 2007 *European Society of Hypertension* (ESH)/*European Society of Cardiology* (ESC) guidelines for the management of arterial hypertension recommend that, for each individual patient, the total cardiovascular risk should be assessed and used as the basis for treatment decisions [8].

Epidemiology of cardiovascular disease

It is well established that the greater part of the burden of CVD is caused not by mortality but by non-fatal cardiovascular events and the associated long-term consequences (fig. 1) [9]. The global incidence of CVD is rising, in part because lifestyle changes are causing increases in CVD risk factors in lower- and middle-income countries as they become more similar to wealthier states. The burden of

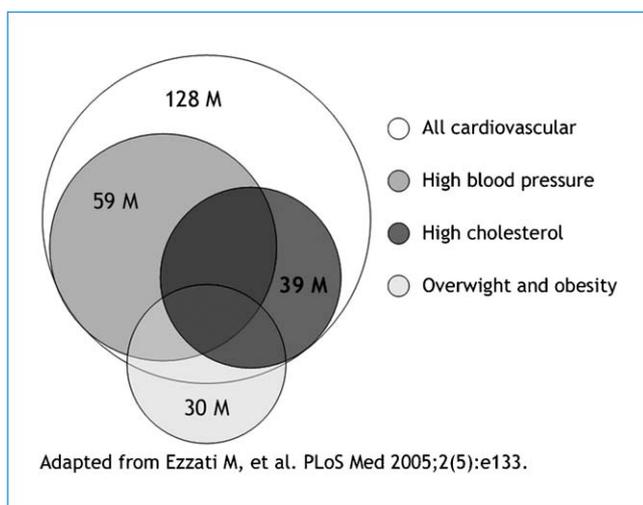


Figure 1 Global burden of disease attributable to CVD and major risk factors for people aged ≥ 30 years. The size of each circle is proportional to the burden of disease [measured in millions (M) of disability-adjusted life years].

CVD is likely to increase in the future, not only because the population is aging but also due to the rising epidemic of hypertension, obesity and related cardiovascular risk factors. The recently published *Reduction of Atherothrombosis for Continued Health* (REACH) Registry [10], which collected global data on atherosclerosis risk factors from approximately 68,000 patients aged ≥ 45 years in 44 countries, found that hypertension, high cholesterol levels, diabetes, obesity and smoking are consistent and common in different ethnic populations and are frequently undertreated and poorly controlled in many regions of the world. A study from Italy [11], in which 450 cardiovascular specialists (cardiologists, internists and diabetes specialists) examined 4,059 consecutive essential hypertensive patients from March to June 2000, revealed that almost 50% of hypertensive patients had two or more additional CV risk factors, and a further 40% had one additional risk factor (fig. 2). Similarly, recent data from the *Pressioni Arteriose Monitorate E Loro Associazioni* (PAMELA) study demonstrated significant correlations between increasing blood pressure, measured in the office, at home, or as mean values over 24 h, and the incidence of hypercholesterolemia, diabetes mellitus or impaired fasting blood glucose (all with $p = 0.05$) [12]. In addition, there appears to be a substantial population of hypertensive patients with subclinical, undiagnosed target-organ damage. Given the pandemic nature of CVD, a unified strategy for CVD prevention would be universally beneficial.

Total cardiovascular risk stratification

The methods used to assess total cardiovascular risk vary between different sets of guidelines. Those published jointly by the ESH/ESC [8] and those from the *World Health Organization/International Society of Hypertension* (WHO/ISH) [13] were written based on criteria from multiple studies, including the *Framingham Heart Study* [14]. These guidelines categorize cardiovascular risk according to the presence of other risk factors, target-organ damage and associated

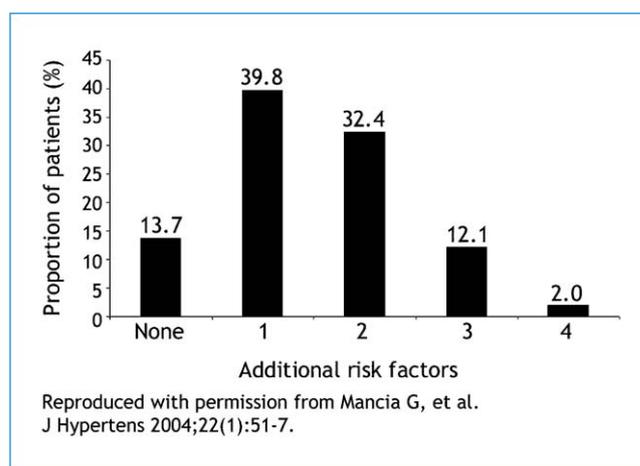


Figure 2 Proportion of hypertensive patients treated in specialist care settings in Italy with or without one or more additional cardiovascular risk factors.

Table 1 Factors influencing total cardiovascular risk, according to the ESC/ESH guidelines.

Risk factors	Target-organ damage	Diabetes mellitus	Associated clinical condition
Systolic and diastolic blood pressure	Left ventricular hypertrophy	Fasting plasma glucose 126 mg/dL	Cerebrovascular disease
Men > 55 years	ECG: Sokolow-Lyons > 38 mm; Cornell echo: LVMI; carotid IMT \geq 0.9 mm or atherosclerotic plaque	Postprandial plasma glucose A 198 mg/dL	Ischemic stroke
Women > 64 years	Increased serum creatinine: 1.3-1.5 mg/dL in males, 1.2-1.4 in females		Cerebral hemorrhage
Smoking	Microalbuminuria: 30-300 mg/24 h; or albumine:creatinine ratio \geq 22 mg/g in males, \geq 31 mg/g in females		Transient ischemic attack
Total cholesterol > 250 mg/dL or LDL > 155 mg/dL or HDL < 40 mg/dL in males and < 48 mg/dL in females			Heart disease
Family history of premature CV disease			Myocardial infarction
Abdominal circumference \geq 102 cm in males or \geq 88 cm in females			Angina
C-reactive protein \geq 1 mg/dL			Coronary revascularization
			Congestive heart failure
			Renal disease
			Diabetic retinopathy
			Serum creatinine > 1.5 mg/dL in males, > 1.4 mg/dL in females
			Proteinuria > 300 mg/24 h
			Peripheral vascular disease
			Advanced retinopathy

LDL = low density lipoproteins; HDL = high density lipoproteins; LVMI = left ventricular mass index; IMT = intima-media thickness. From Mancia G, et al. Eur Heart J 2007;28(12):1462-536, by permission.

clinical conditions, such as a history of cardiovascular disease (*table 1*). Thus, patients can be stratified according to the severity of hypertension and the presence of other risk factors as having a low (< 10%), medium (15-20%), high (20-30%) or very high (> 30%) level of added risk of cardiovascular morbidity or mortality within the next 10 years (*table 2*). Furthermore, the presence of additional risk factors, target-organ damage or associated clinical conditions can result in patients being at high or very high risk of cardiovascular disease, even when blood pressure is normal or high-normal [systolic blood pressure (SBP) 130-139 mmHg and diastolic blood pressure (DBP) 85-89 mmHg].

Several studies have shown an association between increased cardiovascular risk factors and poor prognosis in

hypertensive patients. One such study followed subjects for a mean of 14 years and analyzed the mortality data from 60,343 male patients with hypertension with or without associated risk factors (total cholesterol \geq 250 mg/dL, personal history of diabetes, current smoker, body mass index > 28 kg/m² and heart rate > 80 bpm) and from a matched group of 29,640 normotensive men without associated risk factors for cardiovascular disease [15]. Compared with normotensive individuals, cardiovascular mortality increased 5-fold in younger hypertensive patients (age < 55 years) with one or two additional risk factors and 15-fold in younger patients with more than two associated risk factors ($p < 0.001$). Older hypertensive patients (age \geq 55 years) with up to two associated risk factors showed a 3-fold increase

Table 2 Stratification of cardiovascular risk in the ESC/ESH guidelines.

BP	Normal	High-Normal	Grade 1	Grade 2	Grade 3
Other risk factors and disease history	SBP 120-129 or DBP 80-84 (mmHg)	SBP 130-139 or DBP 85-89 (mmHg)	SBP 140-159 or DBP 90-99 (mmHg)	SBP 160-179 or DBP 100-109 (mmHg)	SBP \geq 180 or DBP 110 (mmHg)
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1-2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
\geq 3 risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Associated clinical conditions	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Approximated 10-years added risk of cardiovascular disease: low (< 15%), medium (15-20%), high (20-30%), and very high (> 30%). SBP = systolic blood pressure; DBP = diastolic blood pressure; TOD = target-organ damage.

From Mancia G, et al. *Eur Heart J* 2007;28(12):1462-536, by permission.

in cardiovascular mortality compared with their normotensive counterparts, whereas older hypertensive individuals with more than two risk factors showed a 4.5-fold increase.

Subclinical target-organ damage and total cardiovascular risk

The ESH/ESC guidelines emphasize that the presence of subclinical target-organ damage confers an increased total cardiovascular risk [8]. Measures of end-organ damage that have been shown to be prognostically important and that can be easily measured in clinical practice, include echocardiographic assessment of left ventricular hypertrophy (LVH), ultrasonographic measurement of carotid artery wall thickness, and measurement of microalbuminuria and renal function. Other approaches, such as examining arterial remodeling, endothelial dysfunction, calcium deposition, or arterial stiffening, are impractical for routine clinical practice.

LVH is a well-recognized risk factor for CVD [16]. A meta-analysis of trials examining antihypertensive treatment showed that, for any given level of blood pressure, concentric LVH was associated with a significant increase in all-cause mortality. In contrast, concentric LVH without an increase in left ventricular mass index (LVMI) or left ventricular wall thickness was associated with a smaller increase in risk [17].

Several studies have shown that the intima-media thickness (IMT) of the carotid arteries is predictive of the risk of myocardial infarction or stroke [18]. The relationship between IMT and CV risk is continuous, but an IMT of \geq 0.9 mm is considered a sign of target-organ damage [8].

The impact of renal function on CV risk has been well studied. Data from the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) trial [19] demonstrated that the composite outcome of cardiovascular death, myocardial infarction, heart failure and stroke occurred in 15% of patients with serum creatinine levels > 133 μ mol/L compared with 6% of those with normal creatinine levels [odds ratio (OR) = 2.89; 95% confidence interval (CI) = 1.92-4.36; $p < 0.001$]. Additionally, the composite outcome occurred in 9% of patients with an estimated creatinine clearance < 60 mL/min but was seen in only 5% of those patients with higher clearances (OR = 1.51; 95% CI = 1.22-1.88; $p < 0.001$).

The presence of microalbuminuria has been shown to predict the development of overt diabetic nephropathy and is also associated with an increased risk of cardiovascular events, in both diabetic and non-diabetic subjects [8]. In one population-based, case-control study, microalbuminuria (defined as a urinary albumin:creatinine ratio > 1.07 mg/mmol) was found to be the strongest predictor of ischemic heart disease (IHD) in subjects with untreated or borderline hypertension [20].

Management of hypertension and concomitant risk factors

Hypertension is reversible, and several lines of evidence have demonstrated that reducing BP affords cardiovascular protection, regardless of which antihypertensive drug is used [21,22]. The Blood Pressure Lowering Treatment Trialists' Collaboration [21] performed a series of prospective overviews of 27 randomized trials ($n = 158,709$) that investigated the effects of different BP-lowering regimens on serious cardiovascular morbidities and fatal events. Reductions in SBP and DBP were seen with diuretics and beta-blockers (10-12/5-6 mmHg), angiotensin-converting enzyme (ACE) inhibitors (5/2 mmHg), calcium antagonists (8/4 mmHg), as compared with placebo. These changes in BP were accompanied by significant reductions in primary outcomes, which included cardiovascular disease (15-22%), coronary heart disease (16-22%), and stroke (28-39%) ($p < 0.05$ vs placebo for all). Angiotensin II receptor blockers (ARBs) were compared with other antihypertensive agents, and they reduced BP by 3/2 mmHg. This effect was accompanied by reductions in the incidence of cardiovascular disease (10%), coronary heart disease (4%), and stroke (21%) ($p < 0.05$ vs other agents, except for coronary heart disease).

A retrospective analysis of the International Verapamil SR-Trandolapril (INVEST) trial ($n = 22,576$) showed that, in patients with hypertension and a history of coronary disease, a clear relationship existed between consistency of BP control during treatment follow-up and the incidence of the primary outcome [22]. Patients were stratified according to the proportion of clinic visits at which BP was controlled to below 140/90 mmHg into the following groups: less than 25% of visits ($n = 3,838$), 25-50% of visits ($n = 3,757$), 50-75% of

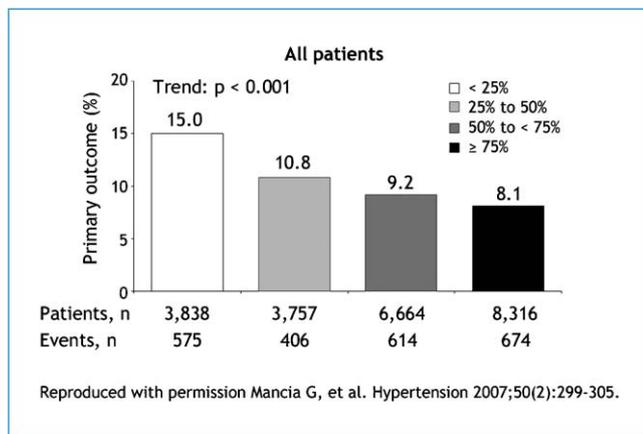


Figure 3 Primary outcome (first occurrence of death, non-fatal myocardial infarction, or non-fatal stroke) occurrence according to proportion of visits (< 25%, 25% to < 50%, 50% to < 75%, ≥ 75%) with blood pressure < 140/90 mmHg in the INVEST trial.

visits ($n = 6,664$), and 75% or more of visits ($n = 8,316$). The risk of experiencing the primary outcome (first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke) decreased progressively as the proportion of visits with BP control increased. The data showed a significant trend ($p < 0.001$), with a 15% risk reduction in the less than 25% of visits group, a 10.8% reduction in 25-50% group, a 9.2% reduction in the 50-75% group, and an 8.1% reduction in the 75% or more group (fig. 3). The association between the consistency of BP control and the incidence of cardiovascular events was independent of baseline characteristics and mean BP during treatment.

In the *Heart Outcomes Prevention Evaluation* (HOPE) study [23], 9,727 patients with a history of coronary heart disease, cerebrovascular disease, peripheral vascular disease or diabetes as well as at least one other cardiovascular risk factor were treated with the ACE inhibitor ramipril or placebo for a mean of 5 years. Ramipril produced only a modest reduction in blood pressure (3/2 mmHg). Nevertheless, this relatively small decrease in BP was associated with a 22% reduction in cardiovascular mortality, a 32% reduction in stroke and a 20% reduction in myocardial infarction ($p < 0.001$ for all). In addition, ramipril treatment was associated with a 16% decrease in all-cause mortality ($p = 0.005$) and significant reductions in a number of secondary outcomes, including the development of congestive heart failure, revascularization, diabetic complications and the development of diabetes.

Intensive antihypertensive treatment has also been shown to be beneficial in normotensive diabetic patients. In the Appropriated Blood pressure Control in Diabetes (ABCD) study [24], intensive treatment aimed at achieving a DBP of 10 mmHg below baseline values produced a significant reduction in the incidence of stroke compared with more moderate treatment aimed at achieving a DBP of 80-89 mmHg. Intensive treatment was also associated with significant reductions in the development of microalbuminuria ($p = 0.012$), the progression to overt proteinuria ($p = 0.028$) and the progression of diabetic retinopathy ($p = 0.019$) compared with moderate treatment.

These results demonstrate that blood pressure reduction decreases the risk of cardiovascular events in high-risk patients with normal or high-normal blood pressure. In addition, the results of the *Hypertension Optimal Treatment* (HOT) study indicate that lowering blood pressure to levels below those generally considered normal is associated with a significant reduction in cardiovascular risk [25]. In this study, diabetic patients randomized to a target DBP of ≤ 80 mmHg experienced an approximately 50% reduction in the risk of cardiovascular events compared with those assigned a more conservative target of ≤ 90 mmHg. Similar findings were obtained in the United Kingdom Prospective Diabetes Study (UKPDS) [26], in which the incidence of fatal or non-fatal myocardial infarction or microvascular disease was lowest in patients with an SBP of <130 mmHg.

Because hypertension is only one factor contributing to total cardiovascular risk, it follows that management of total risk requires control of other risk factors, in addition to blood pressure. As an example of this approach, the HOT study randomized patients to receive low-dose acetyl-salicylic acid (ASA) or placebo in addition to their randomization for a DBP target [25]. Among the patients at highest risk, ASA treatment resulted in a 22% reduction in the incidence of major cardiovascular events compared with placebo (OR = 0.78; 95% CI = 0.65-0.94) [27].

In the *Anglo-Scandinavian Cardiac Outcomes Trial* (ASCOT), 19,342 hypertensive patients with at least three CV risk factors were randomized to one of two antihypertensive regimens, and those with fasting total cholesterol concentrations ≤ 6.5 mmol/L were also randomized to placebo or lipid-lowering therapy with atorvastatin 10 mg [28]. Among patients with a well-controlled BP, lipid-lowering therapy was associated with a significant reduction in the primary end-point of nonfatal myocardial infarction plus death from coronary heart disease [hazard ratio (HR) = 0.64; 95% CI = 0.50-0.83; $p < 0.0005$]. There were also significant reductions in the secondary endpoints, which included stroke, total coronary events and total cardiovascular events.

Conclusions

Many hypertensive patients are at high risk of cardiovascular disease due to the presence of additional risk factors, target-organ damage or associated clinical conditions. Therefore, assessment of total cardiovascular risk is a central element of most current hypertension management guidelines. The effective management of total cardiovascular risk requires intensive lowering of blood pressure as well as treatment of all other reversible risk factors.

Conflict of interest statement

The authors have no conflict of interest.

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