Journal of Human Hypertension (2006) 20, 913–916
© 2006 Nature Publishing Group All rights reserved 0950-9240/06 $30.00
www.nature.com/jhh

COMMENTARY

Towards improving the clinical assessment and management of human hypertension: an overview from this Journal

P Kakar and GYH Lip
University Department of Medicine, City Hospital, Birmingham, UK

Journal of Human Hypertension (2006) **20,** 913–916 doi:10.1038/sj.jhh.1002083; published online 24 August 2006

Hypertension is a growing global problem and is responsible for considerable morbidity and mortality. Newer insights into the diagnosis and treatment have heralded a new chapter and instilled a fresh lease of life into the overall management of this ubiquitous condition. Despite this, recent studies have still shown a poor rate of detection, treatment and – more importantly – control to target blood pressure (BP) levels.[1] It is possible that some of these patients have white coat hypertension and are unnecessarily treated, and improvements in our diagnostic algorithms for this condition may be needed.[2] Nonetheless, our efforts may not be successful, if patients do not appreciate hypertension as a disease entity and are unaware of their BP targets, with knowledge particularly poor among female patients, the elderly, those without any college education or without a documented history of hypertension and those with known diabetes.[3]

Perhaps we are chasing a moving target. We no longer advise to just target 'cutoff' levels to treat BP – after all, hypertension is not a 'yes/no' phenomenon, but a graded continuous relation between stroke and coronary risk – but take a more holistic approach to cardiovascular risk assessment, and management.[4] The implications of risk scoring, by changing from coronary heart disease (CHD) to cardiovascular disease (CVD) risk-based guidelines in different ethnic groups has recently been studied,[5] culminating with the publication of a re-calibrated Framingham risk score to produce a web-based tool for estimating the 10-year risk of CHD and CVD in British UK black and minority ethnic groups.[6] This pragmatic web-based risk calculator (ETHRISK, available at http://www.epi.bris.ac.uk/CVDethrisk/) allows 10-year risks to be estimated in routine primary care settings, for relevant risk factor and ethnic group combinations.

For the sake of uniformity, hypertension management guidelines have been formulated for the benefit of all and sundry. The 2004 British Hypertension Society (BHS) published guidelines[7] were an able effort, and provided recommendations on lifestyle modification, BP drug treatments (based on the AB/CD algorithm) and target BP levels for both diabetics and non-diabetics, as well as aspirin and statin usage.

Following BHS-IV, newer evidence has come forth, with significant changes in our approach to hypertension, necessitating revision of the AB/CD algorithm, given the recent trial evidence – such as that from LIFE (Losartan Intervention For End Point reduction in hypertension study)[8] and Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA).[9] The AB/CD treatment algorithm is now superseded by the new A/CD algorithm (Figure 1), as recommended in the joint National Institute of Health and Clinical Excellence (NICE) and BHS guidelines (issued on 28 June 2006, available at http://www.nice.org.uk/page.aspx?o=CG34). In the recent head-to-head clinical trials, beta-blockers were less effective than comparator drugs at reducing major cardiovascular events, particularly stroke. Beta-blockers were also less effective than an angiotensin-converting enzyme (ACE) inhibitor or a calcium channel blocker at reducing new onset diabetes. Thus, beta-blockers are not ideal as first-line monotherapy in uncomplicated essential hypertension and should only be used in the presence of associated heart disease, for example, atrial fibrillation, left ventricular systolic dysfunction and angina, etc. Calcium-channel blockers or thiazide-type diuretics were still considered to be the most likely drugs to confer benefit as first-line agents for most patients aged 55 years or older. In people younger than 55 years, initial therapy with an ACE inhibitor (or angiotensin

Correspondence: Professor GYH Lip, University Department of Medicine, City Hospital, Birmingham B18 7QH, UK.
E-mail: g.y.h.lip@bham.ac.uk
Published online 24 August 2006

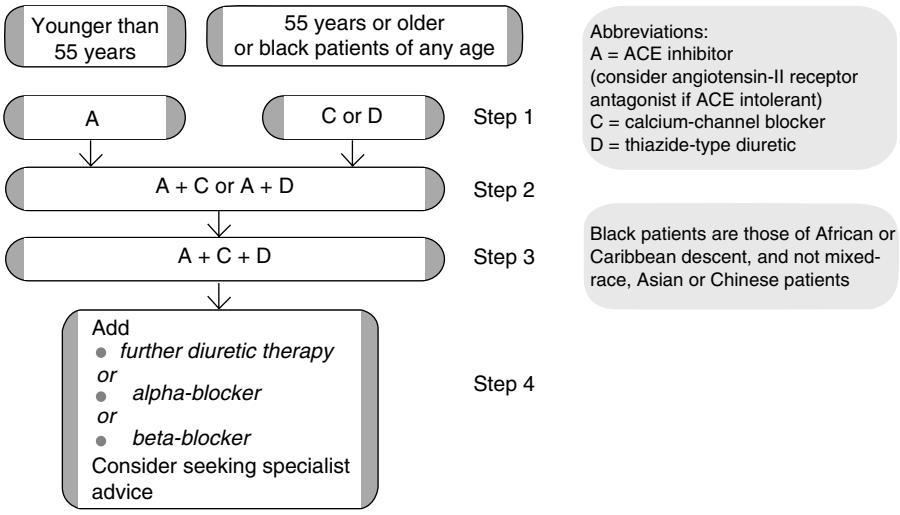

Figure 1 Choosing drugs for patients newly diagnosed with hypertension: the BHS/NICE algorithms (see text for website).

receptor blocker (ARB)) was considered better than initial therapy with a calcium-channel blocker or a thiazide-type diuretic. When using more than one drug, adding an ACE inhibitor to a calcium-channel blocker or a diuretic (or vice versa) was recommended as a logical combination, as commonly done in clinical trials.

The many substudies from large clinical trials, such as the LIFE trial.[8] have also demonstrated a greater reduction in hypertensive target organ damage with losartan compared to atenolol, for example, left ventricular hypertrophy (LVH) regression[10] and reduction of microalbuminuria.[11] Perhaps more focus is needed on these surrogate end points, given the close relationship of some indices of target organ damage (e.g. LVH[12]) to complications of hypertension, such as heart failure[13] and atrial fibrillation.[14] What is very clear is that the renin–angiotensin–aldosterone system (RAAS) is the obvious therapeutic target in our management of these common conditions.

Other evidence of target organ damage (or similar surrogate indices) may provide useful guidance to our management of hypertensive patients. Indeed, 24 h ambulatory BP measurement is a useful assessment of 'BP load' and has been related to cardiovascular outcomes.[15] Also, many patients with essential hypertension have geometrical changes in their left ventricular dimensions as well as structural changes in their carotid arteries, in keeping with a more 'generalized' concept of target organ damage in hypertension, where present. For example, the Assessment Prognostic Risk Observational Survey (APROS) study verified significant association between carotid wall thickening and LVH, with increased prevalence in the elderly with isolated systolic hypertension and in patients with metabolic risk factors.[16] Among the available methods for assessing carotid intima-media thickness (IMT), the Max-IMT appears to be the best parameter for predicting hypertensive target organ damage, including microangiopathy.[17] More subtle changes in cardiac function (especially in diastolic function) can reflect early hypertensive heart disease, and sensitive techniques such as tissue Doppler imaging in patients with essential hypertension may help.[18,19]

Another surrogate index of hypertensive target organ damage may be central artery (aortic) stiffness. The latter is thought to be an independent predictor of hypertension in non-hypertensive subjects, and the Conduit Artery Function Evaluation (CAFE) study found that antihypertensive drugs can have substantially different effects on central aortic pressures and haemodynamic despite a similar impact on brachial BPs.[20] Interestingly, central aortic pulse pressure may be a determinant of clinical outcomes, and Williams *et al*.[20] even suggest that the differences in central aortic pressures may be a potential mechanism to explain the different clinical outcomes between the two treatment arms in ASCOT-BPLA. As measurement of central artery stiffness may sometimes be difficult, Sugawara *et al*.[21] reported that the brachial-ankle pulse wave velocity index may be an alternative measure of central artery stiffness.

Microalbuminuria is long recognized as a marker for cardiovascular risk and declining kidney function in hypertension. Agents that block the RAAS reduce proteinuria and microalbuminuria, lower BP and slow the progression of proteinuric kidney disease, and the use of ACE inhibitor/ARB combination therapy in hypertensive kidney disease may be one therapeutic option.[22,23] In contrast to microalbuminuria, the role of serum uric acid in the context of adverse cardiovascular events in hypertensive subjects is more controversial. Indeed, Tsioufis *et al*.[24] demonstrate that that serum uric acid levels were linked to high BPs, but there was discrepancy in relation to other indices

of target organ damage, such as LVH and microalbuminuria.

With the attention to target organ damage or surrogates of hypertensive heart disease, we should not neglect ancillary therapeutic strategies, such as statins and antiplatelet therapy. Statins have a track record of cardiovascular protection, and interest has been directed to its possible effect on BP.[25,26] Indeed, contrasting effects have been shown with the (controversial) suggestion by Wierzbicki[25] that statins may reduce BP only provided that low-density lipoprotein cholesterol is reduced by 50% or <2 mmol/l, and that these effects may be better demonstrated in lower risk primary prevention populations where endothelial function is easier to normalize. In one study, for example, statin use by hyperlipidaemic hypertensive patients was associated with a significant reduction in aortic stiffness without any marked effect on BP.[27]

Aspirin therapy in hypertension has always attracted controversy, and a Cochrane systematic review[28] on this topic concluded that for primary prevention in patients with elevated BP, antiplatelet therapy cannot be recommended as the magnitude of benefit, a reduction in myocardial infarction, was negated by a harm of similar magnitude, with an increase in major haemorrhage. For secondary prevention in patients with elevated BP, antiplatelet therapy is recommended because the magnitude of the absolute benefit is many times greater. Perhaps the ancillary benefits of aspirin may be more beneficial, with reported effects on improved endothelial function and (more controversially) even a small BP lowering effect.[29]

The holistic management of hypertension should not neglect non-pharmacological measures. The relationship of BP to macronutrients has been extensively investigated in INTERMAP (the International study of macro-and micronutrients and BP), and the data tables from this study have been summarized in this journal.[30] The Dietary Approaches to Stop Hypertension (DASH) diet, which is low in saturated and total fat, is additive to other multicomponent lifestyle interventions in reducing BP.[32] The reduction of sodium intake to <100 mmol/day further enhances the effects of the DASH diet and has a beneficial effect on systolic BP. Indeed, a moderate increase of calcium and potassium intake in children with salt sensitivity, through interaction with sodium, can promote urinary sodium excretion and may contribute to the prevention of hypertension.[32] The observation that the relation of salt intake and BP may be mediated via endothelial nitric oxide synthase polymorphism and nitric oxide production is an intriguing one, and merits further study on the relationship of salt to endothelial (dys)function in hypertension.[33]

Where are we now in relation to improving the clinical management of human hypertension? As evident from the (selective) overview above, a lot has happened in the last few years, changing from our move to a more holistic approach to cardiovascular risk assessment, and the AB/CD to A/CD change. There is also increasing recognition of the role for lifestyle measures and of the need for drugs such as statins and aspirin for cardiovascular prevention. Some indices of target organ damage and surrogate markers are clearly more useful than others, but how these complement clinical assessment and our management of hypertension merits further study.

References

1 Al-Windi A. Detection and treatment of hypertension in general health-care practice: a patient-based study. *J Hum Hypertens* 2005; **19**(10): 775–786.
2 Stergiou GS, Alamara CV, Skeva II, Mountokalakis TD. Diagnostic value of strategy for the detection of white coat hypertension based on ambulatory and home blood pressure monitoring. *J Hum Hypertens* 2004; **18**(2): 85–89.
3 Cheng S, Lichtman JH, Amatruda JM, Smith GL, Mattera JA, Roumanis SA *et al.* Knowledge of blood pressure levels and targets in patients with coronary artery disease in the USA. *J Hum Hypertens* 2005; **19**(10): 769–774.
4 Jessani S, Watson T, Cappuccio FP, Lip GY. Prevention of cardiovascular disease in clinical practice: The Joint British Societies' (JBS 2) guidelines. *J Hum Hypertens* 2006; **20**(9): 641–645.
5 Gomez GB, Kerry SM, Oakeshott P, Rowlands G, Cappuccio FP. Changing from CHD to CVD risk-based guidelines for the management of mild uncomplicated hypertension in different ethnic groups: implications for primary care. *J Hum Hypertens* 2005; **19**(4): 321–324.
6 Brindle P, May M, Gill PS, Cappuccio F, D'Agostino Snr R, Fischbacher C *et al.* Primary prevention of cardiovascular disease: a web-based risk score for seven British black and minority ethnic groups. *Heart*, 8 June 2006; doi:10:1136/hrt.2006.092346 (E-pub ahead of print).
7 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF *et al.* British Hypertension Society Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; **18**: 139–185.
8 Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, *et al.*, LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**(9311): 995–1003.
9 Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M *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.
10 Okin PM, Devereux RB, Liu JE, Oikarinen L, Jern S, Kjeldsen SE *et al.* Regression of electrocardiographic

left ventricular hypertrophy predicts regression of echocardiographic left ventricular mass: the LIFE study. *J Hum Hypertens* 2004; **18**: 403–409.
11 Olsen MH, Wachtell K, Bella JN, Palmieri V, Gerdts E, Smith G *et al.* Albuminuria predicts cardiovascular events independently of left ventricular mass in hypertension: a LIFE substudy. *J Hum Hypertens* 2004; **18**: 453–459.
12 Nadar S, Beevers DG, Lip GY. Echocardiographic changes in patients with malignant phase hypertension: the West Birmingham Malignant Hypertension Register. *J Hum Hypertens* 2005; **19**(1): 69–75.
13 Kazzam E, Ghurbana BA, Obineche EN, Nicholls MG. Hypertension – still an important cause of heart failure? *Hum Hypertens* 2005; **19**(4): 267–275.
14 Boos CJ, Lip GY. Targeting the renin–angiotensin–aldosterone system in atrial fibrillation: from pathophysiology to clinical trials. *J Hum Hypertens* 2005; **19**(11): 855–859.
15 Elliott HL. 24-h blood pressure control: its relevance to cardiovascular outcomes and the importance of long-acting antihypertensive drugs. *J Hum Hypertens* 2004; **18**: 539–543.
16 Cuspidi C, Mancia G, Ambrosioni E, Pessina A, Trimarco B, Zanchetti A. APROS Investigators Left ventricular and carotid structure in untreated, uncomplicated essential hypertension: results from the Assessment Prognostic Risk Observational Survey (APROS). *J Hum Hypertens* 2004; **18**: 891–896.
17 Takiuchi S, Kamide K, Miwa Y, Tomiyama M, Yoshii M, Matayoshi T *et al.* Diagnostic value of carotid intima-media thickness and plaque score for predicting target organ damage in patients with essential hypertension. *J Hum Hypertens* 2004; **18**: 17–23.
18 Rovner A, de las Fuentes L, Waggoner AD, Memon N, Chohan R, Davila-Roman VG. Characterization of left ventricular diastolic function in hypertension by use of Doppler tissue imaging and color M-mode techniques. *J Am Soc Echocardiogr* 2006; **19**(7): 872–879.
19 Przewlocka-Kosmala M, Kosmala W, Mazurek W. Left ventricular circumferential function in patients with essential hypertension. *J Hum Hypertens* 2006; **20**(9): 666–671.
20 Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D *et al.* CAFE Investigators; Anglo-Scandinavian Cardiac Outcomes Trial Investigators; CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; **113**(9): 1213–1225.
21 Sugawara J, Hayashi K, Yokoi T, Cortez-Cooper MY, DeVan AE, Anton MA *et al.* Brachial-ankle pulse wave velocity: an index of central arterial stiffness? *J Hum Hypertens* 2005; **19**: 401–406.
22 Bakris GL, Ruilope L, Locatelli F, Ptaszynska A, Pieske B, Raz I *et al.* Rationale and design of a study to evaluate management of proteinuria in patients at high risk for vascular events: the IMPROVE trial. *J Hum Hypertens*, 2006; **20**(9): 693–700.
23 Mogensen CE. New concepts in blood pressure-lowering management in diabetic patients: the case for early ACE inhibitor combination therapy with diuretics. *J Hum Hypertens* 2005; **19**(Suppl 1): S15–S20.
24 Tsioufis C, Chatzis D, Vezali E, Dimitriadis K, Antoniadis D, Zervoudaki A. The controversial role of serum uric acid in essential hypertension: relationships with indices of target organ damage. *J Hum Hypertens* 2005; **19**: 211–217.
25 Wierzbicki AS. Statins and hypertension. *J Hum Hypertens* 2006; **20**(8): 551–553.
26 Milionis HJ, Liberopoulos EN, Achimastos A, Elisaf MS, Mikhailidis DP. Statins: another class of antihypertensive agents? *J Hum Hypertens* 2006; **20**: 320–335.
27 Ichihara A, Hayashi M, Koura Y, Tada Y, Kaneshiro Y, Saruta T. Long-term effects of statins on arterial pressure and stiffness of hypertensives. *J Hum Hypertens* 2005; **19**(2): 103–109.
28 Felmeden DC, Lip GY. Antithrombotic therapy in hypertension: a Cochrane Systematic review. *J Hum Hypertens* 2005; **19**(3): 185–196.
29 Magen E, Viskoper JR, Mishal J, Priluk R, London D, Yosefy C. Effects of low-dose aspirin on blood pressure and endothelial function of treated hypertensive hypercholesterolaemic subjects. *Hum Hypertens* 2005; **19**(9): 667–673.
30 Stamler J, Elliott P, Dennis B, Dyer AR, Kesteloot H, Liu K, *et al.*, INTERMAP Research Group. INTERMAP: background, aims, design, methods, and descriptive statistics (nondietary). *J Hum Hypertens* 2003; **17**(9): 591–608.
31 Svetkey LP, Erlinger TP, Vollmer WM, Feldstein A, Cooper LS, Appel LJ *et al.* Effect of lifestyle modifications on blood pressure by race, sex, hypertension status, and age. *J Hum Hypertens* 2005; **19**(1): 21–31.
32 Mu JJ, Liu ZQ, Liu WM, Liang YM, Yang DY, Zhu DJ *et al.* Reduction of blood pressure with calcium and potassium supplementation in bchildren with salt sensitivity: a 2-year double-blinded placebo-controlled trial. *J Hum Hypertens* 2005; **19**(6): 479–483.
33 Hoffmann IS, Tavares-Mordwinkin R, Castejon AM, Alfieri AB, Cubeddu LX. Endothelial nitric oxide synthase polymorphism, nitric oxide production, salt sensitivity and cardiovascular risk factors in Hispanics. *J Hum Hypertens* 2005; **19**(3): 233–240.