

The updated 2007 Guidelines for the Management of Arterial Hypertension were released at the 17th European Meeting on Hypertension, held June 15-19, 2007 in Milan. In this interview, Professor Giuseppe Mancina highlights and explains new aspects of the Guidelines.

### **What are the notable differences between the 2003 and new 2007 ESH/ESC Guidelines for the Management of Hypertension?**

The 2007 ESH/ESC Guidelines emphasize the assessment of total cardiovascular (CV) risk, along with proper measurement of blood pressure (BP) to diagnose high blood pressure and guide treatment strategies. The information from both is needed to appropriately guide treatment. Notably, the BP threshold for initiating treatment and the treatment targets are new. In high-risk patients, the treatment target is <130/80 mmHg, for which the evidence is much stronger now, and treatment strategies should include consideration of aspirin and a statin. Importantly, age must be considered when determining CV risk. Total CV risk should be based on absolute risk, that is, the risk of an individual to have an event within 10 years. But, because age is an important factor in total CV risk, few younger persons would have a high total CV risk. Therefore, we may not treat patients who are at apparent low CV risk, but because of the lifetime effect of risk they may become high risk, which is a partly irreversible condition 20 years later. Thus, the Guidelines state that relative risk is a better guide for treatment in younger patients. Relative risk is the increase in risk compared to the average risk of the general population. Therefore, use absolute risk to guide treatment in the elderly and relative risk in younger patients. The Guidelines have some clear statements about government policies, which have been based on arbitrary cut-off values for total CV risk. It must be clearly understood that the Guidelines are not saying that treatment should be only for those persons at high risk. Treatment is needed and recommended for all persons with hypertension.

### **What are the thresholds for initiating treatment of high blood pressure?**

Additional evidence accumulated over the last few years supports the importance of blood pressure reduction per se for protecting hypertensive patients. So, in the 2007 Guidelines, the threshold for initiating drug treatment is set at >140/90 mmHg in all hypertensive patients, and at <140/90 mmHg in patients with a high-risk profile. Thus, drug treatment should be initiated in persons who were considered as normotensive in the previous guidelines. This emphasizes the "flexible threshold" for treatment.

The "flexible threshold" highlights the importance of the total CV risk to guide treatment. For low risk, the threshold for initiating treatment is about 140/90 mmHg, whereas for high risk the threshold is <140/90 mmHg. Figure 1 of the new Guidelines presents a simplified method to assess risk, making it a useful tool for practicing physicians. This method considers subclinical organ damage as a criterion for identifying people at high risk.

### **What are the recommendations in the 2007 Guidelines for the assessment of organ damage?**

There are several new aspects regarding the assessment of subclinical organ damage. Most notably, there are more different measures of organ damage. We have placed more emphasis on this because the evidence has shown more people to have subclinical organ damage than has been previously thought. Further, we state that some of these measures are routine and some are recommended assessments of patients with hypertension. These are clearly laid out in Box 6 of the Guidelines, which is a useful reference for the practicing clinician.

### **What tests should be done for the routine assessment of organ damage?**

Notably, serum creatinine, estimated glomerular filtration rate (GFR) or estimated creatinine clearance, and new to the Guidelines-microalbuminuria. Other more routine measures are listed in the Guidelines.

A marked increase in CV risk with even a slight increase in serum creatinine (>1.4 mg/dL) has now been shown by the accumulated evidence. Further, CV risk is markedly increased in persons with estimated values below 60 ml/min of GFR or creatinine clearance. Both of these can be easily calculated in daily clinical practice using a formula based on age, sex, body weight, and creatinine values.

An enormous amount of evidence now shows that in diabetic patients and in the general population, microalbuminuria predicts both renal outcomes and CV events. Thus, we now include this in routine testing, because it is simple, cheap, and has good predictive value.

### **What are the recommended measures for assessment of organ damage?**

Two new recommended measures are ankle-brachial ratio and pulse wave velocity.

The difference between ankle BP and brachial BP is a marker of advanced atherosclerotic disease. The greater the pulse wave velocity, i.e., the velocity of the transmission of pulse pressure or the pulse wave due to stroke volume to the periphery, the greater the arterial stiffness. There is evidence that this has prognostic importance.

Another new aspect to the 2007 Guidelines is that organ damage should be assessed throughout treatment.

Echocardiography is a recommended test, and the evidence for this is now stronger. We know now that left atrial dimension is prognostically important. The risk of stroke increases with the increase in the dimension of the atrium. Left ventricular hypertrophy (LVH) also is a marker of increased risk. Concentric LVH markedly increases CV risk. Carotid ultrasonography is included to detect plaques and thickening.

### **Please explain about the assessment of organ damage throughout treatment...**

The initial organ damage values and the changes induced by treatment have been shown to have prognostic value by evidence from the last few years. The changes in organ damage with treatment are correlated to changes to events, thus, an improvement in organ damage is a sign of protection. This is very important because it gives physicians a means to know whether or not the treatment is having a beneficial effect for the patient.

Thus, the Guidelines recommend measuring organ damage at various intervals throughout treatment. Table 4 considers the availability, prognostic value, and cost of some of the measures of organ damage.

Microalbuminuria can be assessed every few months, because it is quickly responsive to treatment. LVH can be reassessed every 1 to 2 years, because more time is needed to see the benefits of treatment.

### **Regarding the treatment of high blood pressure, what is new and notable in the new 2007 ESH/ESC Guidelines for the Management of Hypertension?**

Lifestyle changes are recommended for everyone. The Guidelines speak more clearly about the fact that lifestyle changes should not be given the "lip service" it has received in the past. All advice given regarding lifestyle changes should be done seriously, possibly with the help of professionals, and reinforced by the clinician periodically. True support, not lip service, must be given by the clinician.

The patients who are under non-drug treatment, that is pursuing lifestyle changes to reduce blood pressure, should be followed even more closely by clinicians. Blood pressure response to lifestyle

changes is extremely variable between patients and compliance is extremely low, and thus these patients need more follow-up.

Further, drug treatment should not be delayed when there is evidence of a lack of effect.

### **What is an appropriate time frame to use lifestyle changes as treatment before initiating drug treatment?**

Lifestyle measures can be tried for some months to determine if they are effective in persons at low total CV risk, for example, a middle-aged person with a mild BP elevation (146/92 mmHg) and no other risk factors. However, because the relative risk in this person is high, the Guidelines state that drug treatment should be initiated if BP is not normalized within a few months. In contrast, for high-risk patients, lifestyle measures and drug treatment should be initiated simultaneously; too long of a delay in controlling BP in high-risk patients may lead to events.

### **What is new in regard to drug treatment?**

A large proportion of the benefit comes from the reduction of BP per se and the evidence for this is absolutely conclusive. This evidence is discussed in detail in the Guidelines.

Many different drugs have been shown to be protective when they reduce BP. Persons in whom drugs reduce BP to <140/90 mmHg are protected independent of the type of treatment.

There is a close relationship between the degree of BP reduction and the degree of benefit. Many different kinds of evidence support the fact that it is the BP reduction that protects patients, not which drug is used to initiate treatment. For this reason, the Guidelines stick to the statement that initiation and maintenance of antihypertensive treatment can make use of several drug classes. Further, the need for combination therapy in most patients to reach target blood pressure levels negates the importance of which should be the first drug for the treatment of high blood pressure. Thiazide diuretics, ACE inhibitors, calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs), and beta blockers (BBs) are all suitable for antihypertensive treatment.

### **What do the Guidelines say about the appropriate use of beta blockers?**

Beta blockers are maintained among the classes of drugs that are suitable for initiation and maintenance of any BP treatment. This is a clear-cut difference with national guidelines, such as the British Hypertension Society (BHS) guidelines. The BHS Guidelines excluded BB as suitable for initiation of treatment and consider them as fourth-line treatment for hypertension, based on the data from the ASCOT study.

In ASCOT, the combination of a diuretic and beta-blocker was less effective in lowering BP and reducing CV events as compared to the combination of CCB and an ACE inhibitor. The ESH/ESC Guidelines take the position that excluding the use of BB is not justified, because other studies did not show the same results as the ASCOT study.

The INVEST showed a similar reduction in BP and similar incidence of events with an ACE inhibitor plus CCB combination. ALLHAT showed that initiating treatment with a diuretic and then adding a BB was not worse than other strategies. Also, no difference between treatment strategies, including a diuretic and BB, was shown in the STOP-2 trial in elderly patients. Recommendations should not be based on one study, but an overview of the evidence, and therefore, BB are regarded as still an important class of drugs in the European Guidelines. One other consideration is that it is not possible to divide the effect of the diuretic and BB, because they are given together in most trials.

Further, there are conditions in which BB are important, such as angina, post-MI, and heart failure. So, BB are included as a choice for initiation and maintenance to treat hypertension, with the note

that they have a less favorable effect on new-onset diabetes. For patients with a high risk of incident diabetes, such as patients with the metabolic syndrome, BB should not be preferred. Thus, there are specific conditions in which BB should not be considered first choice, but not in the general antihypertensive treatment strategy.

### **What do the Guidelines say about combination therapy?**

Prof. Mancia: The evidence is overwhelming that most persons with hypertension can only have good BP control with combination treatment. Thus, the guidelines state it is not meaningful to discuss what drug should be taken alone for the first 3 or 4 weeks, when it is necessary to take 2 or 3 drugs for a lifetime.

So, the question is not which drug, but which drugs should be used in the combination. There is a strong basis in favor of combination treatment being the most important strategy for BP control. Thus, this is a practical approach, because nearly all patients will require combination treatment to control BP to target levels.

Combination treatment should also be considered as a very good first treatment option. The guidelines are more precise now about what physicians can do. For example, in persons with a very high initial BP or with a mild BP elevation plus high risk in which BP should be lowered more markedly, there is a good basis to start treatment with two drugs.

Also, in high-risk patients, even the first 6 months can be crucial in preventing events, based on the evidence. For example, the VALUE trial showed that in high-risk patients there were fewer events in those whose BP was reduced more effectively in the first 6 months. This also argues for combination therapy to initiate drug treatment.

The Guidelines have a rather detailed description of criteria to use combination treatment, including combinations that have more or less priority.

### **What are the parameters to guide drug selection for initiating treatment and maintenance?**

There are now many more conditions in which there is evidence in favor of some drugs versus others. This can be divided by clinical or demographic conditions, and these laid out in a useful manner for the clinician in Table 6 and Box 11 of the Guidelines.

The goal of treatment is not only prevention of events, but also prevention of worsening of organ damage and prevention of the appearance of high-risk conditions. This reflects the fact that if we treat, say middle-aged patients, the treatment goal is less about preventing a myocardial infarction (MI) in the next 3 or 4 years, but the goal is to prevent the appearance of diabetes or atrial fibrillation or worsening of renal damage, which can in turn markedly increase CV risk.

There is evidence that some drugs are better than others for certain conditions. For the prevention of atrial fibrillation, drugs that work against the renin-angiotensin system (RAS) are more effective. For renal protection, RAS inhibition is more effective. For proteinuria and microalbuminuria, drugs that work against the RAS are much better.

For the metabolic syndrome, a high-risk condition in which new-onset diabetes is extremely common, ARBs, Ace inhibitors, or CCBs are preferred over diuretics or BB. In the new Guidelines, there are many more elective indications to guide drug selection.

### **What are the recommendations about the use of home blood pressure and ambulatory blood pressure monitoring?**

The Guidelines are much more precise about the treatment of conditions based on ambulatory blood pressure (ABP) and home blood pressure (HBP) values.

Isolated office hypertension, where office BP is high but ABP or HBP are within the normal range, is not an innocent clinical condition. It carries a greater risk, based on the evidence. Masked

hypertension, where the OBP is within the normal range, but the HBP or ABP are elevated also is a high-risk condition, and about 1 in 7 persons have masked hypertension.

HBP should be used frequently because of the evidence of its prognostic importance, and because there is evidence that involving patients in the treatment strategies improves compliance. The Guidelines also include data that the three different BP values could be additive in risk prediction. A paper from the PAMELA study showed there is minimal risk in persons in whom all three values are normal, but that risk increases progressively as the number of the different BP measures (office, home, ambulatory) increases.

Central blood pressure is mentioned, but not recommended, in the Guidelines. There is evidence from the CAFÉ study that BP measured in the brachial artery may not be the same as the blood pressure measured in the aorta, and the effect of treatment may not be the same. There is a technique that seems to provide an indirect estimate of central BP from the peripheral BP system. Although this is regarded as interesting, it is not feasible to do in clinical practice and is still in need of more evidence.

### **How is masked hypertension usually identified?**

It is not feasible to measure HBP or ABP in everyone, but I think one must keep in mind that a normal office BP does not automatically mean it is always normal. So, for example, if there is some evidence of organ damage, such as an increase in LV mass or some thickening of the carotid artery, or there are risk factors, such as metabolic risk factors, it is reasonable to use HBP or ABP because there is a chance that BP could be elevated. Hence, good clinical skills and family history are important to identify persons in whom some of these other parameters should be measured and monitored and if they are elevated, use ABP or HBP to determine if there is masked hypertension.

### **What is the appropriate approach to treat patients with diabetes and hypertension?**

The treatment of diabetes and hypertension includes intense lifestyle measures, a lower threshold (high normal blood pressure) for initiating drug treatment, a lower treatment target (<130/80 mmHg), and treatment of other risk factors, particularly a statin and consideration of antiplatelet treatment.

All drugs are useful for the treatment of diabetes and hypertension, including BB and diuretics. In fact, diuretics may be needed because of the need for combination treatment, which is extremely common in diabetics. But, because of the evidence that a blocker of the RAS may exert primary, plus secondary, prevention on renal disease, it is appropriate to include it in the combination treatment. This drug may prevent the appearance of microalbuminuria and diabetic nephropathy and may slow the progression of diabetic nephropathy. Thus, a blocker of the RAS, either an ACE inhibitor or an ARB, should be included in the therapeutic cocktail.

### **Is there a difference in treating patients with metabolic syndrome compared to patients with diabetes and hypertension?**

Yes. Patients with diabetes and/or hypertension also may have metabolic syndrome. In the presence of metabolic syndrome and/or diabetes and/or hypertension, a blocker of the RAS should be included in the treatment strategy. If BP is not controlled, add a CCB, and then a diuretic, at a low dose if possible to minimize the risk of developing diabetes, which is very high in these patients.

The big question is how do we treat patients with metabolic syndrome and high normal BP? There is no evidence. So, the guidelines say these persons are at high risk. If they have metabolic syndrome and their BP is 138/88 mmHg, the incidence of CV events is high. But there is no specific study proving that antihypertensive drugs are beneficial in these patients. The Guidelines

recommend intense lifestyle changes and consideration of drug treatment, because this is a high-risk condition for which there is a lack of evidence.

Extrapolating from data in other high-risk situations, such as diabetes, history of cerebrovascular disease or coronary heart disease, it seems logical that lowering BP to well below <140/90 mmHg in persons with metabolic syndrome plus hypertension is beneficial.

### **Any special recommendations for treatment of women with hypertension?**

The guidelines state there is meta-analyses of data showing that the proportion of benefit of treatment is similar in men and women. The general treatment strategies are the same. The only caveat is that women in the fertile ages should have a special warning against the continuous, unchecked use of drugs acting against the RAS, because of the potential teratogenic properties.

### **What are the guiding principles for the treatment of high BP in the elderly?**

Exactly the same rules as for middle-age persons, keeping in mind that most of the data come from older persons. The only caveat is that because the elderly are more fragile and particularly the homeostatic BP control may be compromised, treatment should start with a lower dose and dose adjustment should be slower and more cautious. The BP threshold for treatment, BP target, types of drug used, combination treatment, everything should be the same for persons up to 80 years of age. Treatment in persons over 80 years old is unexplored territory, with only meta-analyses of trials with a limited number of patients in some trials and the HYVET pilot study. However, the Guidelines say, again based on logic, that if treatment was initiated before 80 years of age, there is no reason to stop successful treatment after this age.

### **The guidelines state a goal of <130/80 mmHg for patients with cerebrovascular disease and with CHD? Is this new?**

This was mentioned in the previous guidelines, but in the 2007 Guidelines this treatment goal is argued much more effectively. A retrospective analysis of the PROGRESS study showed a progressively smaller rate of ischemic stroke and hemorrhagic stroke for achieved systolic blood pressure (SBP) down to about 120 mmHg. In the INVEST study, there was some evidence of a J-curve for MI below <120 mmHg, but for stroke there was progressive reduction in events. Regarding CHD, there are data pointing to <130 mmHg being more protective. These include the EUROPA and CAMELOT studies, and to some extent ACTION. The only negative finding is from the PEACE study and this is stated in the guidelines. The data is not totally convergent, but is by and large good evidence, and weighted in the direction of greater benefit for a SBP <130 mmHg.

### **Any final comments about the 2007 Guidelines?**

A brief but specific comments is made in the 2007 European Guidelines about the ABCD treatment strategy. We believe there is no specific ground for this treatment strategy. Further, the age of 55 years for guiding drug choice is arbitrary because most of the data on ACE inhibitors and ARBs have been obtained in older persons.

Finally, the Guidelines are intended to be educational, not prescriptive. This is because guidelines treat diseases in general, and this could be very different from situations in individual patients. Clinical judgment is required to apply the Guidelines to specific patients in daily clinical practice. Clinicians like simplicity and the European guidelines have taken the approach, in contrast to many other hypertension guidelines, of being educational by explaining the evidence that is the basis for the recommendations and then to have "position statements" that contain conclusive recommendations in a relatively simple fashion that is a highly useful for the practicing fashion. We believe this approach is successful, and are proud to say that that the 2003 ESH/ESC Guidelines are the most widely quoted article in the medical literature.