HYPERTENSION CARE: IT'S TIME TO ACT

This symposium took place on 30th August 2014 (15.30-17.00), as part of the European Society of Cardiology's Annual International Congress

Chairpersons

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Speakers

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Disclosure: Josep Redòn is a consultant to Daiichi Sankyo and the Menarini group. Anthony Heagerty is a consultant to Daiichi Sankyo and has spoken for Daiichi Sankyo and Menarini. Michel Burnier is a consultant to Daiichi Sankyo and the Menarini group. Luis Ruilope has served as an advisor and speaker to Daiichi Sankyo. Roland Schmieder has received grants for his institution from Daiichi Sankyo and is a member of a speakers' bureau, and advisor to Daiichi Sankyo and the Menarini group. Thomas Weiss has received grants and is an advisor for Daiichi Sankyo, and has received lecture fees from Menarini and Daiichi Sankyo. Massimo Volpe received the Award University of Rome Sapienza from the Italian Ministry of Health; he is a member of a speakers' bureau for Menarini International and Daiichi Sankyo Europe, and a consultant/member of an advisory board for Takeda International, Daiichi Sankyo Europe, Actelion, and Novartis Pharmaceuticals Ltd.
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MEETING SUMMARY

The satellite symposium was held in two separate sessions – the first a traditional symposium format, and the second as an interactive panel discussion in which the faculty answered questions from the delegates. The symposium objectives included consideration of the impact of suboptimal blood pressure (BP) control on the high levels of cardiovascular (CV) events in Europe; evaluation of the importance of patient adherence in improving management of BP; consideration of the management of treatment-resistant patients; discussion of a new initiative to drive improved management of hypertension; and how angiotensin receptor blocker (ARB)-based treatments and single-pill combinations may be used to treat hypertensive patients. Professor Burnier discussed the difficulties associated with achieving good BP control in the primary care setting and highlighted the utility of single-pill fixed-dose combinations (FDCs) for improving adherence and BP normalisation. Professor Ruilope discussed the clinical work-up and management of patients with treatment-resistant hypertension, while Professors Schmieder and Weiss outlined some initiatives taking place that aim to improve BP control rates. Finally, Professor Volpe described an ARB-based treatment platform which shows how patients can be effectively treated with single-pill combination therapy.

PART 1: 'THE SATELLITE SYMPOSIUM' THE EXPERTS TALK!

Opening Remarks from the Chair

Professor Josep Redòn

Professor Redòn emphasised the significance of cardiovascular disease (CVD) as a cause of mortality in Europe. CVD is responsible for more than 4 million deaths each year, almost half of all deaths in Europe.[1] There is also a significant economic impact; CVD is associated with costs of €196 billion per year to the European economy.[1] Despite advances in therapies over the past decades, hypertension has been identified as the leading risk factor for death worldwide.[2] Professor Redòn highlighted the importance of following the available treatment guidelines – current guidelines recommend achieving a BP of <140/90 mmHg for the majority of patients[3] – and emphasised the need to engage the different healthcare providers (HCPs) to achieve the best possible outcomes for patients.

Uncontrolled Hypertension: The Crisis in Patient Care

Professor Michel Burnier

CVD is a very common cause of death, particularly as the population ages.[4] Recommendations for hypertension management have remained mostly stable over the past decade,[5-7] suggesting a goal of <140/90 mmHg for all patients and <130/80 in high-risk patients and patients with diabetes, recent guidance adding that a goal systolic BP (SBP) of 140–150 mmHg in elderly patients, and goal diastolic BP (DBP) of <85 mmHg in diabetic patients, may be achievable.[3] Whilst the rates of BP control have increased in Europe, ranging from 34–51% across countries, there is still a need for further improvement.[8-10] This is discordant with the results seen in clinical trials, in which BP control rates of 60–70% are observed in strictly selected patients.[11,12] The European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines[3] have identified key factors for poor BP control as therapeutic/physician inertia, low treatment adherence, and a deficiency in our healthcare systems in relation to chronic disease.

Communication between patients and HCPs as part of a multidisciplinary approach is important to improve the management of hypertension.[3] A meta-analysis of intervention studies found that when pharmacist care was included either alone, or with other HCPs, greater improvements in BP were achieved.[13] Poor adherence to treatment is a major factor in suboptimal BP control.[14,15] While poor patient adherence is an issue, it is also important for physicians to play an active role in monitoring adherence, although this can prove difficult. 'White coat adherence' is a phenomenon in which patients' adherence improves prior to an appointment with their physician, and may lead to inaccurate insights into a patient's drug exposure. A recent study of adherence to a diuretic medication found that, particularly in male patients, adherence progressively decreased following initiation of treatment; however, it increased substantially prior to their consultation.[16]

Adherence to antihypertensive therapy falls over time; an analysis of patients taking part in Phase IV clinical trials showed that after 1 year adherence was approximately 50% of the baseline level.[17] Patients with high levels of adherence (≥80%) have been found to have significantly better BP control compared with patients with lower adherence, when controlled for age, gender, and comorbidities,[18] thus highlighting the importance of achieving good adherence. Good adherence (≥80%) has also been associated with reduced risk of chronic heart failure,[19] coronary artery disease,[20] and cerebrovascular disease.[21]

Pill burden has a major impact on adherence; patients taking multiple pills have significantly lower adherence compared with patients taking a single pill.[22] This may be an issue for older patients, who often need to take multiple drugs to treat various comorbidities. Patient perception of pill burden is also very important in terms of adherence – it is important that patients feel that the drugs they are taking are beneficial for their health.[23] Single-pill FDCs have been shown to improve adherence, and improve the rates of SBP and DBP normalisation by almost one third compared with the same medications given as a free-drug combination (Figure 1).[24]

In summary, for most patients, the target for BP normalisation is 140/90 mmHg; however, suboptimal BP control is caused by a number of factors including therapeutic/physician inertia, poor adherence, and deficiencies in the healthcare system. FDCs may prove useful in improving adherence and thus achieving superior BP control.

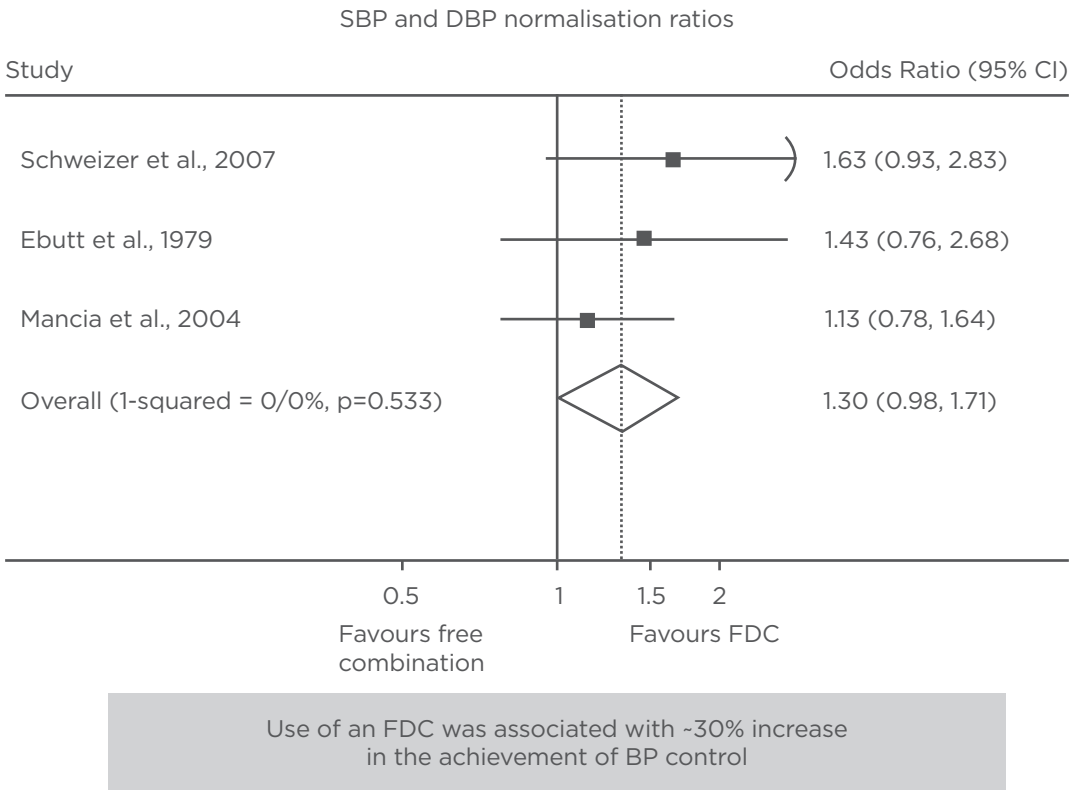

Figure 1: DBP and SBP normalisation ratios with free-drug combination versus FDC.
The use of FDC is associated with improved BP control compared with the equivalent free drug.
CI: confidence interval; BP: blood pressure; DBP: diastolic blood pressure; FDC: fixed-drug combination; SBP: systolic blood pressure.
Adapted from Gupta AK et al.[24]

Increasing Goal Rates by Optimising Clinical Work-Up

Professor Luis M. Ruilope

Hypertension management is a major problem in primary care as it is very common and presents with a wide range of severity, often in conjunction with comorbidities.[25] A recent study has categorised hypertension as 'easy-to-treat' (controlled on ≤3 hypertension medications) or 'difficult-to-treat' (remaining uncontrolled on >3 hypertensive medications) to provide a tool for management of hypertension by primary care physicians.[25] Difficult-to-treat hypertension may include patients with pseudo-resistant and apparent treatment-resistant hypertension, with causes including poor adherence, suboptimal antihypertensive regimens, and 'white coat' hypertension, in which patients display elevated BP in the office or clinic, and normal BP outside.[26,27] A study from the Spanish Ambulatory Blood Pressure Monitoring (ABPM) registry found that, of those patients who appeared to have treatment-resistant hypertension, 37.5% had normal BP when assessed by ABPM.[28]

Treatment-resistant hypertension is defined as BP ≥140/90 mmHg in spite of appropriate lifestyle measures being undertaken and concurrent use of three optimally dosed antihypertensive medications from different classes, one being a diuretic.[3] It is associated with increased risk of CV events.[29] Approximately 2% of patients are estimated to be treatment resistant.[30] Treatment resistance should be confirmed by excluding patients who are poorly adherent, excluding those with pseudo-resistance (through 24-hour ABPM), by identifying and reversing contributing lifestyle factors (for example, sleep apnoea syndrome, obesity, and salt intake), and discontinuing (or minimising) substances that can increase BP.[31] Screening for the most prevalent secondary forms of hypertension should be carried out and those causes treated if possible.[31] Poor adherence has been observed in many patients with apparent treatment-resistant hypertension. Jung et al.[32] found that, of 76 patients with uncontrolled

BP on ≥4 medications, more than half were non-adherent, of which 30% were completely non-adherent, i.e. never taking the medications. Similarly, a study from a UK specialist hypertension clinic showed that, compared with adherent patients, non-adherent patients had higher BP, and 25% of patients referred for renal denervation were completely non-adherent.[33]

Treatment resistance may also be confirmed pharmacologically by assessing drug adherence, checking the drug combination, and optimising the dose regimen (Figure 2).[31] Most patients have been found to respond to the addition of spironolactone to a triple-drug regimen,[34] while large trials such as the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[35] and the Addition of Spironolactone in Patients with Resistant Arterial Hypertension (ASPIRANT) study[36] have found significant decreases in BP following the addition of spironolactone to the existing antihypertensive regimen. A study of a community-based network practice involving >450,000 hypertensive patients has shown that, of the approximate 32% of patients with uncontrolled hypertension, approximately 30% had apparent treatment-resistant hypertension and only 15% were receiving optimal treatment, highlighting the need for optimal pharmacotherapy of hypertension.[37] A recent trial compared renal denervation with clinically adjusted drug treatment for the management of true treatment-resistant hypertension. The study stopped early as the effect of renal denervation on BP lowering was uncertain; adjusted drug treatment was found to be superior in terms of BP lowering compared with renal denervation.[38]

In summary, patients with hypertension represent a large and complex problem for primary care physicians. Poor adherence to treatment may be an issue in apparent treatment resistance, and should be identified and monitored. A full clinical work-up and appropriate pharmacotherapy should help increase the proportion of patients reaching their target BP. Following a checklist[25] may help to address common issues when managing patients with treatment-resistant hypertension. This includes exclusion of pseudo-resistance via 24-hour ABPM, checking for secondary causes of hypertension, maximising lifestyle modifications, evaluating treatment adherence, and optimising drug therapy.

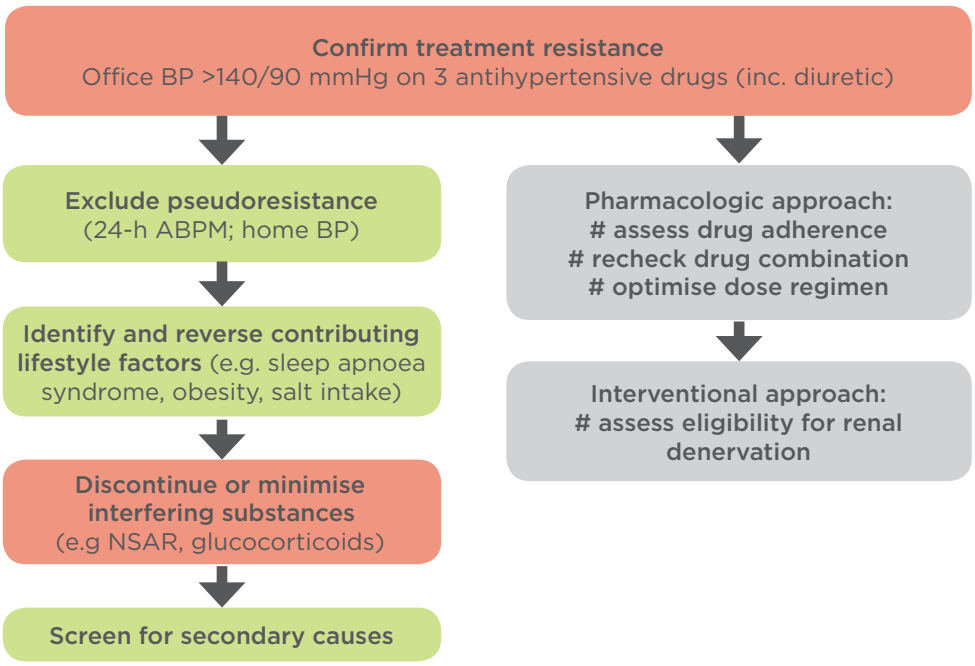

Figure 2: Algorithm for management and treatment of TRH.
TRH should be confirmed by excluding other disorders, reducing any relevant lifestyle factors, and assessing drug adherence and dosing.
ABPM: ambulatory blood pressure monitoring; NSAR: non-steroidal anti-rheumatic agents; TRH: treatment-resistant hypertension; BP: blood pressure.
Adapted from Schmieder et al.[31]

How to Bring Stakeholders Together – A Practical Example: The Low BP Vienna initiative

Professor Roland Schmieder and Professor Thomas Weiss

The Canadian Hypertension Education Program (CHEP) was initiated in 1999 to improve the management of hypertension[39] and provided annual recommendations for lifestyle changes in combination with pharmacotherapy. Substantial increases in the diagnosis and treatment of hypertension were observed, resulting in rates of BP control of 65% in 2009 compared with 13% in 1992.[40] In line with the increased BP control, prescriptions of all antihypertensive agents and FDCs have increased more than 100%,[41] and deaths from acute myocardial infarction (MI) and stroke have significantly reduced by 16% and 6%, respectively.[42] The most important messages identified by the Canadian initiative are the importance of global CV risk assessment and optimisation, lifestyle change, patient knowledge, adherence and motivation, and the use of single-pill combinations in the treatment of hypertension.[43]

The recently initiated Low BP in Vienna study is a prospective, multicentre, randomised, controlled, open-label trial that aims to enhance BP control in primary care, raise practitioner awareness of BP control through intensified antihypertensive treatment, introduce single-pill combinations, provide data on BP control in primary care, and identify patients with treatment-resistant hypertension. An estimated 840 adult patients with BP >140/90 mmHg are expected to be enrolled; exclusion criteria include the presence of chronic kidney disease, malignancy, recent MI or stroke, contraindication or allergy to olmesartan, amlodipine, or hydrochlorothiazide, and women of childbearing age. Across Austria 42 physicians, both family doctors and internal medicine resident specialists, will be randomised 1:1 to treat hypertensive patients with standard of care or a single-pill combination (individually titrated) containing olmesartan, amlodipine, and hydrochlorothiazide. Of note, the use of a single-pill combination permits the individual titration of medications for the patient. 24-hour ABPM will be carried out at baseline and at study completion (6 months), with office BP taken at inclusion and each study visit. The primary endpoint is the proportion of patients with BP <140/90 mmHg at 6 months, while secondary endpoints evaluate improvements in 24-hour ABPM and office BP, and individual changes in SBP and DBP after 6 months. Data are expected by 2016.

The Olmesartan Family: Important Tools to Improve BP Control

Professor Massimo Volpe

Single-pill FDC therapy is key for improving large-scale control of BP; however, its success is dependent on how widely it is applied.[44] Olmesartan-based therapy is a useful treatment option both as monotherapy and in single-pill 2-3 drug FDC therapy. Olmesartan and other ARBs are known to be effective for lowering BP.[45] Olmesartan has been shown to have comparable or greater efficacy in terms of lowering BP in the elderly compared with ramipril over 24 hours, daytime or night time, and even greater efficacy in the last 6 hours of a 24-hour period.[46] Additionally, discontinuation rates for ARBs including olmesartan are lower compared with angiotensin-converting enzyme inhibitors (ACEis).[47]

A meta-analysis of 147 randomised controlled trials found that dual and triple-combination therapies are superior for BP reduction than simply increasing the dose of one drug.[48] The ESH/ESC guidelines recommend FDCs of 2-3 drugs for achieving BP control.[3] The benefits of FDCs include improved BP control and normalisation, increased adherence, improved persistence, and reduced total and CV-related hospitalisation costs.[22,49-51] The guidelines recommend not combining ARBs and ACEis, while other combinations, including calcium channel blockers and thiazide diuretics with ARBs or ACEis, are preferred.[3]

An ARB-centred platform has been developed based on clinical evidence, guidelines, best practice, and clinical experience that classifies patients according to hypertension grade and risk factors, and provides guidance for physicians on the optimal single-pill FDC to use (Figure 3 and Figure 4).[44] This platform shows how the majority of patients with hypertension can be effectively treated using an ARB such as olmesartan combined with amlodipine and/or hydrochlorothiazide.

	Grade 1 SBP 140-159 or DBP 90-99	Grade 2 SBP 160-179 or DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
No risk factors	OLM 10-20 mg	OLM/AML 20/5 mg	OLM/AML 20-40/10 mg
		OLM/HCTZ 20/12.5 mg	OLM/HCTZ 20-40/25 mg
Dyslipidaemia, hyperuricaemia, obesity, or metabolic syndrome	OLM 10-20 mg	OLM/AML 20/5 mg	OLM/AML 20-40/5-10 mg
Fit elderly, <80 years old	OLM 10-20 mg if well tolerated	OLM/HCTZ 20/12.5 mg	OLM/HCTZ 20-40/25 mg
Frail elderly, >80 years old, SBP ≥160 mmHg	Consider OLM 10-20 mg	OLM/HCTZ 10-20/12.5 mg	OLM/HCTZ 20-40/25 mg
Atherosclerosis, arteriosclerosis, or PAD	Consider OLM 10-20 mg	OLM/AML 20-40/5 mg	OLM/AML 20-40/10 mg
LV hypertrophy	OLM 20-40 mg	OLM/HCTZ 20-40/12.5 mg	OLM/HCTZ 20-40/25 mg
Microalbuminuria/proteinuria (CKD Stage ≤3)	OLM 20-40 mg	OLM/AML 40/5 mg	OLM/AML 40/10 mg
Diabetes	OLM 20-40 mg	OLM/AML 40/5 mg	OLM/AML 40/10 mg

Figure 3: ARB platform: hypertensive patients with specific risk factors or subclinical organ damage.
ARB: angiotensin receptor blocker; AML: amlodipine; CKD: chronic kidney disease; DBP: diastolic blood pressure; HCTZ: hydrochlorothiazide; LV: left ventricular; OLM: olmesartan; PAD: peripheral arterial disease; SBP: systolic blood pressure.
Adapted from Volpe M et al.[44]

	Grade 1 SBP 140-159 or DBP 90-99	Grade 2 SBP 160-179 or DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
Atrial fibrillation	OLM 20-40 mg	OLM/HCTZ 20-40/12.5 mg	OLM/HCTZ 20-40/25 mg
Nephropathy (CKD Stage >3), eGFR <30ml/min/1.73m^2	OLM 20-40 mg	OLM/AML 40/5 mg	OLM/AML 40/10 mg
Coronary artery disease	OLM 10-20 mg	OLM/HCTZ 20-40/12.5 mg	OLM/HCTZ 40/25 mg
Previous stroke or transient ischaemic attack	OLM 10-20 mg	OLM/AML 20-40/5 mg	OLM/AML 20-40/10 mg
Heart failure with reduced EF	OLM/HCTZ 10-20/12.5 mg	OLM/HCTZ 20-40/12.5 mg	OLM/HCTZ 20-40/25 mg

Figure 4: ARB platform: hypertensive patients who have overt organ damage.
ARB: angiotensin receptor blocker; AML: amlodipine; CKD: chronic kidney disease; EF: ejection fraction; eGFR: estimated glomerular filtration rate; DBP: diastolic blood pressure; HCTZ: hydrochlorothiazide; OLM: olmesartan; SBP: systolic blood pressure.
Adapted from Volpe M et al.[44]

PART 2: 'THE Q & A TALK SHOW' DISCUSS WITH THE EXPERTS!

Introduction

Professor Redòn opened the discussion by recapping some of the points raised at the earlier satellite symposium. Hypertension is a complex primary care problem, requiring a thorough clinical work-up, including checking for secondary causes, the use of ABPM, optimisation of the treatment regimen, and evaluation of adherence. Adherence to antihypertensives reduces with increasing pill burden; single-pill combinations may simplify treatment and improve BP control. The treatment platform discussed by Professor Volpe provides guidance on the use of a single-pill combination in hypertensive patients. Wider roll-out of programmes such as CHEP (Canada) and Low BP in Vienna (Austria) that aim to achieve greater BP control rates will be beneficial in reducing CV morbidity and mortality, and economic burden in Europe.

Lifestyle

The initiatives needed to achieve lifestyle changes in the general population in terms of food, beverages, and smoking were discussed including one such initiative in Scandinavia that has reduced the salt content of bread. The faculty agreed that reduction of salt is a very important factor in the management of patients with hypertension. It was suggested that national and Europe-wide strategies were required to reduce salt intake in the population, including those patients with normal BP levels. However, the political difficulties in achieving this, and the clinical difficulties in monitoring patient salt intake, were acknowledged.

BP monitoring

Monitoring BP in the physician's office is difficult due to the presence of 'white coat' hypertension. ABPM is superior in providing a more realistic picture, particularly at night, and is easy to conduct. In the UK, ABPM is considered in all newly hypertensive patients. Studies from Spain have shown that more than a quarter (27%) of newly diagnosed hypertensive patients do not have raised BP when measured using ABPM. However, the cost implications can provide a barrier to ABPM for many patients.

The use of ABPM may be a useful strategy in patients with difficult-to-treat hypertension, while office-based measurements could be taken in patients with easy-to-treat hypertension. Professor Schmieder commented that, in practice, he carried out initial office-based measurements for diagnosis and initial treatment, followed by confirmatory ABPM to improve the control. Home-based measurements were agreed to improve patient motivation and adherence, thereby improving BP control. ABPM was flagged as a useful strategy to identify those patients with apparent difficult-to-treat hypertension who are actually achieving good BP control, saving both time and expense on unnecessary testing and medication. It was suggested that patients should measure BP twice in the morning and twice in the evening for 1 week, and determine the average measure from the latter 6 days out of 7 to obtain an accurate level. In addition, the use of a diary was identified as very important in motivating the patient.

Adherence

Several factors influence patient adherence to medication including side-effects of the medication, the number of pills required, the perceived benefit of the pills, cost, and socio-economic status. Young, active male patients have been identified as at highest risk of non-adherence. The importance of advising the patient of potential side-effects before commencement of treatment was emphasised, and the morning was identified as the optimum time for pill administration to promote adherence. A need for multiple pills may worry patients, highlighting the importance of a single-pill FDC. In certain countries, cost may be an issue, and patients with a lower socio-economic status are at higher risk of non-adherence. The issue of missed doses was raised and Professor Redòn described his recent study which investigated the ability of FDCs to maintain BP control in the event of a missed dose. They found that 48 hours after a missed dose BP levels were at almost the pre-missed dose level.

Special populations

The ESH/ESC guidelines recommend achieving a target SBP <150 mmHg in the elderly; however, if the medications are well-tolerated, a level between 130–150 mmHg may be achievable. Professor Volpe commented that the goal BP may be influenced by the patient's age, for example, in patients <65 years of age, achieving SBP <140 mmHg is possible, while <150 mmHg may be more realistic in patients >80 years of age. For those aged

between 60 and 80 years, other factors should be considered, such as the patient's general health.

The faculty discussed the management of hypertension in patients with symptomatic postural hypotension. Professor Schmieder emphasised the need to take each case on an individual basis. Professor Ruilope commented that postural hypotension influences the patients' quality of life, resulting in patients reducing their dosage. However, postural hypotension is a risk factor for poorer CV outcome. The faculty discussed the utility of ABPM and administration of short/rapid-acting medication at night.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend achieving BP levels of ≤130/80 mmHg in patients with proteinuria. These patients have a high level of CV risk. The panel evaluated the matter from different perspectives, for instance in patients with prior CV events a goal of 140/90 mmHg may be more appropriate.

Treatment strategies

Professor Volpe commented that there is more evidence for the use of ARBs in treatment of hypertension compared with ACEis. In addition, the tolerability of ARBs is superior to that of ACEis. The faculty agreed that triple-combination therapy was not an optimal choice for first-line therapy. Professor Ruilope remarked that the Avoiding Cardiovascular events through Combination Therapy (ACCOMPLISH) trial successfully started patients on double therapy, while Professor Burnier highlighted the importance of considering the patient's risk of CV events when deciding on monotherapy or combination therapy as first line. The faculty highlighted that the choice of medications used in combination therapy should be based on the clinical evidence and take into account factors, such as proteinuria and metabolic disorders. Renal denervation should be considered in patients with true treatment-resistant hypertension.

Click here to view the satellite symposium from ESC 2014

REFERENCES

1. Nichols M et al. European Cardiovascular Disease Statistics: 2012 edition. European Heart Network and European Society of Cardiology. 2012.

2. Lim SS et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224–60.

3. Mancia G et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: 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. 2013;31:1281–357.

4. Lozano R et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095–128.

5. Mancia G et al. 2007 Guidelines for the management of arterial hypertension: 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.

6. Mancia G et al; European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009;27:2121–58.

7. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens. 2003;21:1011–53.

8. Banegas JR et al. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study. Eur Heart J. 2011;32:2143–52.

9. Godet-Mardirossian H et al. Patterns of hypertension management in France (ENNS 2006-2007). Eur J Prev Cardiol. 2012;19:213–20.

10. Tocci G et al. Blood pressure control in Italy: analysis of clinical data from 2005-2011 surveys on hypertension. J Hypertens. 2012;30:1065–74.

11. Struijker-Boudier HA et al. The need for combination antihypertensive therapy to reach target blood pressures: what has been learned from clinical practice and morbidity-mortality trials? Int J Clin Pract. 2007;61:1592–602.

12. Jamerson K et al; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359:2417–28.

13. Santschi V et al. Improving blood pressure control through pharmacist interventions: a meta-analysis of randomized controlled trials. J Am Heart Assoc. 2014;3:e000718.

14. Yach D. Adherence to long-term therapies: Evidence for action. Geneva: World Health Organisation. 2003.

15. Hill MN et al; American Society of Hypertension Writing Group. ASH position paper: adherence and persistence with taking medication to control high blood pressure. J Clin Hypertens (Greenwich). 2010;12:757–64.

16. Burnier M et al. Measuring, analyzing, and managing drug adherence in resistant hypertension. Hypertension. 2013;62:218–25.

17. Vrijens B et al. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336:1114–7.

18. Bramley TJ et al. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. J Manag Care Pharm. 2006;12:239–45.

19. Perreault S et al. Better adherence to antihypertensive agents and risk reduction of chronic heart failure. J Intern Med. 2009;266:207–18.

20. Perreault S et al. Adherence level of antihypertensive agents in coronary artery disease. Br J Clin Pharmacol. 2010;69:74–84.

21. Kettani FZ et al. Impact of a better adherence to antihypertensive agents on cerebrovascular disease for primary prevention. Stroke. 2009;40:213–20.

22. Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. Am J Health Syst Pharm. 2007;64:1279–83.

23. Burnier M et al. Drug adherence in chronic kidney diseases and dialysis. Nephrol Dial Transplant. 2015;30:39-44.

24. Gupta AK et al. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010;55:399–407.

25. Schmieder RE et al. A guide for easy- and difficult-to-treat hypertension. Int J Cardiol. 2014;172:17–22.

26. Elliott WJ. High prevalence of white-coat hypertension in Spanish resistant hypertensive patients. Hypertension. 2011;57:889–90.

27. Myat A et al. Resistant hypertension. BMJ. 2012;345:e7473.

28. de la Sierra A et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011;57:898–902.

29. Pierdomenico SD et al. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. Am J Hypertens. 2005;18:1422–8.

30. Daugherty SL et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012;125:1635–42.

31. Schmieder RE et al. Updated ESH position paper on interventional therapy of resistant hypertension. EuroIntervention. 2013;9 Suppl R:R58–66.

32. Jung O et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013;31: 766–74.

33. Tomaszewski M et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart. 2014;100:855–61.

34. Waeber B et al. Diagnosis and treatment of resistant hypertension. Blood Press. 2014;23:193–9.

35. Chapman N et al; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension. 2007;49:839–45.

36. Václavík J et al. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension. 2011;57:1069–75.

37. Egan BM et al. Prevalence of optimal treatment regimens in patients with apparent treatment-resistant hypertension based on office blood pressure in a community-based practice network. Hypertension. 2013;62:691–7.

38. Fadl Elmula FE et al. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. Hypertension. 2014;63:991–9.

39. Campbell NR et al; Canadian Hypertension Education Process and Evaluation Committee. Temporal trends in antihypertensive drug prescriptions in Canada before and after introduction of the Canadian Hypertension Education Program. J Hypertens. 2003;21:1591–7.

40. McAlister FA et al. Changes in the rates of awareness, treatment and control of hypertension in Canada over the past two decades. CMAJ. 2011;183:1007–13.

41. Hemmelgarn BR et al. Trends in antihypertensive drug prescriptions and physician visits in Canada between 1996 and 2006. Can J Cardiol. 2008;24:507–12.

42. Campbell NR et al; Canadian Hypertension Education Program Outcomes Research Task Force. Increases in antihypertensive prescriptions and reductions in cardiovascular events in Canada. Hypertension. 2009;53:128–34.

43. Canadian Hypertension Education Program. 2014 Canadian recommendations for the management of hypertension. 2014.

44. Volpe M et al. ARB-based single-pill platform to guide a practical therapeutic approach to hypertensive patients. High Blood Press Cardiovasc Prev. 2014;21: 137–47.

45. Fabia MJ et al. Antihypertensive activity of angiotensin II AT1 receptor antagonists: a systematic review of studies with 24 h ambulatory blood pressure monitoring. J Hypertens. 2007;25:1327–36.

46. Omboni S et al; Study Group. Twenty-four hour and early morning blood pressure control of olmesartan vs. ramipril in elderly hypertensive patients: pooled individual data analysis of two randomized, double-blind, parallel-group studies. J Hypertens. 2012;30:1468–77.

47. Mancia G et al. Heterogeneity in antihypertensive treatment discontinuation between drugs belonging to the same class. J Hypertens. 2011;29:1012–8.

48. Law MR et al. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.

49. Sherrill B et al. Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs and adherence. J Clin Hypertens (Greenwich). 2011;13:898-909.

50. Taylor AA, Shoheiber O. Adherence to antihypertensive therapy with fixed-dose amlodipine besylate/benazepril HCl versus comparable component-based therapy. Congest Heart Fail. 2003;9: 324–32.

51. Zeng F et al. Adherence and persistence of single-pill ARB/CCB combination therapy compared to multiple-pill ARB/CCB regimens. Curr Med Res Opin. 2010;26:2877–87.

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