Year XII, N. 2, January 2014

CONFERENCE INSIGHT

ESC Congress 2013 31 August - 04 September, Amsterdam, The Netherlands

The European Society of Cardiology Congress, held in Amsterdam this year, represents the world's premier conference on the science, management and prevention of cardiovascular disease. Driven by a very challenging mission – to reduce the burden of cardiovascular disease in Europe – this year's congress numbers were outstanding: 5 days of scientific sessions, 145 cardiovascular topics, more than 27,000 healthcare professionals from more than 150 countries, 10,500 abstracts submitted, 130 industry- sponsored sessions and 200 exhibiting companies. The event hosted the most eminent academic experts in cardiology, and was also open to general practitioners (GPs), nurses and other allied professionals, all participating in clinical seminars, debates, symposia and focus sessions highlighting the most relevant cardiovascular issues. Special attention was dedicated to clinical practice guidelines and to the 2013 ESH/ESC guidelines on hypertension.

It was precisely on the topic of hypertension and related events that was the focus of the interactive satellite symposium organised by Daiichi Sankyo and The Menarini Group. The symposium was aimed at providing a thorough answer to the question, "Why do goal rates in hypertension urgently need to improve?". For this purpose, the session included a patient case, from the first diagnosis through to the development of various complications, leading to the prescription of a triple combination therapy based on olmesartan/amlodipine/hydrochlorothiazide. This therapeutic option has the advantage of being an effective and well-tolerated single pill treatment, with superior benefits in terms of adherence and blood pressure (BP) control. An in-depth analysis of the new 2013 ESH/ESC Guidelines examined the main changes from the previous editions, with particular emphasis on the diagnostic and therapeutic methods to promote adherence and improve achievement of BP goals. In order to improve BP control rates, which are still suboptimal in the real world, the French League against Hypertension has launched a programme for achieving BP control in 70% of treated patients by 2015. The symposium provided an overview and discussion of the approach and implementation of this project.

Daiichi Sankyo and The Menarini Group Satellite Symposium

Why do goal rates in hypertension urgently need to improve?

The symposium was co-chaired by Professor Stéphane Laurent (Paris, France) and Professor Bryan Williams (London, UK). The other faculty members were Professor Roland Schmieder (Erlangen, Germany), Professor Massimo Volpe (Rome, Italy), Professor Josep Redòn (Valencia, Spain) and Professor Jean-Jacques Mourad (Bobigny, France).

Professor Laurent introduced the symposium by summarising the key drivers of the need to improve blood pressure control. **Cardiovascular disease (CVD) is the most common non-communicable cause of death worldwide**, more common than cancer. In Europe, CVD is the main cause of death, with more than 4 million deaths annually (47% of the total) and a huge economic impact with a cost to the economy of €196 billion annually. Coronary heart disease (CHD) and stroke account for the majority of these deaths.

Blood pressure (BP) control is far from optimal in Western Europe. Only 25% to 35% of asymptomatic high-risk patients and fewer than 50% of patients treated in primary care have blood pressure under control, without considering potential patients not under treatment. In higher-risk patients, BP control rates are also poor and still not improving. According to the EUROASPIRE study, in patients with CHD who received treatment, control has decreased from 49% in 1999-2000 to 43.9% in 2006-2007, while the percentage of patients receiving statins has increased. Such a situation could be avoided by simply prescribing antihypertensive drugs.

Stroke death can be used as a proxy for BP control. A study by Redòn et al. (2011) analysed mortality in various European countries and found that, while in countries characterized by very low child and adult mortality, the mortality trend is decreasing, in countries with low child and *high* adult mortality, the trend is increasing. This can be ascribed to the lack of controlled BP, because BP is one of the strongest, if not the strongest, predictor of stroke. Lowering BP is the best way to prevent stroke.

Professors Volpe and Schmieder led an interactive session discussing the best way to effectively and simply treat patients to achieve controlled BP.

The relationship between urinary albumin concentration and CV mortality is already apparent at albuminuria levels considered to be normal (PREVEND study, 2002); based on the results of the ONTARGET/TRANSCEND program (2011), decreasing albuminuria by 50% can significantly reduce the CV event rate, thus albuminuria is not only a renal parameter, but also a vascular parameter which needs to be monitored in the follow-up of some hypertensive patients. According to the ESH/ESC Guidelines, in the case of microalbuminuria, preferred drugs should be ACE inhibitors or ARBs.

Evidence suggests that ARB treatment (olmesartan) effectively lowers BP and al-

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lows BP control in patients with metabolic abnormalities (Omboni et al., 2012) and the use of an ARB effectively decelerates the process towards type II diabetes (Dahlof et al., 2002). Furthermore, as clearly stated in the ESH/ESC Guidelines and resulting from a metastudy including over 30,000 patients (Gupta et al., 2010), fixed-dose combinations (FDCs) significantly improve compliance and persistence. In the case of many poorly-compliant patients, the switch to a FDC therapy allows BP control to be more easily achieved, and also, importantly, the pill burden to be reduced, thus facilitating an increase in adherence.
In clinical practice, where initial diagnosis is through a GP and caution is often exercised in increasing dosages, patients are frequently undertreated. In the past, there has been a strong tendency to use monotherapy with separate combinations and this has often resulted in low compliance. With hindsight, for this type of patient it would be better to take a more aggressive approach from the start and use a combination therapy.

Professor Redòn provided an overview of the **main changes in the 2013 ESH/ESC Guidelines** for hypertension. In the new release, many of the concepts of previous guidelines have been maintained, but some recommendations have been refined and new ones have been introduced, particularly concerning diagnosis stratification, BP goals and how to achieve them.
1. Increased emphasis on the use of out-of-office BP monitoring. Out-of-office BP monitoring represents a more reliable assessment of actual BP compared to office BP and correlates more strongly with organ damage (OD) and CV events. There is an increasing role for home blood pressure monitoring (HBPM) in the diagnosis and management of hypertension, alongside ambulatory blood pressure monitoring (ABPM), and the two methods should be regarded as complementary, rather than alternative.
2. Greater emphasis on assessing total CV risk. The assessment of risk has changed in the new Guidelines; patients with OD or diabetes have been upgraded to a higher risk category. BP goals have been simplified, with a single SBP target for almost all patients (SBP <140 mmHg) regardless of the level of risk. In patients with low to moderate CV risk, diabetes, diabetic or non-diabetic CKD, CHD, previous stroke or TIA, a DBP <90 mmHg is always recommended. There are, however, a few exceptions for special populations such as diabetics and elderly patients.
3. Emphasis on the necessity for combination therapies to achieve the goal of reducing BP below 140/90 mmHg. Initiating treatment with a combination therapy enables more rapid response in a larger number of patients and a greater probability of achieving target BP in patients with higher BP values. The many physiological and pharmacological synergies between different drug classes can provide greater BP reduction and cause fewer side effects. Also, reducing the necessity for many treatment changes encourages patient adherence. The guidelines offer support in selecting the therapy to prescribe by describing the steps required to achieve BP control (Figure 1). In general, whenever the BP target is not achieved, one should move to more intensive therapy, keeping in mind that, despite the drug class selected, it is always preferable to use a combination therapy rather than double the dose, because it increases the probability of response.
4. Encouragement to use combination therapies when BP control is not being achieved. The emphasis on combination therapies is supported by recent studies, such as the APEX study, in which combination therapies were found to be more effective than monotherapy in achieving BP control, with triple combinations allowing levels of control well above 70%.
5. Adherence as a key factor in achieving BP control. Low adherence is linked to poor BP control because it concerns a large number of patients. Its link with high CV risk has been fully documented. Low adherence is extremely common: after six months, at least one-third of patients often stop their treatment and 10% of patients forget to take their medication on a daily basis.
Adherence can be improved through interventions at multiple levels: at the patient level, by improving self-management and self-monitoring; at the treatment level, by simplifying drug regimens; and at the healthcare system level, by intensifying care and developing a multidisciplinary approach. The way that care is delivered can also greatly influence adherence: using telephone calls in addition to office visits can be very effective in changing patient behaviour, allowing more patients to be reached in a timely manner with limited costs, whilst fast-evolving technology is enabling self-monitoring to become part of daily life.

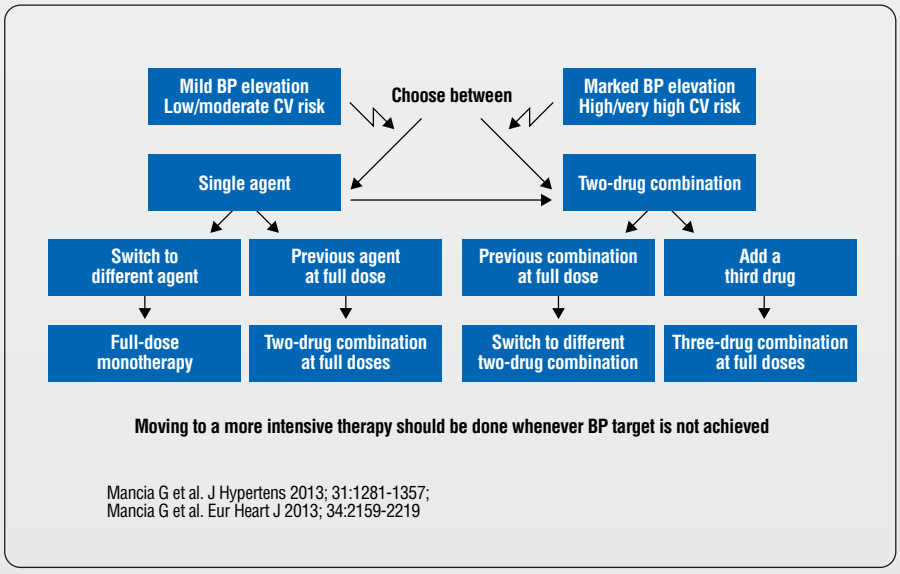

Figure 1. Monotherapy and combination therapy in the 2013 ESH/ESC treatment guidelines.

Professor Mourad discussed how to achieve high levels of BP control in general practice. This has already been done in North America with the NHANES program and in Canada with the CHEP program, enabling BP control to increase from 13.2% in 1992 to 64.6% in 2009. This change has occurred by increasing antihypertensive treatments - mainly FDCs - and the effects on prognosis have been impressive: a decrease of 16% in deaths by acute myocardial infarction (MI) and of 6% of deaths from stroke. The focus has been on **increasing hypertension awareness, increasing the number of patients being treated, and using FDCs**.
In 2010 it was observed that rates of BP control in France had reached a plateau. Therefore in 2012 the French League Against Hypertension launched a program aimed at having **70% of hypertensive patients treated and controlled by 2015**. Medical professionals should change their attitudes towards patients, by changing the focus to the high risk of stroke associated with hypertension. The discourse in relation to treatment should change, so treatment is described as “life-

extending" rather than "lifelong" and doctors should **de-emphasise pill burden and highlight the benefits of treatment**. The program suggests seven key points for optimising the therapeutic management strategy:

1. Confirm that BP is uncontrolled using ambulatory techniques.

2. Actively screen for poor adherence.

3. When BP is uncontrolled, switch from monotherapy to fixed two-drug therapy.

4. In primary care, propose prescription of three-drug therapy in patients who have not achieved control by two-drug therapy.

5. In primary care, screen for specific under-diagnosed secondary causes of hypertension or resistance.

6. Organise a healthcare course for hypertensive patients and provide apparently resistant hypertensive patients with access to specialists.

7. Evaluate the performance of the selected hypertension management.

This approach, which is easy to implement and extremely pragmatic, aims to achieve control within 6 months after treatment initiation, via dynamic and secure up-titration. A similar program, guided by Professor Volpe, is currently underway in Italy.

Professor Williams closed the symposium by reviewing some of the challenges in hypertension. He highlighted how achieving BP control for a patient requires a long and costly period of evaluation and treatment, and the importance of the quality and duration of control. Medical inertia and non-compliance are also key issues. Linking doctor's pay to outcomes, and patient education campaigns to help them understand the consequences of non-adherence, may improve treatment.

Reports from recent original studies

Ji Young Park (Seoul, Republic of Korea) presented an original study aimed at comparing the impact of ACE inhibitors (ACEIs) and ARBs on new-onset diabetes mellitus (NODM) in an Asian population. The sample included 1,856 patients with at least one cardiovascular disease (CVD) or cardiovascular risk, who did not have a history of DM and who had been treated with ACEIs or ARBs. To adjust for potential confounders, a propensity score matched analysis was performed using the logistic regression model, which resulted in 1,024 baseline-adjusted patients being involved in the analysis with a mean follow-up of 3 years. A Kaplan-Meyer curve showed the cumulative incidence of NODM to be higher in the ARB group compared to the ACEI group, even though clinical outcomes up to 3 years were similar between the two groups. However, a larger trial would be required to further investigate the different effects of these two classes of drugs in preventing DM.

Giuseppe Derosa (Pavia, Italy) presented an original study aimed at evaluating the effects of a fixed olmesartan-amlodipine combination therapy compared to single monotherapies on BP control, lipid profile and some insulin resistance parameters. After a 2-week wash-out period, 276 hypertensive patients were randomly assigned to olmesartan 20 mg, amlodipine 10 mg or to a single-pill fixed combination of olmesartan and amlodipine 20/5 mg for 12 months, a long trial duration compared to most other studies. The patients were evaluated at baseline and after 6 and 12 months on a number of parameters, including SBP and DBP, glucose metabolism, insulin resistance parameters, lipid profile and various adipocytokines. Results indicated that a fixed olmesartan-amlodipine combination is more effective that the single molecules in reducing BP and, over a 12-month period, the dual combination is more effective in improving insulin-resistance related parameters and some adipocytokines, such as chemerin and omentin.

Professor **José-Luis Zamorano Gómez** (Madrid, Spain) presented a review on how to improve hypertension management using combination therapy. There is a gap between clinical guidelines and clinical practice, probably caused by therapeutic inertia and poor compliance. There is much evidence that monotherapy is insufficient, that more than one drug, and often more than two drugs, are required to control BP effectively. In a meta analysis by Wald et al. (2009), on 11,000 participants from 42 trials, doubling the monotherapy dose was consistently less effective in lowering BP compared to adding a drug from another class in combination therapy. Compared to initial monotherapy, initial combination therapy is associated with a much lower cardiovascular, coronary and cerebrovascular risk: the higher the number of drugs in the combination, the lower the incidence of stroke and ischaemic heart disease. There is solid evidence of the relationship between time control and cardiovascular outcomes: the better the time control, the lower the incidence of CV events. This could be ascribed to compliance, which is known to decrease as the pill burden grows and to increase with fixed combination therapy. Reducing adverse events is also important for increasing compliance; combination therapy provides a better safety profile compared to monotherapy.

World view on cardiovascular prevention guidelines

Professor Neil Poulter (London, UK) presented a comparison between the ESH/ESC Guidelines (EURGs), the NICE Guidelines (UKGs) published in the UK in 2011, the JNC7 American Guidelines (USGs) last published in 2007, and the WHO Guidelines (WHOGs) issued by the International Society of Hypertension in 2007. He highlighted various points of interest.

Measurement: All four guidelines specify a BP of 140/90 mmHg as the hypertension threshold; however, for the diagnosis to be issued, the UKGs suggest this measurement should be the result of ABPM. Such a choice has strong cost implications, but also supports the intention that treatment should suppress BP variability, the major risk factor in hypertension.

Treatment: While the EURGs and USGs suggest initiating treatment to lower BP above the 140/90 mmHg threshold, the UKGs define a "grey area" between 140/90 mmHg and 160/100 mmHg in which, before intervening with treatment, there should be an evaluation of risk. It is unrealistic to think that all people worldwide whose BP is above 140/90 mmHg can be treated, therefore the WHOGs suggest evaluating resources before initiating

treatment.

Risk assessment: In the USGs there is no mention of risk assessment, while the EURGs and WHOGs adopt a stratified risk evaluation based on 5 and 3 layers, respectively. The UKGs use a simpler chart, based on morbidity and mortality, with the new version (JBS 3) taking into account not only short-term absolute risk, but also lifetime risk in terms of life-years saved.

First-line therapy: All guidelines present algorithms to define how to treat and manage hypertension. The USGs suggest thiazide-type diuretics as a first step; the EURGs suggest using any of 5 types of drugs [ACE-inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), beta-blockers, calcium-channel blockers (CCBs) and thiazide-diuretics]; the WHOGs suggest low-dose diuretics; the UKGs suggest ACEIs/ARBs or CCBs.

All guidelines consider that if the hypertension has compelling indications these should drive the choice of drug. The USGs and EURGs (but not UKGs and WHOGs) suggest initiating treatment with a two-drug combination therapy. The USGs suggest starting with a thiazide diuretic and then adding another drug, and the EURGs indicate ACEIs or ARBs plus a diuretic, ACEIs or ARBs plus a CCB as preferred combinations. The ACEI plus ARB combination should absolutely not be used. The UKGs algorithm is simpler for GPs to use: when the patient is younger than 55, start with an ACEI or ARB, if they are over 55 or of African or Caribbean descent, start with a CCB. In case the initial treatment fails in getting the patient to target, the drugs can be combined (ACEI/ARB plus CCB) and if the BP is still not controlled with this combination, add a thiazide-like diuretic. The age division of 55 years is justified by evidence suggesting that before age 55 renin levels tend to be high and ACEIs and ARBs work most effectively, while CCBs are less effective and tend to work best with low renin levels. If after this escalation BP remains uncontrolled, then patients should be diagnosed with resistant hypertension, an extra diuretic should be added and they should be referred to a specialist. The suggested diuretic is defined as being thiazide-like, which means that it is not thiazide. This UKGs recommendation is based on the fact that studies show no evidence of the benefit of low-dose (up to 25 mg) thiazide versus placebo. In three studies comparing low-dose thiazide with a drug (ANBP2, ASCOT, ACCOMPLISH studies), low-dose thiazide consistently proved inferior. However, there is evidence of the benefits of high-dose thiazide, accompanied by potassium supplements, and good evidence for chlorthalidone and indapamide, which are thiazide-like drugs.

Targets: Though worldwide there seems to be agreement on 140/90 mmHg as the target for uncomplicated hypertension, for patients with diabetes and chronic renal failure there was previously agreement on a 130/80 mmHg target, even if it was based on very limited evidence from clinical trials. In the new EURGs, following a close evaluation of the available clinical trial evidence, a revised target of 140/85 mmHg and 140/90 mmHg was set for diabetic and renal failure patients, respectively.

Future research: The areas indicated by the EURGs and UKGs for future research include: use of ABPM versus HBPM in diagnosis and monitoring, role of central BP and long-term BP variability, benefits of treating low-risk and elderly patients with mild hypertension, lack of trials on managing hypertension in young people (<40 years of age), further research on optimal BP targets and resistant hypertension. Professor Poulter also indicated ethnicity-specific management as an under-researched area, particularly for specific ethnic groups, such as the South Asian community.

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