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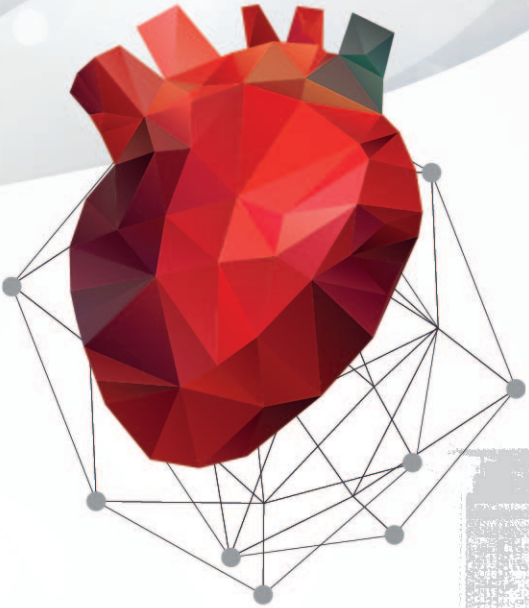

ON HYPERTENSION AND CARDIOVASCULAR PROTECTION

12TH-14TH JANUARY 2017 - BRESCIA (ITALY)

ABSTRACT BOOK

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Genetics of hypertension and precision medicine

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Human primary or essential hypertension is a complex, polygenic trait with some 50% contribution from genes and environment. Richard Lifton and colleagues provided elegant dissection of several rare Mendelian forms of hypertension, exemplified by the glucocorticoid remediable aldosteronism and Liddle's syndrome. These discoveries illustrate that a single gene mutation can explain the entire pathogenesis of severe, early onset hypertension as well as dictating the best treatment.

The dissection of the much more common polygenic hypertension has proven much more difficult. Early studies used a single polymorphic marker such as the I/D polymorphism in the ACE gene and small numbers of cases and controls. Candidate gene studies have been largely non-informative and non-reproducible. These were followed by linkage studies, which used approximately 300 microsatellite markers distributed across the genome. These studies resulted in large peaks covering regions with 50-100 genes, with no easy way to quickly focus on a few genes of causal relevance. The real breakthrough came with the initiation of the genome wide association studies (GWAS) characterised by a much more thorough coverage of the genome with thousands single nucleotide polymorphisms (SNPs). Typically 500,000 – 2,5000,000 SNPs have been used for the big, collaborative GWAS for hypertension. These studies resulted in several "hits" or signals with a genome-wide significance and a high level of reproducibility between studies. These "hits" have been used successfully to calculate genetic risk scores for cardiovascular complications such as left ventricular hypertrophy, stroke and coronary artery disease. Intragenic signals, such as for example Uromodulin, are being used to examine new pathways for cardiovascular protection and possibly new targets for drug discovery as well as new style clinical trials.

The next steps in genomic medicine belong to a combination of the next generation sequencing (NGS) and/or other "omics" data followed

by linkage with electronic health records, including preferably the real time clinical data, biochemistry, imaging, histology as well as longitudinal health outcomes.

Precision medicine involves examining the genetic makeup of patients and their differing responses to drugs designed to treat specific diseases. By building up an understanding of the 'strata' of responses and the genetics of the diseases, we hope to create more personalised and effective forms of treatment for groups of patients most likely to benefit. Significant past investment in Scotland in electronic health records (EHRs) and translational medicine research, coupled with a vibrant healthcare technology industry, positions Scotland as the location to drive forward the precision medicine agenda globally.

Figure 1 (modified from Aronson SJ & Rehm HL, Nature 2015;526:336-342) illustrates the precision medicine ecosystem as currently implemented in very few selected centres word-wide including our own. These modalities of precision medicine are ready for the prime time now.

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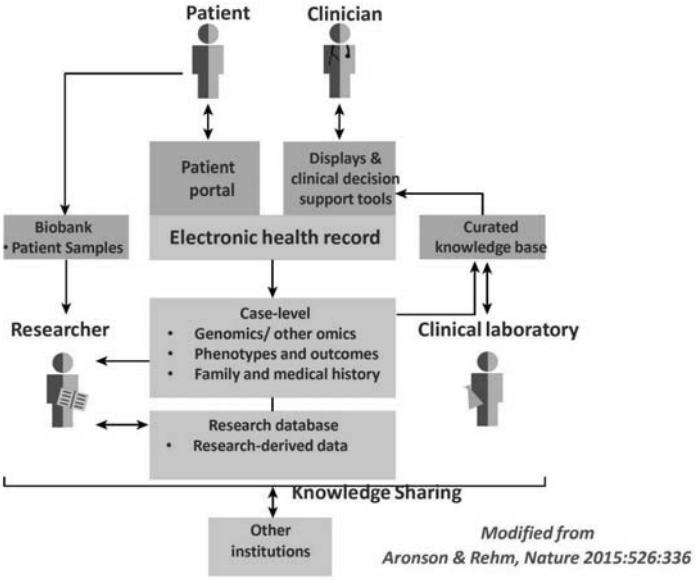
The Precision-Medicine Ecosystem

Figure 1



Adherence to antihypertensive treatment

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In hypertension, lowering blood pressure (BP) to the recommended targets is the most effective way to reduce both total and cardiovascular mortality in hypertensive patients and to decrease the risk of developing cardiac, renal and neurological complications [1-3]. Today, the clinical management of essential hypertension is based essentially on the recommendation of lifestyle changes such as losing weight, eating less salt or exercising more and on the prescription of BP lowering drugs [1]. More recently, the development of interventional treatments such as renal denervation, baroreceptor stimulation or the creation of an iliac arterio-venous fistula has provided additional opportunities to control BP especially in patients with resistant hypertension [4-6].

Whatever the therapeutic alternative proposed to control the patient's high BP, adherence is a major determinant of the success of therapy. Indeed, changes in lifestyle necessitate a long-term perseverance and persistence in order to be efficacious. Similarly, long-term adherence to drug treatments is essential to obtain the clinical benefits of antihypertensive therapy even after interventional procedures. Thus, Mancia et al have reported that the higher the percentage of clinical visits with a normal BP, the lower the incidence of clinical outcomes [7]. In addition, in a cohort of 242 594 patients aged 18 years or older, residents in the Italian Lombardy Region, who were newly treated for hypertension during 2000–2001, those who continued their treatment had a 37% reduced risk of cardiovascular outcomes when compared with those who experienced at least one episode of treatment discontinuation [8]. In patients with very low drug coverage, the risk of cardiovascular events was markedly reduced suggesting that compliance with antihypertensive therapy is crucial for the primary prevention of cardiovascular outcomes [8]. This observation is actually not specific for hypertension since similar observations have been made with other drug classes prescribed for the primary and secondary prevention of cardiovascular diseases [9].

This presentation will address several aspects of the role of drug adherence in hypertension with a special emphasis on the impact of adherence in uncontrolled hypertension.

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Epidemiology of hypertension and related diseases. The use of big data

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Over the last two decades, the status of high blood pressure (BP) has increased from being the fourth risk factor for global disease burden in 1990 to the first in 2010. Consequently, the increase in annual mortality over the time period accounted for more than 2 million deaths. Developments in hypertension management have included new interventions (e.g. renal denervation and carotid baroreceptor stimulation), novel treatments like direct renin inhibitors, new treatment modalities such as fixed-dose combinations and increasing use of out-of-office BP measurement. In 2016, these six key challenges remain and BP control is still sub-optimal with only 39% of hypertensive patients achieving a BP target of <140/90 mmHg; therefore, a challenge for physicians is to get patients to goal and increase the BP control rates. Despite these developments, the lifetime burden of hypertension remains substantial, and highlights the need for new strategies.

Given the advances in information systems and the increase in the number of electronic health records (EHR), it is now possible to develop combined research and surveillance programs that encompass whole populations. Components of this approach have implemented over many years, but until now social security systems have not been sufficiently well developed to provide the framework for a fully comprehensive information system. To be successful, this new approach must rely on existing social security data systems, such as those currently existing in many western European countries. To achieve this major step forward in public health intense collaboration will be required between epidemiologists, statisticians, information scientists, health services researchers, health economists, demographers, clinical physicians, and government officials, among others. Major challenges are faced in the effective integration of the EHR into health systems. At the same time, enormous potential

exists not only to improve individual health care but support research on the effectiveness of health systems as a whole. Given the current array of proven interventions for hypertension and cardiovascular disease (CVDs), the EHR provides unique opportunities to enhance our understanding of the distribution and control of the underlying CV risk factors and other modifying conditions which impact patient outcomes. The EHR system of the Valencia Community, named ABUCASIS II, is the framework for the ESCARVAL (Estudio CARdiometabólico VALencia)-PREVENTION project, a study based on the entire population of this region that is complemented by a large cohort of patients being followed through their experience in usual care.

Recently, the European Comission released a document in which recommendations were developed for ten relevant fields: awareness raising, education and training, data sources, open data and data sharing, applications and purposes, data analysis, governance of data access and use, standards, funding and financial resources, as well as legal aspects and privacy regulation.

Old and new drugs in hypertension

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Guidelines of ESH recognize four main groups of antihypertensive drugs diuretics, betablockers, calcium antagonists and renin-angiotensin system (RAS) blockers[1]. The concept of old and new drugs has been used in the last two decades in two ways, first to differentiate those drugs more commonly used in clinical practice, usually in double or triple combination according to the existing evidences obtained in RCT. This group is composed by RAS blockers, calcium antagonists and diuretics and the combination of two or the three of them is recommended by the most relevant guidelines. The triple combination is followed if needed by the addition of spironolactone[2] and afterwards betablockers enter in the game (except if they are needed before due to any specific indication). On the other hand, this sheme has been accompanied by the development of fixed combinations that have greatly contributed to improve compliance and long-term adherence to treatment[1]. The second way to consider new drugs, depends on the appearance of new drugs with particular mechanis(s) of action and with a higher capacity to facilitate BP control. In this sense two recent examples of drugs improving BP control or side-effects are the combination of sacubitril/valsartan that has demonstrated a significant improvement in heart failure with reduced ejection fraction[3] and an excellent antihypertensive capacity[4] and finerenone a non-steroideal mineralocorticoid receptor antagonist that shows in the preliminary data a significantly lower prevalence of hyperkalemia with a promising effect on BP[5].
Also new oral antidiabetics particularly SGLT2 antagonists and GLP1 agonists have shown to contribute to a better BP control while facilitating a decrease in body weight[6].
BP control can be expected to improve after the new concepts and drugs are widely used.

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Present status and future prospects of blood pressure measurement research

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Office blood pressure (BP) is a recognized marker of cardiovascular (CV) risk over a wide range of values. This is the case both in the epidemiological setting and in treated hypertensive individuals in whom a reduced office BP predicts a reduction of CV outcomes. The relationship between office BP and CV outcomes is not closed, however, regardless whether systolic BP, diastolic BP or pulse pressure is considered. This has led research to investigate other possible BP measurements to determine whether they can improve the quantification of the risk in absence and during treatment. This presentation will discuss the available possibilities, i.e. evidence of the prognostic value of BP self measured at home, over the 24 hours (or day and night periods), in the central arteries and during exercise. It will also be discussed whether different ways of collecting office BP values, such as for example semiautomatic measurements in the unattended patient, may offer clinical advantages. It will be concluded that all pressures have a relationship with CV risk. It is not yet completely clear, however, to what extent BP measurements other than the conventional office one have a better prognostic significance or add to the prognostic estimate provided by office BP. More research is thus needed in this direction, particularly to show the advantages of alternative or complementary BP measurements for the estimate of the protective effect of treatment.

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Hypertension in children and adolescents

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During the last few decades, hypertension in children and adolescents has gained ground in cardiovascular medicine thanks to the progress made in several areas of pathophysiological and clinical research. The available data concerning childhood blood pressure has increased and clinicians can use pediatric reference blood pressure data to determine whether blood pressure is in the normal range or is at a level that warrants evaluation or preventive intervention. It has also become possible to refine blood pressure derived parameters and to identify subclinical end organ damage through measures and markers now far more sensitive than those available years ago.

DEFINITION OF HYPERTENSION

In childhood and adolescents blood pressure increases during growth and maturation, and adolescence is a fast growth period during which body mass and blood pressure change rapidly. These are the main reasons for why reference blood pressure values over the last few decades have been referred to as ones specific to sex, age, and/or height in children and adolescents up to 18 years of age.

Recently, the 2016 Guidelines introduce a new criteria for boys and girls 16 or older since considering the 95th percentile for age, sex and height as the definition of hypertension, a 16 year old boy in the 95th percentile for height would be defined as hypertensive by an office systolic blood pressure of 137-140 mmHg, while a 16 year old girl in the same height percentile by an office SBP of only 132 mmHg. One-two years later, no longer seen by a paediatrician, the girl will now be diagnosed as normotensive or high normal by the family physician on the basis of adult guidelines. Even greater differences in diagnosis will occur in adolescents shorter than the 95th height percentile. Due to these differences in diagnosis, a consensus in the 2016 Guidelines is

given that for boys and girls aged 16 or older, the definition of hypertension should no longer be based on the 95th percentile but on the absolute cut-off used for adults, which defines high-normal (130-139/85-89 mmHg) and hypertension (≥140/90 mmHg).

ETIOLOGY

Pediatric hypertension is associated with a broad spectrum of diseases that changes from childhood through adolescence. Definable causes of hypertension are the rule in the early years of life, whereas essential hypertension is more common in adolescence. Consequently, techniques for the evaluation and diagnosis of hypertension differ, at least in part, among the different age groups.

TARGET ORGAN DAMAGE AND CONSEQUENCES

Blood pressure level and the duration of arterial hypertension result in target organ damage. Heart failure, renal insufficiency, cerebral seizures, hemorrhagic stroke, visual impairment, encephalopathy and posterior reversible leukoencephalopathy are complications associated with severe hypertension in children and even in infants. Nowadays, these complications seldom occur in infants and children due to early diagnosis and efficient antihypertensive treatment.

Because overt morbid cardiovascular events are rare in the majority of hypertensive children, attention has focused on other markers of hypertension injury, such as early renal damage, increased left ventricular mass index and functional or organic vascular abnormalities. Cardiovascular damage develops in parallel to renal damage, although the cardiovascular sequelae of childhood onset hypertension, such as left ventricular hypertrophy and dysfunction and atherosclerosis, may not become clinically relevant before adulthood. More recently, the study of early alterations of central nervous system functions has become a focus of interest.

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Hypertension in Pregnancy

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Hypertension complicates about 10% of pregnancies. The definition of hypertension in pregnancy is based on absolute office (or in-hospital) BP values (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg).

The most important task of classification of hypertension in pregnancy is to establish whether hypertension predates pregnancy (pre-existing hypertension) or whether it is pregnancy-induced hypertension (gestational hypertension). If BP is first recorded after 20-week gestation, the classification is possible only at or after 42 days post-partum (antenatally unclassifiable hypertension) (1).

Pre-eclampsia is defined as gestational hypertension with significant proteinuria (≥ 0.3 g/24 h or ≥ 30 mg/mmol urinary creatinine in a spot urine random sample); it remains a major cause of maternal death worldwide, the fetus is at increased risk of growth restriction and premature delivery. The only solution is delivery.

In the absence of randomized clinical trials, recommendations can only be guided by expert opinion.

Non-pharmacological treatment of hypertension should be considered in pregnant women with systolic BP 140–150 mmHg or diastolic BP 90–99 mmHg. Salt restriction is not recommended nor is weight reduction in obese females.

An SBP ≥ 170 or DBP ≥ 110 mmHg in a pregnant woman should be considered an emergency requiring hospitalization. Drug treatment with intravenous labetalol, or oral methyldopa, or nifedipine should be considered.

The benefits of antihypertensive therapy for mildly to moderately elevated BP in pregnancy (< 160/110 mmHg) have not been demonstrated in clinical trials (2).

The 2013 ESH/ESC guidelines suggest considering drug treatment in all pregnant women with a persistently elevated BP ≥ 150/95 mmHg. The initiation of antihypertensive treatment at 140/90 mmHg is recommended in women with gestational hypertension (with or without proteinuria); pre-existing hypertension with superimposed gestational hypertension; hypertension with subclinical organ damage or symptoms at any time during pregnancy. Methyldopa, labetalol, and calcium antagonists are the drugs of choice for non-severe hypertension. ACE inhibitors, angiotensin 2 antagonists, and direct renin inhibitors should not be used in pregnancy. Women at high or moderate risk of pre-eclampsia should be advised to take 75 mg of aspirin daily from 12 weeks until delivery (3).

Tight versus less tight control of hypertension was associated with less development of severe maternal hypertension, but there was no difference in the risk of adverse perinatal outcomes and overall serious maternal complications (4). A secondary analysis of CHIPS data in severe hypertension clearly showed that women developing severe hypertension have higher rates of pregnancy loss or higher neonatal care for > 48 hours, birth rate < 10th percentile, pre-eclampsia, preterm delivery, platelets < 109/L, elevated liver enzymes with symptoms, and maternal length of hospital stay ≥ 10 days). Maternal death or serious maternal complications were more common in women with severe hypertension and less tight control (5).

A soluble fms-like tyrosine kinase 1 (sFlt-1) to placental-growth factor (PlGF) ratio ≤ 38 can be used to predict the short-term absence of pre-eclampsia in women with clinically suspected syndrome (6). Kits are now readily available and affordable.

Postpartum hypertension is common in the first week. Methyldopa should be avoided because of the risk of postpartum depression (7). Breast-feeding does not increase BP in the nursing mother. All antihypertensive agents taken by the nursing mother are excreted into

breast milk (8), most of them are present at very low concentrations except for propranolol and nifedipine.

Women experiencing hypertension in their first pregnancy are at increased risk in a subsequent pregnancy. The earlier the onset of hypertension in the first pregnancy, the higher the risk of recurrence.

Women developing gestational hypertension or preeclampsia are at increased risk of hypertension, stroke and ischemic heart disease in later adult life (9–10). Lifestyle modifications are primarily indicated to avoid complications in subsequent pregnancies and to reduce maternal cardiovascular risk in the future. Therefore, regular, possibly annual, visits to primary care physicians for BP and metabolic factors check are recommended.

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Hypertension in women: Target organ damage

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In European countries and in the USA, hypertension represents an important risk factor for cardiovascular diseases (CVD) in men and women. Women do not perceive CVD as an important health problem, despite the evidence that women are more at risk to die from hypertension-related CVD than men. In more recent years , hypertension awareness and treatment rates are higher in women than in men while blood pressure control rates are improving , but remain still lower in older hypertensive women.
A correct prevention strategy should more widely acknowledge sex-specific risk factors, such as hypertension in pregnancy, the concomitant presence of autoimmune diseases (such as systemic lupus erythematosus) and the benefit of evaluating subclinical organ damage and of treating hypertension in both men and women.
In accordance to current guidelines, the diagnostic approaches do not differ between men and
women. The use of ambulatory blood pressure monitoring has shown that female sex represents one of the main factors associated with a higher prevalence of white coat hypertension, whereas male sex is related to increased prevalence of masked hypertension. In addition in hypertensive women, the absence of nocturnal dipping has been found associated with a greater LV mass index and concentric geometry than in men.
The response of the LV to pressure overload may differ by sex, suggesting greater sensitivity to pressure overload in women, although this association may vary according to age and ethnic differences.
Obesity may potentiate the effect of hypertension on LVH to a greater extent in women than in men.
Several studies have observed peculiar abnormalities in left ventricular (LV) systolic and diastolic function according to gender, although the possible mechanisms that influence a different cardiac adaptation to chronic pres¬sure overload in men and women are not fully understood.

The increase in LV mass in response to chronic pres¬sure overload is associated with higher LV ejec¬tion fraction in women than in men; when other measures are examined, it has been shown that LV torsion is maintained in women but not in men.
Changes in aortic stiffness that occur with aging may influence cardiac structural and functional changes. Isolated systolic hypertension, reflecting aortic stiffness, is frequent in women. Women with isolated systolic hypertension are more likely to develop concentric LVH, and to suffer from strokes and heart failure with preserved ejection fraction. In older hypertensive women a higher degree of vascular and myocardial stiffness has been observed , as compared with men.
An earlier pulse wave reflection may occur in women due to the shorter height, inducing an increase in augmentation index; this process could be influenced by the hormonal status, and in particular by the lack of estrogen effects after the menopause. Estrogen, but not testosterone levels, may contribute to the cardiac hypertrophic response in rats, while in postmenopausal women an increase in relative wall thickness was observed, suggesting a concentric cardiac adaptation response to increased afterload.
The regression of hypertensive left ventricular hypertrophy is more difficult to be obtained in women, and residual hypertrophy is more common in women than in men despite effective antihypertensive treatment and blood pressure control.

Microalbuminuria is a marker of cardiovascu¬lar and renal risk, and is a sign of target organ damage in essential hypertension [European Society of Hypertension and European Society of Cardiology, 2013].
The prevalence of albuminuria and of reduced estimated glomerular filtration rate (eGFR < 60 ml/min/1.73) are respectively lower and higher in postmenopausal women than in men.
Data are scanty about microvascular structural abnormalities in women , although changes in coronary microcirculation structure and function are most often seen in women. No differences in subcutaneous small artery structure or retinal arterioles has been have observed up to now between hypertensive men and women.

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Recent Meta-analyses of Randomized Trials of Antihypertensive Treatment

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Some of the questions the physician is confronted with daily have not received a definite answer by suitable intervention trials, and this is reflected in the low strength of the recommendations given by most guidelines. The most important of these questions are:
1. When should antihypertensive treatment be initiated, and, in particular, should grade 1 hypertensive individuals at low-moderate cardiovascular risk be treated?
2. What should the systolic/diastolic blood pressure targets of treatment be? Lower than 140 mmHg or lower than 130 mmHg for SBP? Lower than 90 mmHg or lower than 80 mmHg for DBP?

Initiation of antihypertensive treatment. Recent hypertension guidelines, confronted with the question when to initiate antihypertensive treatment have acknowledged that trial-based evidence about the systolic blood pressure threshold deserving treatment is weak.

A meta-analytical approach has recently been followed by our group to investigate this problem. Among all blood pressure lowering trials we have chosen those in which patients had been randomized in absence of current treatment, in order to avoid incorrectly labelling hypertension grade. We identified 32 trials (including 104 359 patients) that could be classified as investigating grade 1, 2 or 3 hypertension on the basis of the average baseline blood pressure in each trial. As some of these trials included patients at high cardiovascular risk, another meta-analysis was done only including trials or trial subgroups with mean baseline SBP/DBP values in the grade 1 range and a low to moderate cardiovascular risk (<5% cardiovascular death in 10 years in the control groups). In the 8975 patients of this meta-analysis, blood pressure-lowering treatment

significantly decreased the risk of stroke, coronary events, the composite of stroke and coronary events and all-cause death. Absolute risk reduction was large, amounting to 21 strokes, 34 major cardiovascular events and 19 deaths prevented every 1000 patients treated for 5 years.
On the whole, despite the absence of a large randomized placebo-controlled trial specifically investigating blood pressure lowering treatment in patients with grade 1 hypertension at low to moderate cardiovascular risk, the data of our meta-analysis provide a much stronger evidence-based support in favour of initiating active drug treatment in grade 1 low-moderate risk hypertensives than the arguments that could be used in the 2013 ESH-ESC guidelines.

Blood pressure treatment targets. Although the target values to which blood pressure should be brought by drug treatment to optimize treatment benefits is of prominent interest for the patients and the treating physician, it is surprising that, among the large number of antihypertensive treatment trials (as many as 70), so few (only 14) have compared the effects of more versus less intense blood pressure lowering treatment, and even less have investigated precise SBP or DBP targets.

In 2014 we published a meta-analysis of 32 blood pressure lowering trials (including 128 232 individuals), showing that risk of all outcomes could be significantly reduced when SBP in the treated group was lowered to values less than 150 mmHg and compared to SBP values above 150 mmHg in the control group, and when it was lowered to values less than 140 mmHg in the treated group and compared to values above 140 mmHg in the control group. However, when SBP values below were compared to SBP above the cutoff of 130 mmHg, only stroke and all-cause death were significantly reduced. After the recent publication of SPRINT, we have updated our meta-analysis of blood pressure lowering trials stratified according to the three different cutoffs of achieved SBP (below and above 150, 140 and 130 mmHg). The meta-analysis now includes 35 trials on 138 452 individuals and shows that lowering SBP below 130 mmHg can significantly reduce most types of outcomes (stroke, coronary events, cardiovascular and all-cause death); however, absolute outcome

reduction was definitely smaller than at higher SBP cutoffs, and permanent treatment discontinuations for adverse events were significantly greater. It should be underlined, however, that even for SBP values less than 130 mmHg mean risk estimates of all outcomes were lower than 1, hence there was no indication of a J-shaped relationship of the risk of any major outcome with achieved SBP, at least down to values several mmHg below 130.

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Heart structure and function assessment

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Heart is most exposed to high blood pressure, as the target organ critically affected by the increased hemodynamic workload. Assessment of the heart status is critical for program of cardiovascular (CV) prevention and possibly to optimally address anti-hypertensive therapy[1]. There are a number of parameters that can be easily evaluated by commonly used transthoracic 2D-echocardiography or even more sophisticated and accurate methods, providing a full spectrum of left heart geometry, function and performance[2].
Specifically in hypertensive patients cardiac evaluation should include assessment of: 1) left ventricular (LV) mass index and LV geometry; 2) LV systolic function; 3) LV pump performance and output impedance; 4) left atrial (LA) size. Deeper evaluation of diastolic function might be useful sometimes.

1. Assessment of LV mass and geometry.
The gold-standard of assessment of LV mass (LVM) is generally considered cardiac magnetic resonance (CMR)[3], which is, however, challenged by 3D-echocardiography[4]. In clinical practice, 2D echocardiography is most used to estimate LV mass, using linear measurement of LV internal dimension (LVID), septal (IVS) and posterior wall thickness (PWT), by consolidated and validated methods[5], despite the intrinsic limitations highlighted in reliability studies[6]:

$$\mathrm{LVM} = 0.832 \times [(\mathrm{LVID} + \mathrm{IVST} + \mathrm{PWT})^3 - \mathrm{LVID}^3] + 0.6$$

One major and unresolved issue is normalization for body size. Although most used, body surface area (BSA) has been demonstrated to be an inefficient measure of body size, especially in overweight/obese patients, in whom height in meters raised to the allometric power of 2.7 should be used[7]. Prognostically validated values for clear-cut LV hypertrophy[1] are 47 g/m$^{2.7}$ for women and 50 g/m$^{2.7}$ for men.

Assessment of LV geometry should be completed by calculating relative wall thickness (RWT), the ratio between wall

thickness and LV transverse radius. The cut point for definition of concentric LV geometry is <0.43. In normal conditions, RWT increases with age and in some circumstance, an age-normalization might be wise to identify truly concentric LV geometry that might be misclassified especially in the youngest age span[8].

Assessment of LV mass is critical for definition of risk profile in hypertensive patients, whereas identification of LV geometric pattern might be important to establish the hemodynamic profile and potentially address treatment[1].

2. Assessment of LV systolic function.

The traditional measure of LV systolic function is ejection fraction (EF) that may be estimated using disk-summation methods by the Simpson rule or by aortic PW Doppler VTI (VTI_{ao}) at the hinging point of aortic valve leaflets together with the aortic valve orifice diameter (AOd), to calculate stroke volume and divide by LV end-diastolic volume (LVEDV), using the following formula:

$$EF = \frac{\pi \times \left(\frac{AOd}{2}\right)^2 \times VTI_{ao}}{LVEDV}$$

The two methods do not provide equal results and cannot be used comparably. Another possible and very rapid approach for simmetrically contractile ventricles is estimation of LVEDV and end-systolic volumes (LVEDS) using the "z-derived" method from LV linear measures[9].

EF is not an efficient and accurate method for evaluation of LV systolic function when LV geometry is concentric[10], a condition in which geometry-independent measures are more accurate, including midwall shortening and strain-imaging[10, 11]. End-systolic circumferential wall stress might also be estimated[10].

3. Assessment of LV pump performance and output impedance.

Being arterial hypertension a condition characterized by a combined pressure and volume overloads, together with the assessemnt of LV geometry, evaluation of pump performance by stroke volume (SV), cardiac output (CO), with the addition of estimated total peripheral resistance is useful and potentially important to evaluate the hemodynamic consistency of anti-hypertensive therapy[1]. Similar to LVM, also SV and CO can be normalized for body height to appropriate allometric exponent (2.04 and 1.8, respectively), to avoid

underestimation in obesity by the traditional use of BSA[12]. LV pump performance might be also evalauted as stroke work (SW) by combining SV with systolic blood pressure (SBP) by:

$$SW = SV \times SBP \times 0.014$$

where 0.014 convert mL×mmHg in grammeters.

Estimation of SW also allows estimation of "inapprorpiate" LV mass, which represents the excess of individual LV mass, compared with the sex-specific amount that would be needed to "compensate" hemodynamic workload at a given body size, a parameter that may be particularly useful in obese patients[13].

Finally, the measure of SBP at the end of the echocardiogram also allows estimation of myocardial "mechano-energetic efficiency", a parameters that interacts with LV mass, with interesting pathophysiologic implications[14].

4. Left atrial (LA) size.

In the absence of valve disease, LA size is a potent bioassay of diastolic dysfunction and a strong predictor of atrial fibrillation[15, 16]. Thus, assessment of LA size is a useful completion of cardiac evaluation of hypertensive patients, especially for risk stratification.

There are different methods to measure LA volumes, but the most recommended are the ones based on area-tracing methods (by Simpson rules or by area-length methods). However also the so called "elliptical method" based on the three orthogonal dimension is not negligible, because it has been shown to be well correlated, by a power regression, with the postero-anterior dimension, detectable in longitudinal parasternal long-axis view, and offers the possibility to estimate LA volume from one linear measure when direct detection of LA volume is not available or possible[17]. Also LA volume should be normalized for body size and the suggested anthropometric parameters to use is height to the second power[18].

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New technologies for large arteries and central BP evaluation

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In the last twenty years, the interest upon the stiffness of large arteries has grown enormously. This was clearly made easier by the opportunity to represent a so complicated parameter (the arterial stiffness) in a simple way, that is, as the measure of the speed of wave transmission along large arteries, the carotid-to-femoral pulse wave velocity (cf-PWV). For this reason, the concept of increased arterial stiffness had the great chance to translate into the field of clinical medicine with success.

It is now well recognized that the cf-PWV is the gold standard for measuring arterial stiffness, and that this measure is a powerful independent marker of cardiovascular risk. This has been showed in at least seven large studies with a high level of evidence [1-7]. The ESH guidelines propose arterial stiffness as a marker of organ damage in hypertension, with high predictive value and cost-effectiveness [8]. The proposed cut-off level of 10 m/s comes from a rough estimate of increased cardiovascular risk from previously cited prospective trials [9]. Moreover, this measure is easy to remember measure and simple to apply.

However, everyone who deals with cf-PWV well knows the major limitations inherent to the cut-off approach. Arterial stiffness may be defined as the resistance opposed to the deformation of the arterial wall for each given increase in volume [10]. Therefore, arterial stiffness depends on the elastic content of the arterial wall, that changes as a function of the aging process [11,12], and to the instantaneous distending blood pressure; moreover it has been experimentally demonstrated that the relationship between pressure and stiffness is not linear [13]. The age- and BP-dependency of arterial stiffness are therefore the two main limiting steps to the use of cf-PWV as a CV risk marker.

The recently published cf-PWV reference values obtained from a large European population, provided normative values of cf-PWV for each age decade and for each BP category [14]. Two recent studies

attempted to gain some knowledge about the meaning of BP-independent measures of cf-PWV. In the Framingham Offspring Cohort, it has been showed that, according to age and sex median values of cf-PWV, subjects with higher-than-predicted cf-PWV, irrespective of BP categories, were at increased CV risk [15]. Another study derived the "estimated PWV" for any individual according to MAP and age, and showed that estimated cf-PWV added independently to score risk equations (SCORE and Framingham) in prediction of combined CV end-points [16]. The perspective to represent the "vascular age" for each individual, which comes from BP and cfPWV values [17], and to compare it with the biological age, is an intriguing finding, but the clinical meaning of this approach has yet to be demonstrated.

The search for BP-independent measures of arterial stiffness opened the horizon to novel approaches.

A recent study showed the significance of the PWV ratio, calculated as the ratio between cf-PWV and carotid-radial PWV, as a MAP-independent marker of CV risk in end-stage renal disease [18]. Moreover, its clinical usefulness remains to be demonstrated in contexts other than CKD.

The so-called -stiffness index, which is measurable from the relationship between pressure inside an artery and its cross-sectional area, is a way to quantify arterial stiffness in a BP-independent way [19]. The working principle of the CAVI index [20], is to derive the -value by assuming that heart-ankle pulse wave velocity can be converted into a single pressure-independent stiffness index. Evidences from clinical studies suggest that CAVI is independently related to LV mass and cardiac geometry [21]. However, its true pressure-independence has been recently questioned [22].

Nevertheless, even if a pressure-independent stiffness index appears to be impossible to measure in clinical practice, the comprehension of the non-linear relationship between arterial wall stress and strain is essential to understand the close link between arterial stiffness and pulse pressure.

When, with aging, the elastic behaviour of large arteries deteriorates, the degree of stretching for any given distending pressure is reduced and, as the vessel is loaded during any cardiac cycle, it effectively stiffens. Since beta represent the degree of the curvature of the

pressure-area relationship, a higher degree of curvature result in a higher pulse pressure. Arterial stiffness represent the slope of the pressure-area relationship at any point, while “stiffening” represent the degree of curvature. As a consequence, pulse pressure depends on both arterial stiffness (a static measure) and arterial “stiffening” (a dynamic measure) [Gavish]. It has been postulated that the calculation of the arterial stiffening beyond arterial stiffness may be useful to refine the CV risk of an individual [23].

This hypothesis challenges the traditional view of PP as the result of the superimposition of forward and backward wave components, which are determined from the timing and amplitude of wave reflection. On this issue, a relevant study with appropriate methodology showed that, even for different levels of pulse pressure, the morphology of the backward pressure wave bears a constant relationship to that of the forward wave [24]. Moreover, the contribution of earlier arrival of backward wave seems to not affect the ratio between backward and forward wave amplitude. Despite some indexes of wave reflection are demonstrated to be strongly and independently related to CV risk [25-27], their exact meaning still remains to be fully elucidated.

The phenomenon of peripheral wave reflection is assumed to be one major determinant of the pulse pressure amplification from center to periphery, which is a prognostically relevant parameter which expresses the relationship between central and peripheral BP [28].

The availability of novel devices enabling the ambulatory non-invasive estimation of central BP simultaneously to oscillometric-derived brachial BP, coupled with wave separation and the estimation of cf-PWV from a single-point, will shead new lights on a better comprehension of these phenomena. Preliminary data suggest that 24-h central BP and 24-h cf-PWV may be more strongly related to indexes of organ damage such as LV hypertrophy [29] and retinal narrowing [30], than peripheral 24-h, yet these results needs to be confirmed in further studies.

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New technology for retinal arterioles to address the microcirculation

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Although the prognostic value of structural alterations in small subcutaneous arteries has been confirmed by two independent studies, according to the Guidelines for the management of arterial hypertension of the European Society of Hypertension and of the European Society of Cardiology "the invasiveness of the method makes this approach unsuitable for general use" (1).
Hence, the development of new, non invasive approaches for the evaluation of microvascular damage is needed. The interest of researchers was focused, in the last decade, on the retinal vascular district, since it represents the only microvascular bed that may be directly viewed with relatively simple approaches, such as an ophthalmoscope or a slit lamp (2). In addition, it is of interest that cerebral and retinal circulation share anatomic, physiological, and embryological features (3). In fact, we observed that the same kind of structural alterations previously observed in subcutaneous small resistance arteries are also present in cerebral small arteries of hypertensive patients.
One of the first attempt to precisely quantify structural alterations of retinal microcirculation was made by Wong et al. (4). By means of an automated computerized method, the authors have calculated the ratio between the arteriolar and venular external diameters (arteriolar to venular ratio: AVR) in circular segments of the retina. AVR resulted lower in hypertensive patients compared with normotensive controls (4). Recently, a meta-analysis has confirmed that retinal arteriolar narrowing and venular widening are independently associated with an increased risk of hypertension (5). However, its prognostic meaning is still controversial, since a correlation between AVR and incidence of cardiovascular events was detected only in women (4). Further studies have substantially challenged the ability of this parameter to correctly stratify hypertensive patients according to the extent of target organ

damage. Indeed, no relationship between quartiles of AVR and left ventricular mass, carotid artery intima-media thickness or urinary albumin excretion was observed (6). The relationship of retinal vessel calibre to future stroke events has been analysed in a systematic review and individual participant meta-analysis: wider retinal venular calibre predicted stroke, whereas the calibre of retinal arterioles was not associated with stroke (1). Even more recently, Harazny JM et al. proposed a further, interesting and promising approach (7). The method is based on the association between a confocal measurement of the external diameter of retinal arteriole, and an evaluation of the internal diameter with a laser Doppler technique (Heidelberg Retinal Flowmeter, Heidelberg Engineering, Germany), with calculation of the ratio between wall thickness and internal lumen (WL) (7). The same Authors, using this approach, could observe that WL ratio is increased in untreated essential hyprtensive patients compared with normotensive controls (8), and that an even more marked increase is present in hypertensive patients with a history of cerebrovascular events (7). Finally, a close relationship was observed between WL ratio and urinary albumin excretion, expression of the microvascular damage at the kidney level (9). When WL ratio and AVR of retinal vessels was evaluated in the same patients, only the first parameter was progressively higher comparing normotensives, treated hypertensives and hypertensives with a history of a cerebrovascular event, and these differences closely paralleled those observed for carotid artery intima-media thickness (10). A recent study compared in the same subjects and patients, WL ratio of retinal arterioles evaluated with scanning laser Doppler flowmetry and media/lumen ratio of subcutaneous small resistance arteries evaluated by wire micromyography, that is commonly considered the reference approach for the measurement of structural alterations in the small vessels, due to accuracy and well demonstrated prognostic value. A rather good agreement between the two techniques, with a Pearson's correlation index of 0.76 was observed (11).

A couple of years ago a novel and extremely promising approach was made commercially available: the direct measurement of WL ratio of retinal arterioles using an adaptive optics imaging system. This is a markedly improved version of a traditional fundus camera based on the approach originally applied to correct for aberrations in

astronomic optical systems (12). The system provides images of a quality and resolution never previously obtained. Vessel walls are clearly visible in most circumstances, provided that the eye fixation is correct and that the ocular media are clear. Rosenbaum D et al. (13) observed that blood pressure and age both independently increased WL ratio by thickening arterial wall. A short term reduction in blood pressure obtained by antihypertensive treatment induced a WL ratio decrease due to lumen dilatation rather than to wall thickness changes. By contrast, no modifications were observed in subjects with no reduction in blood pressure (13).

In conclusion, the results of the few available studies support the possible clinical relevance of the measurement of retinal arteriolar structure in clinical practice. Possible advantages related to the evaluation of WL ratio of retinal artery with adaptive optics are clear, in terms of no invasiveness and consequent possibility to obtain prognostic data about the presence and the regression of retinal microvascular alterations by antihypertensive treatment, which are presently lacking.

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Uric Acid and hypertension

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Cardiovascular diseases are the major cause of death in the Western world as a consequence of the extensive prevalence and the inadequate control of cardiovascular risk factors in the general population. Elevated levels of serum uric acid (SUA) are the ethiological mechanism in the development of gout and also significantly contribute to the increase in the relative risk of CV diseases in addition with the more consolidated CV risk factors (e.g. hypertension, lipid disorders, diabetes, etc). Among the mechanisms involved in the risk of CV disease in patients with hyperuricemia, a remarkable role is played by hypertension, whose prevalence is significantly increased in patients with elevated serum uric acid. The hypothesis linking uric acid with hypertension and cardiovascular disease is well grounded in animal models where the development in hyperuricemia is associated with an increase in blood pressure that can be prevented by the use of xantine-oxidase inhibitors leading to a decrease in serum uric acid. Similar data have been published in humans and in particular in the adolescent population where the levels of SUA are directly associated with the blood pressure levels or the develoipment of hypertension later in life. The relationship between hyperuricemia and the development of hypertension has been confirmed by several observational studies and after adjustment for almos all of the confounding risk factors. In particular the results of NHNANES and MRFIT studies clearly support a patogenetic role of elevated SUA in patients with initially normal blood pressure values. Very recently an abnormality in genetic profile has been identified in subjects with hyperuricemia prone to the development of hypertension confirming the pathogenetic role of serum uric acid in the onset of cardiovascular diseases.

Data from observational studies and physiological experiments suggest that there may be a causal relationship between plasma levels of SUA, hypertension and the incidence of cardiovascular and renal disease. An increase in the incidence of mayocardial infornction,

stroke and cardiovascular disease has been reported by the Rotterdam Study and by many others in the same field. In addition, elevated SUA have been reported to worsen the clinical prognosis af overt cardiovascular disease including congestive heart failure and coronary artery disease thereby supporting the possibility that an increase in uric acid levels may be involved in the development and progression of the vascular disease.

As far as the possible mechanism of action, there is a possibility that the levels of SUA must be considered only as the marker of the oxidative stress associated with the activation of xantino oxidase that is involved in its production. This hypothesis might open an interesting interpretation of the role of SUA in CV disease that should involve a functional difference among patients whose plasma levels of SUA ar due to an excessive production when compared to subjects whose hyperuricemia is the consequence of a reduced renal excretion or an exaggerated tubular re-absorption who would be more prone to tissue deposion of urate and gout. However despite these limitations in the methodological approach, the possible association between s.uric acid and cardiovascular disease is well supported by several epidemiological observation, can be reasonably explaind by a mechanicistc approach and might be favorably modified by appropriate treatment strategies involving both a biochemical and a structural approach addressing the protection of target organ.

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New antidiabetic drugs and the effects on blood pressure

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The prevalence of hypertension is strikingly high in diabetic patients, especially those with type 2 diabetes mellitus. The co-existence of hypertension and diabetes mellitus substantially increases the risk of macrovascular complications, including stroke, coronary heart disease, congestive heart failure and peripheral vascular disease, and contribute to excessive cardiovascular mortality. The cardiovascular risk is high even in newly diagnosed, asymptomatic hypertensive diabetic patients without overt cardiovascular disease and target organ damage.

Data from randomised trials have clearly shown the benefits of blood pressure control in patients with type 2 diabetes. The UKPDS Study, HOT Study and ADVANCE trial have clearly documented that blood pressure control in patients with hypertension and type 2 diabetes achieves a clinically important reduction in the risk of deaths related to diabetes and cardiovascular complications related to diabetes. In patients with diabetic nephropathy, the rate of progression of renal disease is closely related to blood pressure control. As documented by the STENO-2 Study, treatment of associated risk factors is of primary importance in patients with diabetes.

Two recent studies established benefits of empagliflozin and liraglutide at reducing the composite primary endpoint of major cardiovascular events. (CV death, nonfatal myocardial infarction, and nonfatal stroke). In the EMPA-REG trial, patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. In the LEADER trial, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.

In the EMPA-REG BP trial, empagliflozin for 12 weeks reduced 24-hour blood pressure versus placebo, irrespective of the number of antihypertensives and use of diuretics or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. There are several mechanisms which contribute to blood pressure lowering effect of empagliflozin including better nephroprotection and favourable effects on markers of arterial stiffness and vascular resistance.
In the LEADER trial, the systolic blood pressure was 1.2 mm Hg lower in the liraglutide group, the diastolic blood pressure was 0.6 mm Hg (95% CI, 0.2 to 1.0) higher and the heart rate was 3.0 beats per minute faster in the liraglutide group.

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The Sympathetic Nervous System in Hypertension

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The sympathetic nervous system plays an important role in the pathogenesis of primary hypertension and in certain secondary forms of hypertension. Although hypertension is a disease of multifactorial etiology, the pathophysiological role of neuroadrenergic factors is well established, however. This has been confirmed by a relevant number of studies, which assessed adrenergic drive either indirectly, by measuring circulating blood levels of the adrenergic neurotransmitters epinephrine and norepinephrine or by evaluating via the power spectral approach vagal and sympathetic frequency components, or directly, by quantifying efferent postganglionic muscle sympathetic nerve traffic in peripheral nerves as well as regional norepinephrine release and reuptake by adrenergic nerves via the norepinephrine radiolabeled technique. In recent years, such information has been expanded with collection of new data, allowing to confirm previous findings and in the meantime to generate new hypotheses. The main purpose of this presentation is to provide to the reader an update and critical overview of our knowledge on the behavior of the sympathetic cardiovascular function at normal and elevated blood pressure, focusing mainly on data collected in human studies and only briefly mentioning, for space-saving reasons, mechanisms, and therapeutic implications of the findings.
The new concepts developed in the last few years and the areas of future research will be finally emphasized.

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Hypertension and heart rate

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Mounting evidence shows that heightened sympathetic activity is associated with a greater risk of developing hypertension and atherosclerosis and that it is a potent predictor of cardiovascular morbidity and mortality. These relationships have been shown not only in general populations but also among hypertensive individuals, with important implications for the treatment of hypertension. Recent evidence suggests that the predictive power of resting heart rate for cardiovascular mortality is even greater than indices derived from analysis of heart rate variability. Results from the HARVEST and other studies showed that besides the resting heart rate also the changes in heart rate over time are predictive of outcome. The distribution of heart rate in a given population is often explained by a mixture of two homogeneous subpopulations. The identification of the two subpopulations can be obtained with "mixture analysis", a statistical test used in biological sciences to investigate whether a mixture of normal distributions better explains the variation of a trait than a single distribution. In the Tecumseh, HARVEST and Belgian populations, we could identify with mixture analysis threshold levels between normal and high heart rate varying from 80 to 85 bpm in keeping with the cutoffs suggested by the epidemiologic data.
Subjects with tachycardia exhibited the features of the insulin resistance syndrome. Long-term studies also showed that high heart rate is a precursor and predictor of obesity, abdominal obesity, insulin resistance and diabetes. In a recent analysis of the HARVEST study, subjects with heightened sympathetic activity as determined by analysis of heart rate variability showed a worse metabolic evolution and a faster progression to established hypertension. The clustering of several risk factors for coronary artery disease in subjects with fast heart rate also found in a number of epidemiologic studies suggests that sympathetic overactivity accounts in part for the increased cardiovascular morbidity in subjects with tachycardia. Moreover, tachycardia has a direct connection with cardiovascular events. Tachycardia increases artery wall stress and left ventricular stiffness,

leading to endothelial dysfunction and left ventricular systolic dysfunction, thus increasing the risk of heart failure, coronary events, and sudden death. Interesting results have been recently obtained also from heart rate recorded with 24h ambulatory monitoring. Within the frame of the ABP-International study, we found that ambulatory heart rate added to the risk stratification for fatal combined with nonfatal cardiovascular events in hypertensive patients.

In spite of this evidence high heart rate is still overlooked as a risk factor, but the fact that in most studies the risk related to fast heart rate remained highly significant after controlling for major risk factors for atherosclerosis suggests that it plays a direct role in the induction of the risk. Indeed, a significant association between elevated heart rate and cardiovascular mortality was found by our group also in elderly subjects from the CASTEL study and from the Syst-Eur study. In the Framingham, the CASTEL, the VALUE and the ABP-International studies, the significant relationship between heart rate and mortality held true when the patients who died within the first few years after baseline assessment were discarded from the analysis, suggesting that the heart rate-mortality association was not due to subjects with tachycardia having un underlying chronic disease.

Data obtained in the experimental animal and pooled data from intervention studies in patients with myocardial infarction or congestive heart failure suggest that drug-induced reduction of heart rate may be beneficial in several clinical conditions. Tachycardia (heart rate ≥ 80 bpm) has been found in over 30% of the hypertensive patients and thus reduction of high heart rate appears as a desirable additional therapeutic goal in a large proportion of the hypertensive population. Heart rate should be lowered homogeneously during the 24 hours, including the night-time period, as night-time heart rate has shown the strongest association with adverse outcome. In spite of this evidence, some authors claim that heart rate lowering in hypertension is conducive to increase cardiovascular mortality. This statement is mainly based on a meta-analysis of 9 clinical trials encompassing over 60,000 hypertensive patients. However, caution is needed when interpreting these findings for the possible fallacy of meta-analyses based on aggregate data. Analyses of individual patient data made in those trials actually led to opposite results as in all of the trials post-treatment heart rate (lower on beta-blocker treatment) was a better

predictor of cardiovascular events than baseline heart rate. These results are clearly in contrast with those extrapolated from aggregate data. Also increased arterial stiffness as an explanation for the detrimental effect of heart rate lowering in hypertension is a questionable mechanism. There is no doubt that a lower heart rate is accompanied by a greater augmentation index but this cannot be translated "tout court" into increased arterial stiffness because the augmentation index is modulated by many other variables. Acute studies have shown that pulse wave velocity, a well-accepted index of arterial stiffness, actually increases with increasing heart rate and increased heart rate is a powerful predictor of accelerated progression of arterial stiffness in the long term. In addition, a recent analysis of the HARVEST has shown that ambulatory heart rate is a positive long-term predictor of the augmentation index contrary to what is currently observed for resting heart rate measured at the time of the arterial elasticity assessment. The claimed profibrotic effect of beta-blockers on the arterial wall which would result in increased arterial stiffness is thus unlikely to occur. Indeed, a pooled analysis of 4 major IVUS trials demonstrated that beta-blocker treatment was associated with a statistically significant reduction in the yearly progression rate of coronary atherosclerosis (atheroma reduction, 2.4 mm^3/y). Thus, whether, how, and to what level heart rate should be decreased in hypertension is still a subject for debate and only a clinical trial will clarify this controversial issue.

According to the latest ESH/ESC Guidelines and a recent ESH Consensus Document the practicing physician may use the heart rate for cardiovascular risk stratification. When facing a hypertensive patient with high heart rate the first goal for the clinician should be to improve an unhealthy lifestyle. Sedentary habits, smoking, excessive alcohol consumption and heavy coffee use increase the sympathetic activity with consequent effects on resting heart rate. Regular physical activity causes a reduction of sympathetic tone and an increase of vagal activity with beneficial effects on both blood pressure and heart rate. Finally, in hypertensive patients with symptomatic tachycardia there is no evidence that reducing heart rate by available drugs (mostly beta-1 selective beta-blockers) would be unsafe.

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Hypertension and coronary artery disease

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Pathophysiological aspects
In essential hypertension remodeling of the small arteries (100–300mm of diameter) is the most prevalent and earliest form of target organ damage. At the level of the coronary artery tree it causes increased vascular reactivity and a reduction in coronary flow reserve at maximal vasodilation [1-2]. Coronary remodeling in the form of media thickening is mainly caused by complex haemodynamic and neurohumoral interactions.The dimensionsof the epicardial coronary arteries remain constant resulting in an elevated coronary flow velocity [3]. This may increase longitudinal shear stress, causing premature atherosclerosis. It should be noted that changes in microcirculation maintain the increase in vascular resistance that is common in hypertension. Exposure of the large coronary arteries to high pulsatile pressure and blood flow velocity can lead to an increase in endothelial shear stress, resulting in endothelial dysfunction responsible for the increase in the endothelial permeability and deposition of lipoproteins in the arterial wall and eventually the formation of atherosclerotic plaques [4].
In hypertensive patients, the structural alterations of the intramyocardial arteries of the coronary tree contribute to the reduced coronary vasodilator capacity and to an increased minimal coronary resistance independently of the presence of left ventricular hypertrophy [5]. Studies have documented a reduced coronary reserve in most of the hypertensive patients even in the absence of coronary artery disease. Responsible of this impaired coronary vasodilator reserve are considered mainly the intramyocardial arterioles that largely contribute in the coronary vascular resistance and the autoregulation of myocardial perfusion. Arterial hypertension increases the wall-to-lumen ratio of theintramyocardial arteries by inducing arterial medial hypertrophy that in turns leads to wall thickening and lumen reduction. Moreover, the coronary vasodilator capacity can be influenced by vascular tone, endothelial dysfunction,

increase of vascular collagen biosynthesis, interstitial and periarteriolar fibrosis or/and noxious interactions between structural and functional components of a thickened arterial wall.

Considering that the adverse functional microcirculatory changes could cause insufficient coronary perfusion and impaired wall function during stress, the presence of attenuated coronary flow reserve even in hypertensive patients without left ventricular hypertrophy identifies a subgroup at greater risk. Moreover, repeated stress and regional ischemia lead to fibrosis, which also impairs cardiac function leading to heart failure in the absence of obstructive coronary disease. Interestingly, coronary flow reserve attenuation might constitute the earlier phase of the hypertensive insult to the arterial coronary tree.

Clinical aspects

Coronary heart disease is multifactorial, but the level of blood pressure over a large and continuous range is one of the important factors, with a steeper association above a systolic blood presure of about 140 mmHg. The INTERHEART study showed that hypertension accounts for about 25% of the cardiovascular risk.

ESH/ESC guidelines reported that RCTs of antihypertensive treatment do not provide consistent evidence that systolic blood pressure goal should be <130 mmHg in hypertensive patients with overt coronary artery disease, nor is there consistent evidence that antihypertensive treatment should be initiated with high-normal blood pressure [6]. On the contrary, a number of the correlative analyses raising suspicion about the existence of a J-curve relation between achieved blood pressure and cardiovascular outcomes included a high proportion of heart disease patients, and it is not unreasonable that if a J-curve occurs, it may occur especially in patients with obstructive coronary disease. The recommendation to lower SBP to <140 mmHg is indirectly strengthened by a post-hoc analysis of the INVEST study (all patients with coronary artery disease) showing that outcome incidence is inversely related to consistent systolic blood pressure control (i.e. <140 mmHg) throughout follow-up visits as well as by the recent SPRINT trial's findings [7,8]

There is evidence for greater benefits of beta-blockers after a recent myocardial infarction, a condition in which ACE inhibitors have also been successfully tested. Later on, all antihypertensive agents can be

used. Beta-blockers and calcium antagonists are to be preferred, at least for symptomatic reasons, in case of angina [9].

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Hypertension and congestive heart failure

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Congestive heart failure (CHF) is a leading cause of morbidity, hospitalizations, disability, and death [1]. The current crude prevalence is approximately 2% and the incidence is approximately 3.2/100 person years, in both women and men, although these numbers increase with age [2]. Prognosis remains poor with a five year survival rate in a general population of CHF below 50% [2]. Indeed, five year survival rates for patients admitted to hospital for heart failure is lower than for the four most common cancer forms specific for women and men [3]. The cost of care and treatment of CHF constitute a considerable burden for health care [4], and the direct costs of CHF account for approximately 2% of the total health care budget in many European countries.

Although a myocardial infarction is associated with the highest hazard ratio for incident CHF the prevalence of hypertension is much higher than coronary heart disease. Hence, hypertension constitutes the greatest attributable risk for the development of CHF, particularly in women [5]. Antihypertensive drug treatment in hypertensive patients reduces incident CHF. The benefit of treatment seems greatest on preventing stroke and CHF, with a crude 28-46% reduction in heart failure hospitalizations and deaths by a 10 mm Hg reduction in systolic blood pressure [6,7]. This benefit appears to be present across all systolic blood pressure strata from 130 mm Hg and above before treatment [7]. In crude hypertensive populations, heart failure events are reduced more by blood pressuring lowering treatment with diuretics, and less by calcium blockers, as compared to other antihypertensive drug classes [7,8]. However, hypertensive patients may have different aetiology of their CHF, i.e. heart failure with preserved, mid range, or reduced left ventricular systolic function (HFpEF, HFmrEF, and HFrEF respectively) [9], which may favour

different antihypertensive drug classes and treatment to different target blood pressure values.

Hypertensive patients with coronary heart disease are typically at high risk for left ventricular dysfunction. In patients with left ventricular systolic dysfunction the benefit of treatment with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) is well established [9], although the evidence for ACE inhibitors may be considered more favourable. The benefit of beta blockers is also well supported in patients with left ventricular systolic dysfunction [9]. In patients with symptomatic CHF, the addition of mineralocorticoid receptor antagonists (MRA) are of benefit, and when congestion is present, diuretics should be used to reveal symptoms [9]. Thus, ACE inhibitors, ARB, MRA, beta blockers and diuretics are well suited antihypertensive drugs in patients with left ventricular dysfunction with or without symptoms (although the benefit on outcome by antihypertensive treatment with beta blockers appears weaker than by other drug classes). Given their well documented benefit in HFrEF, there should not be major concern about asymptomatic hypotension. Amlodipine and felodipine are dihydropyridine type channel blockers shown to be safe in HFrEF, whereas non dihydropryidne calcium channel blockers (i.e. verapamil and diltiazem) have negative inotropic effects and should be avoided in patients with left ventricular systolic dysfunction (but appears safe in HFpEF).

HFpEF is typically present in older hypertensive patients with a high prevalence of atrial fibrillation, and are more often female. This condition is associated with left ventricular hypertrophy with inappropriate myocadial fibrosis [10]. Careful control of blood pressure is important in HFpEF in order to prevent symptomatic heart failure and to prevent atrial fibrillation. Activation of the renin-angiotensin-aldosterone system is associated to myocyte hypertrophy and myocardial fibrosis, and is implicated in arrhythmias [10,11]. However, large outcome studies in patients with HFpEF have not yet been able to show benefit for specific antihypertensive drug classes [9]. Thus, concomitant conditions and symptoms should guide antihypertensive drug treatment in these patients in order to obtain

optimal blood pressure control. Target blood pressure in patients with HFpEF has not yet been well established; however current evidence suggests a target blood pressure of 130-135/80-85 mm Hg in these high risk hypertensive patients [6,7].

In summary, CHF is a leading cause of morbidity, hospitalizations, disability, and death. Hypertension constitutes the greatest attributable risk for the development of CHF. Antihypertensive treatment and control can markedly reduce incident CHF.

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Atrial fibrillation and Hypertension

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Atrial fibrillation is the most common sustained arrhythmia in humans and its prevalence is 1-2% of the general population worldwide. It affects 6 million people in Europe, while it is expected that its incidence will increase up to 2.5-fold over the next 50 years. It is estimated that atrial fibrillation poses a high economic burden for the healthcare system, since it is responsible for up to one third of the hospitalizations for cardiac arrhythmias. Subjects who have reached the age of 40, present a lifetime risk of 25% for developing atrial fibrillation and its incidence increases as the population ages. Atrial fibrillation affects significantly morbidity and mortality (2-to 7-fold increased risk for stroke, 2-3 fold increased risk for dementia and 3-fold increased risk for heart failure), while it is responsible for approximately 20% of all strokes. Finally, undiagnosed or silent episodes of atrial fibrillation may be the main cause of cryptogenic strokes.

Different risk factors are responsible for the development of atrial fibrillation. Among the most established and well identified, are age, hypertension (which forms a physiopathologic substrate favoring atrial fibrillation), coronary artery disease (>20% of the patients with AF), heart failure (30% of the patients with AF), valvular disease, congenital heart disease, hyperthyroidism, chemotherapeutic agents, obesity, diabetes mellitus, chronic obstructive pulmonary disease, sleep apnea and chronic kidney disease. Hypertension (HTN) is the most common cause of atrial fibrillation encountered in clinical practice. Epidemiologic studies have shown that HTN is associated with 1.8-fold increased risk of developing new-onset atrial fibrillation and 1.5-fold risk of progression to permanent atrial fibrillation. In an analysis of the Framingham Heart Study, men and women with hypertension had 50% and 40% higher risk of developing atrial fibrillation respectively. In many different atrial fibrillation clinical trials, 49%-90% of the participants suffered from HTN, indicating that these two entities usually coexist. Hypertension is the most prevalent

concomitant medical condition in patients with atrial fibrillation, in both Europe and USA.

Hypertension is likely to be a reversible causative factor of atrial fibrillation. Untreated or suboptimal treated hypertension leads to left ventricular hypertrophy, one of the most important subclinical organ damage responsible for major cardiovascular events including atrial fibrillation. In the Framingham Heart Study the levels of the systolic blood pressure and the duration of hypertension predicted the adverse atrial remodeling. Moreover, pulse pressure was associated with the incidence of atrial fibrillation. Many studies gave proof that hypertension is an independent risk factor for atrial fibrillation. In an analysis of 5,000 individuals in the Cardiovascular Health Study it was found that patients with 10 mmHg higher baseline systolic blood pressure had an 11% increased risk of atrial fibrillation over the 3-year follow-up. Once left ventricular hypertrophy is established, left ventricular compliance decreases, stiffness, filling pressures as well as left ventricular wall stress increase, and as a consequence the sympathetic nervous system and the renin-angiotensin-aldosterone system are activated.

Moreover, in the atria, alterations characterized by proliferation and differentiation of fibroblasts into myofibroblasts, enhanced connective tissue deposition, fibrosis, intracellular substrate accumulation and inflammatory changes, lead to structural remodeling. These structural alterations result in electrical dissociation between atrial muscle bundles and local conduction heterogeneities that facilitate the initiation and perpetuation of atrial fibrillation. Over the time, tissue remodeling promotes and maintains atrial arrhythmia. Atrial remodeling consists of three components: electrical remodeling mainly due to intracellular changes in calcium handling, contractile remodeling and structural tissue remodeling which needs weeks or months to occur and affects the function of the heart muscle.

Hypertension and the kidney

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The study of the relationship between the kidney and hypertension dates back to the work of Franz Volhard and coworkers, at the beginning of the 20th century, and possibly earlier, to the observations of Richard Bright, who had noticed that abnormal urine production by enlarged kidneys was associated with enlarged hearts. Nowadays it is widely accepted that the kidney plays a central role in blood pressure (BP) regulation, possibly being both culprit and victim in the pathophysiology of hypertension. Hypertension is an independent predictor of chronic kidney disease progression and represents the second leading cause of end-stage renal disease after diabetes mellitus. Furthermore, in hypertensive patients, even mild abnormalities in albumin excretion and glomerular filtration rate are markers of increased CV risk. In particular, preclinical renal damage in hypertension has been found associated to increased left ventricular (LV) mass, concentric geometry, impaired LV function, and to increased intima media thickness of the carotid arteries, to greater arterial stiffness and to structural changes in small resistance arteries. Importantly, available data clearly indicate that even mild reductions in estimated glomerular filtration rate (eGFR) and/or urinary albumin excretion are associated to a significant increase in the risk of cardiovascular (CV) events and chronic kidney disease (CKD) progression, independently of other CV risk factors. For this reason current hypertension Guidelines recommend the assessment of eGFR and urinary albumin excretion for a better assessment of global CV risk. Despite the clearly defined role of assessment of preclinical renal damage for cardiovascular risk stratification in hypertension, the role of serial assessments of markers of kidney damage during treatment is less clearly defined. A recent a systematic review and meta-regression analysis of available trials (16 randomized controlled trials and 48 580 patients) has shown that reduction in albuminuria under antihypertensive treatment is associated with reduced risk of cardiovascular events, suggesting that changes in albuminuria may represent a reliable intermediate end point in hypertensive patients.

Antihypertensive treatment is associated with significant reduction in CV events and mortality and slowing of renal disease progression in patients with CKD. Renin angiotensin system (RAS) blockers are particularly indicated in the presence of microalbuminuria or overt proteinuria; combination therapy is required in the majority of patients. Large prospective trials evaluating BP targets with respect to CKD progression are lacking; based on available evidence, ESH Guidelines recommend that in patients CKD (diabetic or non-diabetic), systolic BP should be lowered to less than 140 mmHg and also suggest that when overt proteinuria is present BP could be lowered to less than 130 mmHg, with careful attention of changes in eGFR. However it should be kept in mind that attainment of BP targets is difficult in these patients: a recent study reported that as much as one third of patients with CKD under nephrologist care have apparent treatment resistant hypertension and have an increased risk of CV events in the follow up. In addition, measurement of out of office BP could be particularly important in hypertensive patients with CKD, because of the marked alterations in 24-hour (BP) profile, with reduced BP dipping during the night, and the high prevalence of white coat and masked hypertension. However to date no randomized trial has tested the hypothesis that antihypertensive treatment strategies based on out of office BP are superior to strategies based on BP measured in the office.

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Obesity and hypertension

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Obesity is associated with a wide spectrum of metabolic and cardiovascular disorders, including arterial hypertension. Both the degree and the distribution of excess adipose tissue impact on the risk of hypertension and associated cardiovascular diseases.

The mechanisms that may lead to hypertension in obese individuals include increased adrenergic activity, impaired insulin sensitivity with hyperinsulinemia, sodium retention, increased uric acid generation, and impaired nitric oxide-dependent vascular relaxation.

All of the above abnormalities are interrelated in a complex fashion, making it difficult to determine which, if any, of them is the primary process leading to progressive blood pressure elevation in obese individuals. Nonetheless, there is no doubt that metabolic abnormalities and blood pressure levels are reduced by weight loss and chronic exercise, providing a strong rationale for hypocaloric diets and aerobic exercise in the treatment of obesity-related hypertension.

Patients who fail to achieve acceptable blood pressure control with diet and exercise therapy obviously require pharmacologic treatment. Of the available antihypertensive agents, calcium entry blockers, ACE-inhibitors and ARBs appear to offer good blood pressure control without worsening - and sometimes while improving - the lipid and carbohydrate abnormalities that often occur in obese patients. New drugs developed to favour urinary glucose (and uric acid) excretion show promise as antihypertensive agents as well, and may prove to be ideal in reversing multiple cardiovascular risk factors in obese, hypertensive patients.

Update on hypertension, the brain and cognitive function

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High blood pressure has been implicated in the development of cognitive dysfunction, vascular dementia and Alzheimer's disease in geriatric patients. Hypertension induces long-term remodeling and endothelial dysfunction in the brain arteries and subclinical damage (WML, microbleeds) may be detected using cerebral magnetic resonance imaging (MRI). Several studies have examined the relationship between WML severity and cognitive decline over time and found that subjects with severe periventricular WML had more rapid cognitive decline. Also silent lacunar infarcts and cerebral microbleeds are related with cognitive decline. Our group found an association between WML in brain MRI and poorer neuropsychological test results in middle-aged, asymptomatic, never-treated essential hypertensive patients. In this sense, results from cross-sectional and longitudinal studies have shown a correlation between systolic BP and WML, CMBs, and cognitive function in the elderly. Data from the Ohasama study show that increased home SBP and increased day-to-day SBP variability are associated with an increased risk of cognitive decline.
The mechanisms underlying hypertension-related cognitive changes are complex and not yet fully understood. Some data suggest that high pulse pressure is associated with an increased risk of dementia. Because increased pulse pressure is a clinical indicator of arterial stiffness, it has been postulated that functional changes in the arterial system are involved in the pathogenesis of dementia. Correlations between the severity of cerebral WML or MCBs and cognitive decline, and correlations between cognitive dysfunction and elevated BP provide indirect evidence that structural and functional changes in the brain over time may lead to reduced cognitive functioning when BP control is poor or lacking.

There is some evidence that antihypertensive drug treatment could play a role in the prevention of cognitive impairment, vascular dementia and Alzheimer's disease through BP control. Blood pressure lowering is beneficial in the vast majority of patients with vascular risk factors to prevent stroke, but only two observational studies and a meta-analysis suggest that prevention of WML progression and cognitive decline by lowering BP is possible, but this suggestion requires verification in large randomized clinical trials including appropriate cognitive endpoints. Concerning the incidence of dementia, al least five randomized trials comparing active treatment with placebo have shown a significant reduction, although no specific antihypertensive drug or strategy has demonstrated to be superior. In summary, current evidence supports the view that hypertension in mid-life, especially if not treated effectively, negatively affects cognition and contributes to the development of dementia in late life. High BP in the middle-aged implies a long-term cumulative effect leading to increased severity of atherosclerosis and more vascular co-morbidities in late life.

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Clinical trials of hypertension in China and collaboration with ESH

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In China, the prevalence of hypertension prevalence increased from 7.7% in 1980 to over 25% in 2012. In contrast to the complications of hypertension in the Caucasians, stroke rather than myocardial infarction is still the major complication of hypertension in the Chinese population which was repeatedly proven by epidemiological studies as well as outcome clinical trials which were carried out in China.

During the past 30 years, there were 6 major outcome trials which were carried out in the hypertensive patients in China, including Shanghai Trial of Nifedipine in the Elderly (STONE, 1996), Systolic Hypertension in China (Syst-China, 1998), Post-stroke Antihypertensive Treatment Study (PATS, 1995), Felodipine Event Reduction Study (FEVER, 2005) and the Chinese Hypertension Intervention Efficacy Study (CHIEF, ongoing). The most recently published study is the China Stroke Primary Prevention Trial (CSPPT, 2015) in which the effect of folic acid supplementation was tested in hypertensive patients in two provinces in China.

The two earlier trials (STONE, SYST-CHINA) were able to show a significant reduction in the incidence of stroke and other cardiovascular outcomes by actively reducing blood pressure with calcium antagonists (nifedipine retard and nitrendipine) in comparison with placebo treatment. In both these trials, conducted with alternative drug assignment or systematic allocation rather than randomized allocation, the systolic blood pressure (SBP) goal was either less than 160 mmHg [5] or less than 150 mmHg and achieved SBP was approximately 150 mmHg, that is, far above the value of under 140 mmHg now recommended by all guidelines, including Chinese Hypertension Guidelines.

Post-stroke Antihypertensive Treatment Study (PATS) was a randomized, double-blind and placebo-controlled trial, which aimed at determining whether antihypertensive treatment could reduce the risk of fatal and nonfatal stroke incidence in patients with a history of stroke or transient ischemic attack (TIA). 5,665 patients were randomized by a sealed envelope system. SBP ranged from 80 to 280 mm Hg and DBP from 50 to 150 mmHg. The average SBP was 154 mmHg and average DBP 93 mmHg. The mean age was 60 years. Among the patients, women accounted for 28%. In 71% the latest stroke was ischemic. Average follow-up approximated to 2 years. The three-year average SBP was 149 mmHg for the placebo group and 144 mmHg for the indapamide treatment group, and the three-year DBP was 89 mmHg and 87 mmHg respectively. The three-year first incidence of fatal and nonfatal stroke was 12.3 per 100 patients placebo treatment and 9.4 per 100 with indapamide. The relative risk by proportional hazards regression analysis was 0.71 ($P = 0.0009$). For deaths from all causes, the relative risk was 0.91. ($P > 0.05$). The findings of this trial indicate that in patients with a history of stroke or TIA, blood pressure reduction of 5/2 mmHg with 2.5 mg indapamide reduced the first incidence of fatal and nonfatal stroke by 29%, with three-year absolute benefit of 29 events per 1000 participants.

FEVER trial was an investigator-designed, prospective, multicentre, doubleblind, randomized, placebo-controlled, parallel group trial. It enrolled 9800 Chinese patients, of either sex, aged 50–79 years, with one or two additional cardiovascular risk factors or disease, whose blood pressure, 6 weeks after switching from previous antihypertensive therapy to low-dose (12.5 mg a day) hydrochlorothiazide, was in the range 140–180 mmHg (systolic) or 90–100 mmHg (diastolic). These patients were randomly assigned either to low-dose felodipine extended release or placebo, and followed at 3-month intervals for an average of 40 months.

In the felodipine group, blood pressure decreased (from randomization to study end) from 154.2/91.0 to 137.3/82.5 mmHg, and in the placebo group from 154.4/91.3 to 142.5/85.0 mmHg, with an average difference throughout the trial of 4.2/2.1 mmHg. In the felodipine group, the primary endpoint (fatal and non-fatal stroke) was reduced

by 27% (P< 0.001). Among secondary endpoints, all cardiovascular events were reduced by 27% (P < 0.001), all cardiac events by 35% (P =0.012), death by any cause by 31% (P= 0.006), coronary events by 32% (P =0.024), heart failure by 30% (P =0.239), cardiovascular death by 33% (P= 0.019), cancer by 36% (P = 0.017) in the felodipine group. No significant differences were found in new-onset diabetes.

The Chinese Hypertension Intervention Efficacy Study (CHIEF) is a multi-centre randomized controlled clinical trial comparing the effects of amlodipine+angiotensin II receptor blocker (group A) and amlodipine+diuretics (group B) on the incidence of cardiovascular events, represented as a composite of non-fatal stroke, non-fatal myocardial infarction and cardiovascular death events in high-risk Chinese hypertensive patients. The study also evaluates the long-term effects of lipid-lowering treatment and lifestyle modification. From October 2007 to October 2008, 13,542 patients were enrolled into the study in 180 centres in China. Patients will be followed up for 4 years. There was no difference in baseline characteristics between the two blood pressure arms. After 8-week treatment, mean blood pressure in group A and B were reduced to (133.0 +/- 11.0)/(81.0 +/- 7.6) mm Hg, (132.9 +/- 11.6)/(80.6 +/- 7.9) mm Hg respectively. Blood pressure control rates reached 72.1% and 72.6% in group A and T, respectively.

The China Stroke Primary Prevention Trial (CSPPT) is a randomized, double-blind clinical trial conducted from May 19, 2008, to August 24, 2013, in 32 communities in Jiangsu and Anhui provinces in China. A total of 20,702 adults with hypertension without history of stroke or myocardial infarction (MI) participated in the study. Eligible participants, stratified by MTHFR C677T genotypes (CC, CT, and TT), were randomly assigned to receive double-blind daily treatment with a single-pill combination containing enalapril, 10 mg, and folic acid, 0.8 mg (n = 10,348) or a tablet containing enalapril, 10 mg, alone (n = 10,354). The primary outcome was first stroke. Secondary outcomes included first ischemic stroke; first hemorrhagic stroke; MI; a composite of cardiovascular events consisting of cardiovascular death, MI, and stroke; and all-cause death.

During a median treatment duration of 4.5 years, compared with the enalapril alone group, the enalapril-folic acid group had a significant risk reduction in first stroke (2.7% of participants in the enalapril-folic acid group vs 3.4% in the enalapril alone group; hazard ratio [HR], 0.79; 95% CI, 0.68-0.93), first ischemic stroke (2.2% with enalapril-folic acid vs 2.8% with enalapril alone; HR, 0.76; 95% CI, 0.64-0.91), and composite cardiovascular events consisting of cardiovascular death, MI, and stroke (3.1% with enalapril-folic acid vs 3.9% with enalapril alone; HR, 0.80; 95% CI, 0.69-0.92). The risks of hemorrhagic stroke (HR, 0.93; 95% CI, 0.65-1.34), MI (HR, 1.04; 95% CI, 0.60-1.82), and all-cause deaths (HR, 0.94; 95% CI, 0.81-1.10) did not differ significantly between the 2 treatment groups. There were no significant differences between the 2 treatment groups in the frequencies of adverse events.
In conclusion, among adults with hypertension in China without a history of stroke or MI, the combined use of enalapril and folic acid, compared with enalapril alone, significantly reduced the risk of first stroke. These findings are consistent with benefits from folate use among adults with hypertension and low baseline folate levels.

There are also several completed or ongoing trials which are in collaboration with our colleagues from Italy, Australia, Canada and United Kingdom, including PRGOGRESS, ADVANCE, HYVET, ONTARGET, ESH-CHL-SHOT studies, etc.

Apart from the collaboration in major trials between the Chinese Hypertension League and ESH, we also initiated bilateral joint academic programs since 2010, including joint sessions during the annual meeting of ESH and drafting major documents in the management of hypertension. Future collaborations will be focus on the introduction of CME programs to the Chinese doctors.

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