doi: 10.1111/j.1742-1241.2008.01821.x

Clinical Practice

Managing hypertension in cardiology practice according to risk profile

M. Volpe, ^{1,2} G. Tocci¹

Linked Comment: Dominguez-Rodriguez. Int J Clin Pract 2008; 62: 1303–4.

SUMMARY

Cardiologists play a central role in managing hypertensive patients, although recent surveys reveal a marked discrepancy between cardiologists' appreciation of their patients' risk status and the measures taken to reduce that risk. The diagnosis and the management of hypertension, in fact, must be viewed today not in isolation, but as part of a patients' global cardiovascular (CV) risk, resulting from the concomitant presence of a variety of risk factors, organ damage (left ventricular hypertrophy, carotid or peripheral atherosclerosis, microalbuminuria or impaired glomerular filtration rate), and hypertension-related clinical conditions. The choice of timing and the intensity of antihypertensive treatment should be based on blood pressure (BP)-lowering efficacy and the propensity to favourably impact patient's individual absolute CV disease risk profile. As part of this paradigm shift in CV disease prevention strategy, cardiologists can take several key steps to help improve standards of hypertension control: (i) increase the awareness of total risk management; (ii) initiate an integrated management strategy tailored to the individual patient's global CV risk (e.g. hypertension, hypercholesterolaemia, diabetes, age, smoking and gender); (iii) use any elevation in BP as a gateway to begin total risk management and (iv) utilise combination therapies (particularly fixed-dose combinations) to achieve more rapid and persistent BP control and improve patient compliance/persistence with therapy. To help improve standards of hypertension control in the cardiology setting, this review examines the concept of treating hypertension using a global risk assessment approach and proposes effective hypertensive therapy as part of global risk management in patients typically seen in cardiology practice.

Review Criteria

A comprehensive Medline literature search was performed using the keywords cardiovascular disease, hypertension, cardiovascular risk factors, organ damage and antihypertensive therapy. Papers included in this review were manually selected based on their relevance to cardiovascular risk management in hypertension. Other references were selected on an ad hoc basis to provide support for the information provided.

Message for the Clinic

All physicians, but especially cardiologists, who play a central leadership role in managing hypertensive patients, should consider moving away from the traditional cardiovascular disease management approach in which multiple independent risk factors are individually managed. Instead, they should recognise and embrace the importance of integrated identification of all risk factors (e.g. hypertension, hypercholesterolaemia, diabetes, organ damage, age, smoking and gender) and initiate a management strategy tailored to the individual patient's global CV risk to rapidly, effectively and persistently reduce the global burden of cardiovascular diseases. ¹Division of Cardiology, II Faculty of Medicine, University of Rome 'La Sapienza', Pozzilli, IS, Italy ²IRCCS Neuromed, Pozzilli, IS, Italy

Correspondence to:

Prof. Massimo Volpe, Division of Cardiology, II Faculty of Medicine, University of Rome 'La Sapienza', Sant'Andrea Hospital, Via di Grottarossa, 1035-39, 00189 Rome, Italy Tel.: + 39 06 3377 5654 Fax: + 39 06 3377 5061 Email: massimo.volpe@uniroma1.it

Disclosures

Massimo Volpe has received honoraria for scientific presentations at meetings as well as for participation in advisory boards by Bayer, Boehringer Ingelheim, Merck and Co., Novartis, sanofiaventis and Bristol-Myers Squibb, and has received a research grant by Pfizer; Giuliano Tocci has no conflict of interest to disclose.

Introduction

Hypertension continues to evolve into a healthcare problem of global proportions (1,2). In 2000, approximately 972 million adults worldwide had hypertension, a statistic that is expected to increase to over 1.5 billion by the year 2025 (3). In this perspective, hypertension increases the risk of a variety of cardiovascular (CV) events, notably coronary heart disease (CHD), stroke, peripheral arterial disease (PAD) and heart failure (HF), shortens life expectancy, and represents one of the leading cause of disability-adjusted lifeyears (4–6). International surveys and data derived from major clinical trials on hypertension consistently demonstrated poor blood pressure (BP) control in the general populations of hypertensive patients, mostly in high-risk hypertensive patients (e.g. patients with diabetes mellitus), further contributing to poor prognosis in hypertension (7–10).

Although a central contributory role to the individual's overall CV risk (11), hypertension rarely occurs in isolation, being more often associated with other additional, modifiable risk factors (12), such as diabetes mellitus, dyslipidaemia, smoking, and obesity, and signs of hypertension-related organ damage, including left ventricular hypertrophy (LVH) (13) and microalbuminuria (MAU) (14). Thus, the diagnosis and management of hypertension should be viewed today not in isolation, but in the context of an individual's total or global CV disease (CVD) risk assessment (15). According to this approach, the choice of timing and intensity of antihypertensive treatment should be based not only on BP-lowering efficacy of a given treatment, but also on the propen-

sity to favourably impact patient's individual absolute CVD risk assessment (16,17).

The responsibility for hypertension management in the general population largely rests with primary care physicians, although rates of successful hypertension control in primary care are often disappointingly low in many countries (18-22). A recent large analysis of population and clinical surveys in Italy, involving 52,715 diagnosed hypertensive patients, for example, demonstrated the persistence of poor BP control and high prevalence of risk factors (23). In this analysis, a significant difference was observed with regard to systolic BP control, but not for diastolic BP control, in a large proportion of patients followed by cardiologists or general practitioners. In the same analysis, patients were at high or very high CV risk according to 2003 European Society Hypertension of (ESH)/European Society of Cardiology (ESC) recommendations (24), despite the fact that they were professionally managed for hypertension. Many physicians, in fact, systematically tend to underestimate CV risk in their perceptions by almost threefold compared with calculated risk (25), in part because of limited interaction with their patients (26). Even after establishing that a patient is at risk of CHD, 65% of primary care physicians spend < 15 min discussing management (22). Collectively, these findings support the need for more effective, comprehensive and urgent actions to improve the clinical management of hypertension in the primary care setting, with an emphasis on preventing hypertension-related CV and renal diseases (27-29).

In addition to primary care practitioners, cardiologists may also play a 'central' role in the clinical management of hypertension, and are well placed to offer leadership in the treatment of hypertension. Nevertheless, although cardiologists are relatively more successful at lowering BP than some other categories of practitioners (23), they also substantially tend to underestimate a patient's CV risk and fail to implement the appropriate therapeutic measures to reduce the risk of major CV events (22,25,26).

To help improve the standards of hypertension control in the cardiology setting, the present article reviews the concept of treating hypertension using a global risk assessment approach, rather than a single risk factor-based approach, by presenting the multitude of factors contributing to the global risk in hypertensive patients, and proposing the effective hypertensive therapy as part of global risk management in patients typically seen in cardiology practice.

The concept of global cardiovascular risk in patients with hypertension

In the past, the CV disease prevention has focused on modifying single risk factors, notably hypertension, dyslipidaemia and type 2 diabetes mellitus (30-32). With respect to hypertension, solid evidence exists showing that the relative risk of CV events is approximately linearly and continuously related to BP levels over the range 115/75 to 180/105 mmHg (33). According to a prospective, longitudinal analysis of a 36-year follow-up data from the Framingham Study, the presence of hypertension in both men and women contributes to an increase risk (on average, two- to threefold) of all major CV disease outcomes, including CHD, stroke, renal failure and HF (4). In this latter regard, while CHD and stroke are often considered the most frequent and dramatic consequences of high BP levels, a recent analysis of clinical trials in hypertension performed over the last decade, demonstrated a persistently high rate of HF development in hypertensive patients, particularly in elderly, black, diabetic or very high-risk individuals (34).

A key finding of these studies in the context of global risk was the observation that hypertension often clusters with glucose and lipid abnormalities as well as obesity, occurring in isolation in < 20% of patients (4,12-14,23). Thus, the concomitant presence of hypertension with one or more additional metabolic risk factors and organ damage exponentially increases absolute global CV risk to a level greater than the 'algebraic' sum of the individual components of risk (12,35-37). Results from the Framingham Heart Study also support this hypothesis on increased risk of major CV events, notably stroke, in hypertensive patients with or without various additional stroke risk factors, including age, systolic BP, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, prior CV events, atrial fibrillation (AF) and LVH (38). Of interest, the highest risk of stroke occurred in patients who would likely be managed in a cardiology setting (e.g. those with prior CV events, LVH or AF). Collectively, these and other clinical studies demonstrate that today hypertensive patients require to be classified not only with respect to severity of their hypertension but mostly with respect to their global CV risk, resulting from the concomitant presence of a variety of risk factors, organ damage (LVH, carotid or PAD, MAU, or reduction in glomerular filtration rate), and hypertension-related clinical conditions (15).

Assessing global cardiovascular risk

While identification of high global CV risk is relatively straightforward in specific subsets of hypertensive individuals (e.g. those with previous CV events, diabetes mellitus or severely elevated levels of individual risk factors) (11), it is less intuitive and poorly applied in the clinical practice of hypertensive patients, who are characterised by the presence of multiple, concomitant risk factors or clinical conditions, as those listed in Table 1, each of which can impact on global CV risk and long-term clinical prognosis (35–37).

The usefulness of risk assessment tools depends on several important criteria, including: (i) the inclusion of risk factors that can be easily and affordably quantified; (ii) the coverage of a wide age range in both sexes; (iii) the inclusion of ethnic-specific data (when appropriate); (iv) the prediction of well-defined CV disease events (fatal and non-fatal events); (v) the availability of validation data in the target population. Although none of the currently available risk assessment tools fulfil the above-mentioned criteria, being entirely precise and widely applicable, a number of validated methods can be used to approach

Table 1 Summary of key factors that can potentially impact prognosis and should be used to stratify global risk Risk factors SBP and DBP Pulse pressure Age Smoking Dyslipidaemia Fasting plasma glucose Abnormal GTT Abdominal obesity Family history of CVD Subclinical I VH organ damage Carotid wall thickening/plaque Carotid-femoral pulse wave velocity Ankle/brachial BP index Increase in plasma creatinine Low GFR Microalbuminuria Established CV Cerebrovascular disease (ischaemic or renal disease stroke, cerebral haemorrhage, TIA) Heart disease (MI, angina, revascularisation, HF) Renal disease (diabetic nephropathy, renal impairment, proteinuria) PAD Retinopathy SBP/DBP, systolic or diastolic blood pressure; GTT, glucose tol-

erance test; LVH, left ventricular hypertrophy; GFR, glomerular filtration rate; TIA, transient ischaemic attack; MI, myocardial infarction; HF, heart failure; PAD, peripheral artery disease; CVD, cardiovascular disease; BP, blood pressure. Adapted from Ref. (15).

the estimation of global risk, with useful educational and clinical implications (39,40).

After accumulating evidence suggested that the Framingham risk score may overestimate coronary risk in some European populations (41-43), the ESH/ESC Committee recently formulated the European Systematic COronary Risk Evaluation (SCORE) system, which allows determination of a European patient's 10-year risk of fatal CV disease (44). Using a graphically display of risk estimations in simple risk charts, SCORE allows physicians to estimate quickly a patient's total fatal CV risk. This system differs from the Framingham risk score (12) in that it considers total CV mortality (not just CV events), and provides separate charts for lower- and higherrisk areas across European countries. Using the SCORE approach (44), global CV risk can be stratified into four broad categories (low, moderate, high and very high) and is expressed as the absolute risk of having a CV event within 10 years. In a large cohort of Italian hypertensive patients (n = 37,813), global CV risk stratification according to 2003 ESH/ESC guidelines (24) revealed that almost twothirds of patients were considered to be at moderate (33.9%) or high risk (30.2%) with a smaller proportion of patients at low (23.2%) or very high added risk (12.7%) (23).

Hypertension: a glimpse on current cardiologist's perspective

A recent 2007 internet survey provides important insights into the clinical habits, priorities, perceptions and knowledge of Italian cardiologists with regard to hypertension and stroke prevention (G. Tocci, S. Sciarretta, F. Giovannelli, A. Ferrucci, G.B. Zito, M. Volpe, Cardiology, II Faculty of Medicine, University of Rome "La Sapienza", Sant'Andrea Hospital; Associazioni Regionali Cardiologi Ambulatoriali, Rome; IRCCS Neuromed - Pozzilli (IS), Italy, Italian Cardiologist Survey, manuscript submitted). The survey interviewed via e-mail 900 Italian cardiologists operating in outpatient clinics in April-May 2007, of which, total of 203 cardiologists (22.5% of the sample) gave complete responses to the survey questionnaire. The interviews were co-ordinated through Regional Association of Outpatient Cardiologists (Associazioni Regionali Cardiologi Ambulatoriali, the largest Italian organisation of cardiologists operating in outpatient clinics) and involved anonymous responses to a total of 15 questions on four major areas of the clinical practice of hypertension and stroke prevention: (i) to estimate the prevalence of hypertension and perceived BP control; (ii) to achieve information on the perceived global CV risk

profile; (iii) to evaluate the extent to which hypertension-related organ damage is searched and influences the diagnostic and therapeutic strategies; (iv) to evaluate whether prevention of specific complications of high BP levels are considered of relevance for the choice of antihypertensive therapy.

According to the information provided by the Italian cardiologists surveyed, arterial hypertension was detected in the vast majority of their patients followed in outpatient clinics, most of which were considered to be at high or very high risk of CV events according to the criteria of the 2003 ESH/ESC guidelines (24). The most prevalent CV risk factor in hypertensive patients was obesity (50.9%), followed by hypercholesterolaemia (25.1%), diabetes mellitus (13.5%) and smoking (10.4%). In addition, twothirds (61%) of cardiologists said that more than 20% of their patients had evidence of organ damage, and that more than half of them said that a percentage ranging from 5% to 15% had AF.

Despite the evidence that cardiologists were managing patients at overall high risk for CV events and, thus, needed to have their BP reduced to low levels [e.g. BP levels < 130/80 mmHg advocated by the 2007 ESH/ESC guidelines (15)], surprisingly a small proportion of cardiologists reported using combination antihypertensive regimens (34% used combination therapy as first-line strategy in 20-40% of hypertensive patients), with a clear preference in those antihypertensive drug classes that counteract the renin-angiotensin system (G. Tocci, S. Sciarretta, F. Giovannelli, A. Ferrucci, G.B. Zito, M. Volpe, Cardiology, II Faculty of Medicine, University of Rome "La Sapienza", Sant'Andrea Hospital; Associazioni Regionali Cardiologi Ambulatoriali, Rome; IRCCS Neuromed - Pozzilli (IS), Italy, Italian Cardiologist Survey, manuscript submitted). According to this perception, the most important major CV event that cardiologists wished to prevent by lowering BP levels was stroke (50.5%), followed by MI (20.1%), HF (17.9%) and renal disease (11.5%). Collectively, these findings indicate a marked discrepancy between cardiologists' appreciation of their patients risk status and the measures taken to reduce that risk, and highlight the need for integrated identification and management of risks factors contributing to CV risk.

Modern therapeutic options to optimally manage the hypertensive patient

Nowadays, treatment decisions with respect to the type of antihypertensive drug, the threshold and target for BP treatment, and use of single or combination therapies should be based on the assessment of global CV risk and the global risk reduction goal (rather than on the baseline value of an individual risk factor or particular BP level) (16,17). In other words, global risk should play a central role in arriving at decisions regarding whom to treat, when to treat, how to treat and how much (that is to what target level) to treat (16,17).

Antihypertensive therapy therefore represents at the same time a key priority, but also only one of effective strategies able to reduce global risk (45-47). Thus, other risk-reducing options should also be considered and integrated, including smoking cessation, lifestyle changes, low-dose aspirin and lipidlowering therapies (48). In this view, prioritising treatment for an individual patient with multiple risk factors, organ damage and concomitant CV diseases is challenging (11). However, several factors may be useful in this regard, including nature, immediacy and magnitude of expected benefits and likelihood of compliance for physicians, availability, feasibility and costs of treatment options for physicians, competing risks from various conditions, expected interactions with other concomitant treatments, and patient and healthcare provider preferences and values.

Appropriately, targeted and 'tailored' antihypertensive therapy does represent one of the most effective methods for CV disease prevention and health maintenance, and, as such, demands a substantial commitment of healthcare resources. In light of the enormous global burden of hypertension (49), it is perhaps appropriate to consider using hypertension as a gateway to subsequent integrated measures aimed at substantially and persistently reducing global CV risk (50–52).

Five major classes of antihypertensive drug are currently available and likewise recommended for the clinical management of hypertension, including angiotensin II receptor blockers (ARBs), angiotensinconverting enzyme (ACE) inhibitors, diuretics, calcium channel blockers (CCBs) and beta-blockers (BBs), all of which can be used either as monotherapy or, more frequently, as combination therapy with two or more agents of different pharmacological classes (15). As suggested by the ESH/ESC guidelines (15) and summarised in Figure 1, the decision to choose monotherapy or combination therapy as the initial treatment for the strategy required to get BP goals should be based on the degree of elevation of BP, the global CV risk profile, and the recommended BP target for any particular patient. According to these recommendations (15), combination therapy with a two-drug combination at low doses should be reserved for high-risk patients, such as those with markedly elevated BP or with mildly elevated BP with multiple concomitant risk factors, organ

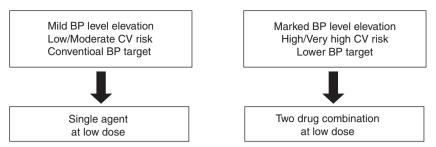


Figure 1 Choosing monotherapy or combination therapy according to degree of blood pressure elevation, CV risk and blood pressure target as a first step of antihypertensive strategy. Adapted from Ref. (15)

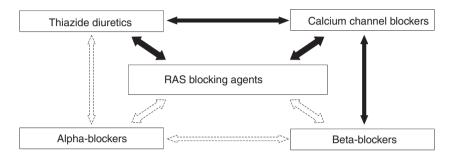


Figure 2 Possible combinations between some classes of antihypertensive drugs. In this schematic representation, the central role of renin–angiotensin system (RAS) blocking agents, mostly including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, is highlighted. Those combinations proven to be beneficial in controlled intervention trials in hypertensive population are represented as thick arrows. The dashed arrows indicate combinations currently not recommended for hypertension management. Adapted from Ref. (15)

damage, diabetes, renal or CV disease. Figure 2 shows possible preferred combinations among some classes of antihypertensive drugs in the general hypertensive population, according to ESH/ESC guidelines (15). Such an approach has demonstrated favourable effects in terms of better BP control, organ protection and long-term clinical outcome, but it may also impact patient's compliance to long-life antihypertensive regimen (53–60).

The question then becomes: which combination therapy should be selected? A wide variety of possible combinations of between classes of antihypertensive drugs are available (15), the most common of which include low-dose thiazide diuretic plus ACE inhibitor, ARB, BB or CCB, and other based on CCB plus ACE inhibitor or ARB, and CCB plus BB. As a general guiding principle, combinations of agents from different antihypertensive classes should be based on three important factors: complementary mechanisms of action, evidence of additive BP-lowering effects and a favourable tolerability profile (50-52). In addition, fixed-dose combinations may provide an evident additional benefit as to simplify treatment and improve patient compliance and persistence with therapy (50-52).

Evidence of outcome or strategy benefit of one therapy over another is still poor for antihypertensive agents, and the outcome benefits of most antihypertensive agents are what can be predicted from reductions in risk from BP changes per se (45-47). Although some clinical trials on hypertension, including Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (53), Anglo-Scandinavian Cardiac Outcomes Trial (54), Study on Cognition and Prognosis in the Elderly (55), Nordic Diltiazem study (56), Valsartan Antihypertensive Long-term Use Evaluation (57), Controlled Onset Verapamil Investigation of Cardiovascular End Points (58) and International Verapamil-Trandolapril Study (59) demonstrated treatment-related benefits for several specific outcomes, the superiority of one treatment modality is absent in the setting of equivalent BP control between study groups. In hypertensive patients with LVH, however, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study showed that for the same reduction in BP achieved by an atenolol-based regimen, a losartan-based regimen resulted in a further 25% decrease in the risk of stroke as well as risk of new onset diabetes (60). Of particular note, the antihypertensive strategy most frequently adopted was losartan 100 mg plus hydrochlorothiazide (HCTZ) 12.5 mg and approximately 56% of patients received at least one dose of the combination of losartan 100 mg plus HCTZ 12.5 mg at some time during the study (61). A number of subanalyses of LIFE have also shown that, compared with an atenolol-based regimen, an antihypertensive therapy based on losartan has favourable effects in terms of organ damage protection and CV risk factor correction, as manifested by differential beneficial changes in MAU, LVH, left atrial diameter, AF, brain natriuretic peptide, vascular structure, serum uric acid, new-onset diabetes and lipid metabolism (62–72). Similarly, in patients with diabetes and renal insufficiency, ARBs resulted in greater benefits in improving MAU and slowing progression to end-stage renal disease (ESRD) than comparator drugs (73–77).

In summary, although evidence of superiority is lacking for most agents, some antihypertensive treatments (either as monotherapy or as combination therapy) are preferred to others in specific clinical settings, as expounded in the 2007 ESH/ESC guidelines (15). These preferred therapies are recommended on the basis of favourable clinical trial evidence of a given class in particular patients, beneficial effects on subclinical organ damage, renal disease, or diabetes, side effect profile, and potential interactions with drugs used to treat concomitant diseases (15). Ultimately, decisions on selecting an antihypertensive regimen should be based on evidence-based medicine combined with good clinical practice and personal experience of physicians (16, 17).

Lowering blood pressure as part of global risk management in patients seen in cardiology practice

As a general guiding principle, the overall management strategy for any patient at risk of CV disease is to improve their global risk status by identifying all modifiable components and then initiating an effective therapeutic strategy (which may include metabolic status control, antihypertensive, lipid-lowering or anti-platelet therapies) to reduce CV risk (15). In this context, it is important to highlight the importance of addressing modifiable risk factors early before patients become severely compromised or experience a clinical event (27).

The basic elements of good treatment for hypertension, regardless of the disease setting, should take into account several key aims (78): (i) to decrease the CV risk associated with elevated BP levels; (ii) to decrease the risk from coexisting CV risk factors; (iii) to improve quality of life and encourage a healthy lifestyle (e.g. especially smoking cessation); (iv) to choose therapeutic agents likely to do more good than harm in the context of each patient's social circumstances, preferences, coexisting medical conditions, and risk factors; (v) to minimise the adverse effects and inconveniences from prescribing such therapies.

Several basic non-pharmacologic means to lower BP (as well as to improve the efficacy of pharmaco-

Blood pressure (mmHg)					
Other risk factors,	Normal	High normal	Grade 1 HT	Grade 2 HT	Grade 3 HT
OD	SBP 120-129	SBP 130-139	SBP 140-159	SBP 160-179	SBP≥180
or Disease	or DBP 80-84	or DBP 85-89	or DBP 90-99	or DBP 100-109	or DBP≥110
No other risk factors	Average	Average) di olu	Moderate	High
	risk	risk	added risk	added risk	added risk
1-2 risk factors	Low	Low	3 toderate	Me 2 ate	Very high
	added risk	added risk	adustrisk	adc 1 risk	added risk
3 or more risk factors,	Moderate	High	High	High	Very high
MS, OD or Diabetes	added risk	added risk	added risk	added risk	added risk
Established CV	Very high	Very high	Very high	Very high	Very high
or renal disease	added risk	added risk	added risk	added risk	added risk

Figure 3 How to achieve cardiovascular (CV) risk reduction in hypertension. The dashed line indicates how definition of hypertension may be variable, depending on the level of total CV risk. Arrows indicate different strategies to achieve significant CV risk reduction in hypertensive patients: example strategy num. (1) Blood pressure reduction; example strategy num. (2) Intervention on associated risk factors, organ damage or diabetes mellitus; example strategy num. (3) Combination of the two strategies. SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, cardiovascular; HT, hypertension; OD, subclinical organ damage, MS, metabolic syndrome. Low, moderate, high or very high risk refer to 10-year risk of a CV fatal or non-fatal event. The term added indicates that in all categories risk is greater than average. Adapted from Ref. (15)

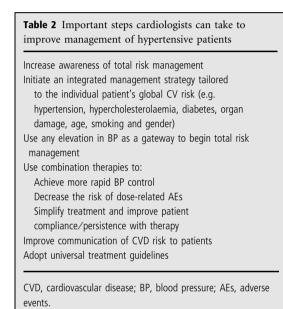
logic BP-lowering therapy), including weight reduction, adoption of the dietary approaches to stop hypertension (DASH) diet, dietary sodium restriction, physical activity and moderation of alcohol consumption, can be useful and effective management tools and should not be neglected (79). Nevertheless, hypertensive patients with organ damage, known CV or other coexisting diseases, such as those with LVH, AF, diabetes, postmyocardial infarction, HF or nephropathy, are at particularly high risk of future clinical events and need intensive management of their hypertension and other concomitant risk factors (27).

As noted earlier, for these types of patients, the threshold to initiate BP management as well as the target BP values should be determined for individual patients based on their absolute level of CV risk. In this latter regard, it should be also note that not all antihypertensive drug treatments are equal and not all BP-lowering effect will reduce CV events; in fact, several evidence are available demonstrating that, even if BP levels are lowered, antihypertensive therapy based on BBs do not reduce CV events, when used as firstline therapy for hypertension management (80), and it is no longer recommended by National Institute for Clinical Excellence (NICE) guidelines (81).

Finally, when therapeutic goal is based on global CV risk reduction rather than on BP levels alone, two strategies can be effectively adopted, as illustrated in Figure 3, which is based on risk stratification algorithm proposed by 2007 ESH/ESC guidelines (15). In this view, a larger use of combination therapy, especially fixed combination based on a single daily administration, may provide a significant

Managing hypertension in cardiology practice

step forward in the direction of a better BP control. The ESH/ESC hypertension guidelines (15), in fact, encourage this type of approach as the initial therapy in patients at high or very high risk. This recommendation is based on the results of international, randomised, controlled clinical trials, that have consistently demonstrated that fixed-dose combination therapies with different classes of antihypertensive agents are often required in the clinical management of hypertensive patients, to achieve effective BP control (53– 60,82) or significant global CV risk reduction (83), and on recent meta-analysis demonstrating that



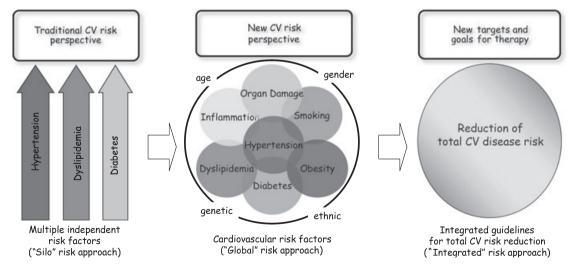


Figure 4 Change in management of cardiovascular disease (CVD) from the traditional approach of managing multiple independent risk factors ('silos' approach) to a new paradigm of integrated identification and the management of all risk factors contributing to CVD risk (global approach). Reproduced from Volpe et al. (50)

fixed-dose combinations significantly improve medication compliance in hypertensive population (84).

Conclusions

All physicians, but especially cardiologists who play a central leadership role in managing hypertensive patients, should consider moving away from the traditional CV disease management approach in which multiple independent risk factors are individually managed in a 'siloed' approach (Figure 4) (50). Instead, they should recognise and embrace the importance of integrated identification of all risk factors (e.g. hypertension, hypercholesterolaemia, diabetes, organ damage, age, smoking and sex) and initiate a management strategy tailored to the individual patient's global CV risk (50). As part of this paradigm shift in CVD prevention strategy, cardiologists can take several key steps (Table 2), including increasing the awareness of total risk management, using any elevation in BP as a gateway to begin total risk management, and utilising combination therapies (particularly fixed-dose combinations) to achieve more rapid BP control. As clearly stated in the most recent international guidelines on hypertension (15), therapeutic strategy aimed at lowering BP levels still represents today the key priority for treatment of hypertension and prevention of CV and renal consequences, even in patients with mild elevation in BP levels, but with risk factors.

Acknowledgements

Writing assistance for this paper was provided by Jan S. Redfern PhD, Goshen NY and funding was provided by Merck & Co., Inc., Whitehouse Station, NJ 08889.

References

- Lawes CM, Vander HS, Law MR et al. Blood pressure and the global burden of disease 2000. Part 1: estimates of blood pressure levels. J Hypertens 2006; 24: 413–22.
- 2 Lawes CM, Vander HS, Law MR et al. Blood pressure and the global burden of disease 2000. Part II: estimates of attributable burden. *J Hypertens* 2006; **24**: 423–30.
- 3 Kearney PM, Whelton M, Reynolds K et al. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; 365: 217–23.
- 4 Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA 1996; 275: 1571–6.
- 5 Ezzati M, Lopez AD, Rodgers A et al. Selected major risk factors and global and regional burden of disease. *Lancet* 2002; 360: 1347–60.
- 6 Franco OH, Peeters A, Bonneux L et al. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women: life course analysis. *Hypertension* 2005; **46**: 280–6.
- 7 Wolf-Maier K, Copper RS, Banegas JR et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* 2003; **289**: 2363–9.

- 8 Boersma E, Keil U, De Bacquer D et al. for the EUROASPIRE I and II Study Groups. Blood pressure is insufficiently controlled in European patients with established coronary heart disease. J Hypertens 2003; 21: 1831–40.
- 9 Lim SS, Gaziano TA, Gakidou E et al. Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs. *Lancet* 2007; 370: 2054–62.
- 10 Mancia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. J Hypertens 2002; 20: 1461–4.
- 11 Ruilope LM, Volpe M. The case for blood pressure control in risk groups. Int J Clin Pract 2004; 58: 844–9.
- 12 Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. Am J Hypertens 2000; 13: 3S-10S.
- 13 Mancia G, Ambrosioni E, Rosei EA et al. for the ForLife study group. Blood pressure control and risk of stroke in untreated and treated hypertensive patients screened from clinical practice: results of the ForLife study. J Hypertens 2005; 23: 1575–81.
- 14 Volpe M. Microalbuminuria screening in patients with hypertension: recommendations for clinical practice. *Int J Clin Pract* 2008; 62: 97–108.
- 15 Mancia G, De Backer G, Dominiczak A et al. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25: 1105–87.
- 16 Alderman MH, Furberg CD, Kostis JB et al. Hypertension guidelines: criteria that might make them more clinically useful. Am J Hypertens 2002; 15: 917–23.
- 17 Volpe M, Alderman MH, Furberg CD et al. Beyond hypertension toward guidelines for cardiovascular risk reduction. *Am J Hypertens* 2004; **17**: 1068–74.
- 18 Bramlage P, Thoenes M, Kirch W et al. Clinical practice and recent recommendations in hypertension management – reporting a gap in a global survey of 1259 primary care physicians in 17 countries. *Curr Med Res Opin* 2007; 23: 783–91.
- 19 Llisterri Caro JL, Rodriguez Roca GC, Alonso Moreno FJ et al. Blood pressure control in Spanish hypertensive patients in Primary Health Care Centres. PRESCAP 2002 Study. *Med Clin (Barc)* 2004; 122: 165–71.
- 20 Amar J, Vaur L, Perret M et al. Arterial hypertension management in general practice in France according to global risk factors. Arch Mal Coeur Vaiss 2001; 94: 843–5.
- 21 Oriol-Zerbe C, Abholz HH. Primary prevention of cardiovascular diseases by lipid-lowering treatment in German general practice: results from GPs ignoring guidelines and risk calculators. *Eur J Gen Pract* 2007; **13**: 27–34.
- 22 Hobbs FD, Erhardt L. Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in five European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey. *Fam Pract* 2002; **19**: 596–604.
- 23 Volpe M, Tocci G, Trimarco B et al. Blood pressure control in Italy: results of recent surveys on hypertension. J Hypertens 2007; 25: 1491–8.
- 24 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for the management of arterial hypertension. J Hypertension 2003; 21: 1011–53.
- 25 Backlund L, Bring J, Strender LE. How accurately do general practitioners and students estimate coronary risk in hypercholesterolaemic patients? *Prim Health Care Res Devel* 2004; 5: 145–52.
- 26 Volpe M, Dedhiya SD. Physicians, patients, and public knowledge and perception regarding hypertension and stroke: a review of survey studies. *Curr Med Res Opin* 2006; 22: 1319–30.
- 27 Volpe M, Tocci G, Pagannone E. Less mega-trials and more clinically oriented studies in hypertension research? The case of blocking Renin–Angiotensin–Aldosterone System J Am Soc Nephrol 2006; 17: S36–43.
- 28 Volpe M, Tocci G. Antihypertensive therapy and cerebrovascular protection. Curr Opin Nephrol Hypertens 2006; 15: 498–504.

- 29 Volpe M. Evidence-based indications in hypertensive patients: helping doctors in the initial choice. *High Blood Press Cardiovasc Prev* 2004; **11**: 1–7.
- 30 Joint National Committee on Prevention. Detection, Evaluation and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC VI report. Arch Intern Med 1997; 157: 2413–45.
- 31 Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the second report of the National Cholesterol Education Program (NCEP) (Adult Treatment Panel II). JAMA 1993; 269: 3015–23.
- 32 World Health Organization (WHO)/International Society of Hypertension (ISH) guidelines for the management of hypertension. J Hypertens 1999; 17: 151–83.
- 33 Lewington S, Clarke R, Qizilbash N et al. for the Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–13.
- 34 Tocci G, Sciarretta S, Volpe M. Heart failure development in recent hypertension trials. J Hypertens 2008; 26: 1477–86.
- 35 Multiple Risk Factor Intervention Trial Research Group. Relationship between baseline risk factors and coronary heart disease and total mortality in the Multiple Risk Factor Intervention Trial. *Prev Med* 1986; 15: 254–73.
- 36 Martiniuk AL, Lee CM, Lawes CM et al. for the Asia-Pacific Cohort Studies Collaboration. Hypertension: its prevalence and population-attributable fraction for mortality from cardiovascular disease in the Asia-Pacific region. J Hypertens 2007; 25: 73–9.
- 37 Yusuf S, Hawken S, Ounpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. *Lancet* 2004; 364: 937–52.
- 38 Wolf PA, D'Agostino RB, Belanger AJ et al. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991; 22: 312– 8.
- 39 Tunstall-Pedoe H. The Dundee coronary risk-disk for management of change in risk factors. *BMJ* 1991; **303**: 744–7.
- 40 Voss R, Cullen P, Schulte H et al. Prediction of risk of coronary events in middle-aged men in the Prospective Cardiovascular Munster Study (PROCAM) using neural networks. *Int J Epidemiol* 2002; **31**: 1253–62.
- 41 Haq IU, Ramsay LE, Yeo WW et al. Is the Framingham risk function valid for northern European populations? A comparison of methods for estimating absolute coronary risk in high risk men. *Heart* 1999; 81: 40–6.
- 42 Menotti A, Puddu PE, Lanti M. Comparison of the Framingham risk function-based coronary chart with risk function from an Italian population study. *Eur Heart J* 2000; 21: 365–70.
- 43 Thomsen TF, McGee D, Davidsen M et al. A cross-validation of risk-scores for coronary heart disease mortality based on data from the Glostrup Population Studies and Framingham Heart Study. Int J Epidemiol 2002; 31: 817–22.
- 44 Conroy RM, Pyorala K, Fitzgerald AP et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003; **24**: 987–1003.
- 45 Blood Pressure Lowering Treatment Trialists Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; 362: 1527–45.
- 46 Turnbull F, Neal B, Algert C et al. Effects of different blood pressure lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus. *Arch Intern Med* 2005; 165: 1410–9.
- 47 Blood Pressure Lowering Treatment Trialists' Collaboration, Turnbull F, Neal B et al. Blood pressure-dependent and independent effects of agents that inhibit the renin–angiotensin system. J Hypertens 2007; 25: 951–8.

- 48 Pignone M, Mulrow CD. Evidence based management of hypertension: using cardiovascular risk profiles to individualise hypertensive treatment. *BMJ* 2001; **322**: 1164–6.
- 49 Hypertension: uncontrolled and conquering the world. Lancet 2007; 370: 539.
- 50 Volpe M, Erhardt LR, Williams B. Managing cardiovascular risk: the need for change. J Hum Hypertens 2008; 22: 154–7.
- 51 Tocci G, Sciarretta S, Facciolo C, Volpe M. Antihypertensive strategy based on angiotensin II receptor blockers: a new gateway to reduce risk in hypertension. *Expert Rev Cardiovasc Ther* 2007; 5: 767–76.
- 52 Ruilope LM, Rosei EA, Bakris GL et al. Angiotensin receptor blockers: therapeutic targets and cardiovascular protection. *Blood Press* 2005; 14: 196–209.
- 53 ALLHAT Officiers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALL-HAT). JAMA 2002; 288: 2981–97.
- 54 Dahlof B, Sever PS, Poulter NR et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**: 895–906.
- 55 Lithell H, Hansson L, Skoog I et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 2003; 21: 875–86.
- 56 Hansson L, Hedner T, Lund-Johansen P et al. Randomised trial of effects of calcium antagonists compared with diuretics and betablockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000; 356: 359–65.
- 57 Julius S, Kjeldsen SE, Weber M et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. *Lancet* 2004; **363**: 2022–31.
- 58 Black HR, Elliott WJ, Grandits G et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA 2003; 289: 2073–82.
- 59 Pepine CJ, Handberg EM, Cooper-DeHoff RM et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 2003; 290: 2805–16.
- 60 Dahlof B, Devereux RB, Kjeldsen SE et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995–1003.
- 61 Devereux RB, Dahlof B. Potential mechanisms of stroke benefit favoring losartan in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. *Curr Med Res Opin* 2007; 23: 443–57.
- 62 Devereux R, de Faire U, Fyhrquist F et al. Blood pressure reduction and antihypertensive medication use in the losartan intervention for endpoint reduction in hypertension (LIFE) study in patients with hypertension and left ventricular hypertrophy. *Curr Med Res Opin* 2007; **23**: 259–70.
- 63 Okin PM, Devereux RB, Jern S et al. Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: The Losartan Intervention for Endpoint reduction in Hypertension (LIFE) Study. *Circulation* 2003; **108**: 684–90.
- 64 Ibsen H, Wachtell K, Olsen MH et al. Does albuminuria predict cardiovascular outcome on treatment with losartan versus atenolol in hypertension with left ventricular hypertrophy? A LIFE substudy. J Hypertens 2004; 22: 1805–11.
- 65 Hoieggen A, Alderman MH, Kjeldsen SE et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int* 2004; **65**: 1041–9.

- 66 Gerdts E, Oikarinen L, Palmieri V et al. for the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. Correlates of left atrial size in hypertensive patients with left ventricular hypertrophy: the Losartan Intervention For Endpoint reduction in hypertension (LIFE) Study. *Hypertension* 2002; **39**: 739–43.
- 67 Wachtell K, Hornestram B, Lehto M et al. Cardiovascular mortality and morbidity in hypertensive patients with atrial fibrillation: the LIFE study. J Am Coll Cardiol 2005; **45**: 705–11.
- 68 Wachtell K, Lehto M, Hornestram B et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention for Endpoint reduction (LIFE) study. J Am Coll Cardiol 2005; 45: 712–9.
- 69 Olsen MH, Wachtell K, Tuxen C et al. Opposite effects of losartan and atenolol on natriuretic peptides in patients with hypertension and left ventricular hypertrophy: a LIFE substudy. J Hypertens 2005; 23: 1083–90.
- 70 Lindholm LH, Ibsen H, Borch-Johnsen K et al. Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. J Hypertens 2002; 20: 1879–86.
- 71 Olsen ME, Wachtell K, Beevers G et al. Losartan has positive effects on lipid metabolism compared to atenolol in patients with hypertension and electrocardiographic left ventricular hypertrophy. The LIFE study [abstract]. *J Am Coll Cardiol* 2005; **45 (Suppl A)**: 423A.
- 72 Olsen MH, Wachtell K, Neland K et al. Losartan but not atenolol reduce carotid artery hypertrophy in essential hypertension. A LIFE substudy. *Blood Press* 2005; 14: 177–83.
- 73 Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressureindependent effect. *Circulation* 2002; **106**: 672–8.
- 74 Parving HH, Lehnert H, Brochner-Mortensen J et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; **345**: 870–8.

- 75 Lewis E, Hunsicker L, Clarke W et al. Renoprotective effect of the angiotensin-receptor antagonist Irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; 345: 851– 60.
- 76 Lindholm LH, Ibsen H, Dahlof B et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 1004–10.
- 77 Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; 345: 861–9.
- 78 Mulrow CD, Pignone M. What are the elements of good treatment for hypertension? BMJ 2001; 322: 1107–9.
- 79 Israili ZH, Hernandez-Hernandez R, Valasco M. The future of antihypertensive treatment. Am J Ther 2007; 14: 121–34.
- 80 Bangalore S et al. Cardiovascular protection using beta-blockers: a critical review of the evidence. J Am Coll Cardiol 2007; 50: 563–72.
- 81 Williams B, Poulter NR, Brown MJ et al. for the British Hypertension Society (BHS) Guidelines. Guidelines of management of hypertension: report of the fourth working party on British Hypertension Society BHS IV. J Hum Hypertens 2004; 18: 139–85.
- 82 The Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial: a hypertensive population at high cardiovascular risk. Preliminary results presented at ACC '08 Meeting, Chicago, IL, 31 March 2008.
- 83 Gaede P, Lund-Andersen H, Parving HH et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008; **358**: 580–91.
- 84 Bangalore S, Kamalakkannan G, Parkar S et al. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med 2007; 120: 713–9.

Paper received March 2008, accepted May 2008