SPEDALI CIVILI DI BRESCIA
AZIENDA OSPEDALIERA

Sistema Sanitario Regione Lombardia

International Symposium on:

MANAGEMENT OF CARDIOMETABOLIC RISK AND HEALTHY AGING

Brescia (Italy), January 15th – 17th, 2015

Organized by
DEPARTMENT OF CLINICAL AND EXPERIMENTAL SCIENCES
UNIVERSITY OF BRESCIA

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FONDAZIONE
INTERNAZIONALE
MENARINI

ABSTRACT BOOK

Auditorium di Santa Giulia (Via Piamarta, 4)
Aula Magna, Università degli Studi di Brescia (Viale Europa, 11)

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CONTENTS

Genetics of Cardiovascular Risk

Anna F. Dominiczak
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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) characterized 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.

The next steps in genomic medicine belong to a combination of the next generation sequencing (NGS) and its linkage with electronic health records, including preferably the real time clinical data, biochemistry, imaging, histology as well as longitudinal health outcomes. These modalities of stratified or precision medicine are ready for the prime time now.

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Blood Pressure Variability

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This presentation will focus on the short and long-term variations that characterize blood pressure (BP).
As regards the short-term variations evidence will be presented that 1) several mechanisms are responsible for the pronounced BP changes that occur throughout the day and night; 2) these changes increase with the increase in BP, being thus greater in hypertension than in normotension, the opposite phenomenon occurring, regardless the drug employed, with antihypertensive treatment and 3) 24h BP variations are an independent predictor of cardiovascular risk.
The presentation will then touch long-term BP variability, i.e. the BP tendency to be different between days, months and seasons. Particular emphasis will be given, however, to the late description of visit-to-visit BP variability, i.e. the frequent inability of BP to remain controlled from one visit to another during antihypertensive treatment. It will be mentioned that little information is available on the factors responsible for this phenomenon, but also that several data suggest it to be prognostically important, calling for a greater effort by physicians to achieve consistent BP control between visits.

Nutrients and cardiovascular risk

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Dietary habits are well known to deeply influence the individual cardiovascular risk profile. Diet, in particular, can directly influence various risk factors, such as serum LDL or HDL cholesterol concentrations, blood pressure and uric acid levels, adipose tissue accumulation, and glycaemia. In addition, nutrients – and calories *per se* – can also directly modify disparate cardiac and vascular functions, mood, kidney ability to handle salt and water, etc. Thus, junk foods – or in any case an "*unhealthy diet*" - are generally expected to accelerate atherosclerosis. In contrast, an healthy diet is correctly believed to reduce the risk not only of cardiovascular events but also of cerebrovascular accidents, renal failure, peripheral vascular disease and cognitive impairment of both mild and advanced degrees.

Most evidence on the relationship between diet and cardiovascular diseases is based on epidemiological studies while very few data derive from controlled intervention trials. As regards the first ones, interesting data have been obtained in the Kuna Indians of Panama. These Amerinds are virtually free of hypertension and cardiovascular disease, but this is changing with migration to urban areas, i.e. is not genetically-induced.

When compared to the indigenous diet of Kuna Indians living on remote San Blas islands in Panama (Ailigandi island), whose lifestyle is largely hunter-gatherer, those who have moved to a suburb of Panama City (Vera Cruz) manifested huge differences in diet patterns. In particular, the Kuna in Ailigandi reported consuming a 10-fold higher amount of cocoa-containing beverages, 4 times the amount of fish, and twice the amount of fruit as urban Kuna ($P<0.05$ by t test). Surprisingly, salt added was ample among those living in Ailigandi and Vera Cruz according to both self-report (7.1 ± 1.1 and 4.6 ± 0.3 tea spoon weekly) and urinary sodium levels ($177\pm$and 160 ± 7 mEq Na/g

creatinine), respectively. Therefore, the Kuna indians living in the San Blas islands seem to be the only known hypertension-free population adding to ingested foodsan european-like amount of sodium. As far as the flavanol matter is concerned, Kuna Indians living in San Blas drink a flavanol-rich cocoa as their main beverage, contributing more than 900 mg/day and thus probably have the most flavonoid-rich diet of any population. Although a cause-relationship interaction cannot be proposed by these findings, it is worthnoting that during 4 years there were 77,375 deaths in Mainland Panama and 558 deaths in the San Blas. In Mainland Panama cardiovascular disease was the leading cause of death (83.4$\pm$0.70 age adjusted deaths/100,000) and cancer was second (68.4$\pm$1.6). In contrast, the rate of cardiovascular and cancer among island-dwelling Kuna was much lower (9.2$\pm$3.1) and (4.4$\pm$4.4) respectively. Similarly, deaths due to diabetes mellitus were much more common in the Mainland (24.1$\pm$0.74) than in the San Blas (6.6$\pm$1.94).

Based on the above findings, we started to conduct a series of in vitro and in vivo experiments and were able to demonstrate that flavanols from tea and cocoa were able to induce a significant degree of nitric-oxide dependent vasorelaxation in isolated aortic ring from WistarKioto rats and – when ingested as dark chocolate bars/beverage or tea cup - to improve flow mediated, i.e. nitric oxide-dependent, vasorelaxation and to decrease office blood pressure levels. In addition, healthy chocolate bars were also able to reduce serum LDL cholesterol and ameliorate insulin sensitivity in hypertensives with and without additional risk factors. Of note, we also indicated that even a single cup of tea per day or a small amount of cocoa per day were able to significantly decrease blood pressure levels, thereby indicating that excess calorie intake is not a forced consequence of a cocoa-containing diet.

Long-term clinical trials are obviously needed to definitively clarify the benefits deriving from long-term consumption of flavanol-rich foods, particularly focussing on the lowest effective levels as well as synergism or antagonistic actions between different classes of flavonoids commonly found in foods.

However, based on both epidemiological and experimental findings it seems extremely likely that tea – a beverage containing "zero calories" – and chocolate – in a small amount containing few calories – should now be considered as novel components of an healthy *mediterranean diet*. This is not a revolutionary approach: starting from Greeks, Romans etc., the so-called *mediterranean diet* progressively acquired a number of additional components – such as tomatoes – that were not present in its original version. Even considering their pleasant taste, is now the time to use sugar-free tea for the morning breakfast and eat a small amount of dark chocolate per day.

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Pharmacological research in cardiovascular medicine

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Hypertension is the most common cardiovascular disease and remains the most prevalent risk factor for cardiovascular diseases and a major cause of death worldwide. New drug discovery and development is however a high-risk enterprise that requires significant investments in capital, time and scientific expertise. Understanding of the multiple pathways that modulate 1) vascular smooth muscle cell contraction and growth involved in the regulation of vascular tone and 2) urine sodium excretion involved in the regulation of volume have provided valuable insight in identifying new therapeutic targets.
The design of mechanism-based pharmacodynamic biomarkers and sophisticated Phase 1B and phase 2 investigations appear as an important key to successful drug development in the field. Finally, this approach allows the choice of appropriate end points and homogeneous clinical settings for Phase 3 trials.
Indeed, precise quantification of the intensity of AT1 receptor blockade with different RAS inhibitors and with different doses of the same inhibitor is difficult in hypertensive patients. The BP dependence on the prevailing RAS is a major determinant of the pharmacodynamic response to RAS blockade, but the contribution of theRAS to the BP level is highly heterogeneous and is strongly dependent on age, sodium intake and genetic factors. Physiological variability in BP and the difficulties encountered in its measurement also contribute to the large interindividual variabilities that have been observed in the antihypertensive response to an inhibitor of the renin-angiotensin system in hypertensive patients. These factors minimize the chances of differentiating between two drugs especially those with a similar mechanism of action. An alternative approach for studying inhibitors of the RAS, which gives valuable information in dose-finding trials with hypertensive patients, is to use strictly controlled conditions and highly selected individuals (such as renin-dependent normotensive subjects or hypertensive patients) for

pharmacokinetic/pharmacodynamic modeling. As a prerequisite to clinical studies in patients with hypertension or congestive heart failure, it was possible to investigate the biological effects of various blockers of the the renin angiotensin system (RAS) in a human model of mild stimulation of renin release induced by the combination of a 40-mg furosemide–induced sodium depletion followed by a 36-hour low sodium diet. This model of mild sodium depletion in normotensive volunteers provides an experimental condition in which BP is consistently dependent on the RAS. By contrast to the heterogeneity of the RAS of hypertensive patients, sodium-depleted normotensive volunteers have homogeneous levels of plasma active renin, and all have a diuretic-induced BP renin dependency. This model induces a twofold to threefold increase in plasma active renin, aldosterone, and angiotensins and provides optimal conditions to unmask the renin dependency of blood pressure in normotensive subjects. This approach has been used to determine the appropriate doses for renin inhibitors, angiotensin converting enzyme (ACE) inhibitors and AT1 receptor blockers, and vasopeptidase inhibitors and newer classes of drugs such as dual angiotensin II neprylisin inhibitors and aldosterone synthase inhibitors. Other pharmacokinetic/pharmacodynamic models have also been used for other antihypertensive drugs, including calcium channel blockers.

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Molecular mechanisms of development of target organ damage in hypertension

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In last two decades, many studies have clarified the molecular basis of target organ damage (TOD) in essential hypertension. The principal aspect that emerged is that development of TOD is a complex and multifactorial process which involves mechanical forces, growth factors, neuro-hormonal stimulation and oxidative stress. Among the different molecular mechanisms involved in the pathogenesis of TOD, the renin-angiotensin system (RAS) has been expensively investigated. At this regard, has emerged that Angiotensin II (Ang II) plays a key role in the pathogenesis of left ventricular hypertrophy (LVH). Studies *in vitro* have demonstrated that Ang II is involved in stretch-induced hypertrophy in neonatal rat cardiac myocytes. In fact, treatment with Ang II receptor antagonists such as [Sar1 Ile8] Ang II (antagonist for the Ang II type I and II receptors) and losartan and TCV11974 (antagonists for the Ang II type I receptor) inhibits the expression of major markers of cardiac myocytes hypertrophy, such as the re-activation of fetal gene program. More interestingly, in cardiac myocytes, it has been documented that mechanical stretch up-regulates the gene expression of all component of the RAS, such as angiotensinogen, renin, ACE, and Ang II receptor. These results indicate that RAS mediates the development of cardiac hypertrophy, in response to mechanical stress, acting through an autocrine/paracrine mechanism, and by a positive feedback increasing the molecular machinery for transduction of Ang II signal. Further studies have extended the knowledge regarding the molecular mechanism that account for Ang II-mediated development of LVH. In particular, it has been documented in transgenic mice lacking the gp91phox subunit of NADPH oxidase, that 2 week-stimulation of sub-pressor doses of Ang II stimulation failed to induce LVH, this was associated with inhibition to superoxide production.

The result of this study indicated that oxidative stress is centrally involved in the direct cardiac hypertrophic response to Ang II. In addition, molecular and cellular biology studies have clarified also the pathways that account for adaptive and maladaptive cardiac hypertrophy. For instance, it has been demonstrated that transgenic mice deficient in adenylyl cyclase type 5, a major isoform of adenylyl cyclase in the heart, can tolerate pressure overload, thereby exhibiting well-maintained LVH and LV chamber size compared with wild-type littermates. In contrast, it has been also reported that mitogen-activated protein kinase and ERK kinase kinase 1 (MEKK1) knockout mice are more susceptible to pressure overload and develop decompesated LVH compared with the control wild-type (MEKK1+/+) mice. These studies suggest that modifying a particular signaling mechanism could exhibit profound effects on the maintenance of cardiac function in response to hemodynamic overload thus normalizing the wall stress. The translational implication of these studies is that, from clinical point of view, it is important to identify which molecular mechanisms make cardiac hypertrophy good or bad. Furthermore, the important target of treatment of cardiac hypertrophy is not necessarily the reduction of LV mass itself but rather may be the correction of the molecular pathways that account for the cardiac hypertrophy-related complications and/or the enhancement of the activity of cellular signals mediating cytoprotective actions. Development of chronic kidney disease (CKD) share with LVH many pathogenic mechanisms such oxidative stress, endothelial dysfunction, disregulation of RAS. In fact, it has been documented that Ang II, in the kidney, regulates not only the hydro-saline homeostasis and peripheral vascular resistances but, exerts also a control on cell growth, inflammation, and fibrosis. Experimental evidence indicate that Ang II exerts the detrimental effect on the kidney by modulating the redox status and the immune system. In fact, Ang II increases tumor necrosis factor-production in the kidney, as well as, upregulates other proinflammatory mediators, including interleukin 6, monocyte chemotactic protein-1, and nuclear factor-B, resulting in a large spectrum of glomerular damage.

These results allow the hypothesize that Ang II is involved into the pathogenesis of CKD by modulating the activation immunocompetent cells There are several evidence showing that some of the beneficial effects of the RAS blockade may be related to an anti-inflammatory action. In particular, it has been reported in monocytes that exposure to captopril affects the cytokine-induced translocation of nuclear factor-kB translocation from the cytoplasm to the nucleus. Coincidently, it has been reported in patients with end-stage of renal disease, that ACE-inhibitor-based treatment reduces plasma levels of tumor necrosis factor-α and C-reactive protein. Ang II plays a pivotal role not only in the development of atherosclerosis but also in the vulnerability of atherosclerotic plaques. In fact, It has been reported that Ang II regulates the gene expression and synthesis of adhesion molecule (VCAM-1, ICAM-1, P-selectin), cytokine, chemokine, and growth factor of the arterial wall. In addition, RAS positively regulates the complement system, resulting in vascular inflammation and mobilization/and activation of inflammatory cells. The RAS interferes also with coagulation cascade and platelet aggregation. Several evidence clearly indicate that RAS blockade exerts potent antiatherosclerotic effects, not only reducing blood pressure, but also through anti-inflammatory, antiproliferative, and antioxidant effects. At this regard, it has been reported that treatment with the ACE-inhibitor trandolapril reduces endothelial dysfunction in hyperlipidemic rabbits. In addition, administration of quinapril reduced macrophage infiltration in atherosclerotic lesions in femoral arteries in rabbits through the direct inhibition of macrophage chemoattractant protein (MCP)-1 expression. There is a large consensus that the anti-atherosclerotic properties of both ACE-inhibitors and ARBs are independent from of blood pressure reduction, since the use of other antihypertensive drugs did not produce similar actions. However, the positive effects of the RAS blockade have been also reported in animal models of hypertension. In particular, in stroke prone spontaneously hypertensive rats (SHR-SP) administration of ramipril reduced mortality and improved left-ventricular hypertrophy, cardiac and endothelial functions, indicating that ACE inhibitors reduce cardiovascular risk and atherosclerosis in animal model of essential hypertension.

These pharmacological effects in SHR-SP rats were documented also for losartan and telmisartan.
The results of the studies in molecular biology of the last two decades helped to clarify the mechanisms involved in the pathogenesis of TOD in hypertension, and improved the scientific basis for their prevention and treatment.

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Central blood pressure

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The Gold standard for measuring blood pressure (BP) and diagnosing hypertension is the brachial cuff, thus favoring a distal site accessible to non invasive measurement. However, two concepts have gained an important audience these last years: the loss of pressure amplification between central and peripheral arteries with aging, hypertension and diabetes; and higher damaging effect of local BP than brachial BP on target organs in hypertensive patients.

The arterial pressure waveform which is measured centrally (ie at the site of the ascending aorta) is a composite of the forward pressure wave created by ventricular contraction and a reflected wave. Indeed, the arterial tree is not a simple tube but a complex structure with a reflection site at its distal end (1). From the heart towards the periphery, arteries continuously decrease in diameter (i.e. geometric taper) and increase in stiffness (i.e. elastic taper, also named "arterial stiffness gradient") while also continuously branching. The stiffness gradient, together with the geometric taper, local arterial branching and lumen narrowing, creates an impedance mismatch causing partial reflections of forward pressure waves travelling back to the central aorta (reflected wave). Forward and reflected pressure waves overlap and the final amplitude and shape of the pulse pressure wave are determined by the phase relationship (the timing) between these component waves. In young healthy subjects, reflected waves arrive late and do not superimpose to the forward wave, thus central systolic (SBP and pulse (PP) pressures are lower at the central level than at the peripheral level, a phenomenon named "pressure amplification". By contrast, in elderly, hypertensive, and diabetic patients the reflected waves superimpose to the forward wave in early systole, thus increases central SBP and PP, and the amplification phenomenon disappears (1)

An increasing number of physiological studies, as well as pathophysiological, epidemiological and pharmacological studies, have underlined the importance of measuring not only brachial

systolic and pulse pressures, but also central SBP and PP. Several reviews have made recommendations for adequate measurements of central BP (2). Arterial pressure waveform should be analysed at the central level, i.e. the ascending aorta, since it represents the true load imposed to the heart, the brain, and the kidney, and more generally to central large artery walls. The pressure waveform can be recorded non-invasively with a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer. The most widely used approach is to perform radial artery tonometry and then apply a transfer function to calculate the aortic pressure waveform from the radial waveform.

The haemodynamic mechanisms leading to end-organ damage are complex, probably organ-specific and not fully understood. They likely include not only a direct effect of pressure pulsatility on conduit artery but also an effect on smaller resistive arteries. Indeed pressure pulsatility can stimulate hypertrophy, remodelling (increased media-to-lumen ratio), or rarefaction in the microcirculation, leading to increased resistance to mean flow. Significant relationships have been demonstrated between brachial PP and either glomerular filtration rate (GFR), microalbuminuria, or white matter lesions; between arterial stiffness and either GFR, urinary albumin, retinal arteriolar narrowing, white matter lesions or cognitive function; and between carotid stiffness and GFR. Although not all these relationships are independent of confounding factors, there is a large amount of evidence for linking the pulsatility of BP to target organ damage (1, 3-6).

Since the early 2000s, several longitudinal studies showed that central PP had independent predictive value for all-cause and CV mortality. Central augmentation index and pulse pressure, either directly measured by carotid tonometry, or estimated using a transfer function from radial artery tonometry were both independent predictors of all-cause mortality in ESRD patients, in patients undergoing percutaneous coronary intervention, and in the hypertensive patients of the CAFÉ study. Eleven studies performed in population at various CV risk and totalizing 5,648 subjects with a mean follow-up of 3.8 yrs were included in a recent meta-analysis (7). In six of them, the RR of total CV events for an increase of central PP by 10 mmHg was 1.14 [1.06-1.21]. It was 1.09 [1.04-1.14] for central

SBP. A consistent limitation of all the above mentioned central BP prognostic studies is that they are observational, and causality between elevated central BP and CV risk cannot be inferred. Whether central SBP and PP are surrogate end-points, i.e. their reduction translates into a reduction in CV events, has never been demonstrated and longitudinal controlled studies should be performed.

The pharmacological classes which induce a larger decrease in central SBP relative to brachial SBP, in other words which restore pressure amplification, are mainly angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) whereas diuretics and vasodilating beta-blockers are less efficacious (8,9). Non vasodilating betablockers (such as propranolol and atenolol) are the least effective agents for reducing central SBP/PP. Instead of increasing SBP amplification, they reduce it by inducing a lower decrease in central SBP relative to brachial SBP. The mechanisms by which they exert such a deleterious effect are detailed below. Nitrates, which are not indicated for hypertension, increase SBP amplification.

Combination therapies exert also differential effects on brachial and central BP. The available evidence, originating from the CAFÉ, EXPLOR and J-CORE studies, indicates that this is a combination of CCB and either ACEI or ARB, which is the most effective for reducing central SBP, for a given reduction in brachial SBP (10).

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Mechanisms of hypertension in diabetes

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Diabetes has been consistently associated with both hypertension and increased cardiovascular risk. It is clear that diabetes-related hypertension is a multi-factorial disorder. Its genesis and evolution depend on several genetic and environmental factors. While diabetic subjects are prone to hypertension, hypertensive subjects also appear to be prone to glucose intolerance. Therefore, the relationship between diabetes and hypertension might be described as a "two-way street", implying an individual susceptibility to both conditions or common environmental features.

Several mechanisms appear to be implicated in the development of hypertension associated with diabetes. These include alterations in the renin-angiotensin-aldosterone system, increased sympathetic nervous system activity, insulin resistance, leptin resistance, altered coagulation factors, inflammation, and endothelial dysfunction. Diabetes has also been associated with increased stiffness and early vascular aging.

Diabetes-related obesity might lead to hypertension also by increasing renal sodium reabsorption, impairing pressure natriuresis and volume expansion. Furthermore, diabetes may also cause marked structural changes in the kidneys that eventually lead to chronic renal failure and further increases in blood pressure. Tubular injury, as the first sign of renal damage in hypertension, is closely linked to metabolic disturbances. In patients with established renal disease, both diabetes and hypertension accelerate disease progression. Hypertension, metabolic abnormalities, and renal factors interact and potentiate their individual impact on cardiovascular risk. The number of nephrons is reduced in patients with hypertension. In these patients, diabetes may confer an increased risk of chronic kidney disease, especially when additional factors, such as lipid abnormalities, are superimposed.

Obesity-related hypertension and diabetes are associated with the accumulation of "dysfunctional" adipose tissue, characterized by the presence of "large" adipocytes, which may be directly involved in the production of angiotensinogen, pro-inflammatory cytokines, and reactive oxygen species.
There is growing evidence that obstructive sleep apnea might contribute to the link between diabetes, hypertension and cardiovascular disease. These conditions often coexist and interact, sharing multiple pathophysiological mechanisms including activation of the sympathetic nervous system.

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Assessment and management of early vascular aging

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For many years the interest in atherosclerosis, primarily affecting the arterial intima layer, has been growing and mechanism leading to cardiovascular events well described and defined. However, prior to this in time is a period in early life with stiffening of the large elastic arteries, primarily affecting the arterial media, a phenomenon that has been shown to be an important risk marker for future cardiovascular events and mortality beyond well-known cardiovascular risk factors [1, 2]. Measurement of arterial stiffness is preferably performed by use of carotid-femoral Pulse Wave Velocity (c-f PWV) according to a consensus document [3]. This can be done directly by devices such as SphygmoCor® or Complior®, or indirectly by devices such as Arteriograph® or Mobil-o-Graph®. There are also other ways to investigate the arterial distensibility by ultrasound technologies. A value of arterial stiffness with c-f PWV more than 10 m/s is a risk marker based on European consensus.

Arterial stiffness is known to be strongly associated with age and hypertension [4, 5], findings also confirmed in a longitudinal study [6]. The arterial ageing is tightly inter-correlated with blood pressure and causes the increase in pulse pressure seen in aged individuals [4]. In some individuals, the arterial stiffening seen with increasing age is more pronounced and occurs earlier in life, a phenomenon described as Early Vascular Ageing (EVA) [7]. A number of non-haemodynamic components are thought to affect the arterial ageing, among the markers of glucose metabolism and insulin resistance influencing dyslipidaemia [7]. Several cross-sectional studies have shown an association between arterial stiffness and diabetes as well as with markers of impaired glucose metabolism [8-10]. Individuals with end-stage renal disease (ESRD) are also known to exhibit an increased central arterial stiffness but results from studies investigating the association between arterial stiffness and stages of chronic kidney

disease have presented conflicting results [11]. Results from a prospective study showed that central obesity predicts arterial stiffness over a time period of 16 years [12], whereas a 20-years follow-up study including men indicates that heavy smoking, c-reactive protein (CRP) and pulse pressure (PP) are predictors of arterial stiffness. New intervention studies test the benefits of reducing arterial stiffness in a targeted way, for example the SPARTE study in France.

In summary, EVA is a new concept to explain some of the increased cardiovascular risk also in patients with diabetes. New interventions are needed to address the role of glycaemia and Advanced Glycaemic End (AGE) products for promoting EVA. It is possible to assess arterial stiffness, both with direct and indirect methods.

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Cardiorenal changes with aging

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World population is increasingly ageing. While in 2005 the percentage of people in the world aged 60 and over was 8%, corresponding to 500 million individuals, in 2050 this number is expected to increase to 16.1% and 1.5 billion individuals. Given the huge prevalence of hypertension in older people, it is self-evident that the burden of CV mortality in the elderly, is mainly attributable to hypertension. The prevalence of isolated systolic hypertension in people aged 80 and more is greater than 90%, mainly attributable to age-related changes in large arteries compliance.

The ageing process is characterized by arteriosclerosis, a profound remodeling of arterial walls, more pronounced in the aorta and its proximal branches.

When stiffness of large arteries is increased, their cushioning function is impaired: in particular the lacking of aorta's buffering function of ventricular ejection during systole and elastic recoil during diastole is responsible of the well known increase in systolic and pulse pressure and decrease in diastolic BP, which is present both in normotensive and in hypertensive elderly.

While aortic stiffness increases steeply after 60 years, this does not happen to muscular arteries, diminishing the normal impedance mismatch between central aorta and periphery. As a result, reflection from proximal reflecting sites may be attenuated, leading to increased transmission of pulsatile energy into smaller arteries and the peripheral microcirculation, and thus to microvascular damage in parenchimal organs such as the brain and the kidney.

Effects of arterial stiffness on heart are even more deleterious. Among structural changes, left ventricular wall thickness progressively increases in both sexes, even among normotensive individuals, in order to compensate the increased afterload due the increase of central systolic and pulse pressure; this results in normalization of systolic

wall stress and preservation of left ventricular systolic function. Increased afterload is a cause of increased myocardial oxygen consumption, contributing to imbalance of oxygen demand/supply, and thus favouring ischemia. Furthermore left ventricular hypertrophy has long-term negative consequences, since it predisposes per se to increased myocardial oxygen demand, subendocardial ischemia and to diastolic dysfunction. Arterial stiffness can favour diastolic dysfunction with further mechanisms, such as structural fibrotic changes within the left ventricular myocardium and prolonged contractile activation from the preceding systole, causing a reduction in early diastolic filling. These changes represent the physiological basis of the great prevalence of heart failure with normal ejection fraction in the elderly. Impaired left ventricular relaxation is compensated by a more vigorous atrial contraction, so that left ventricular end-diastolic volume index is unchanged. The consequent atrial hypertrophy is responsible of the increased prevalence of atrial fibrillation with aging. In such conditions of increased myocardial oxygen demand, the age-related reduction of diastolic BP could overcome coronary autoregulation and critically reduce coronary flow, which tipically occurs in diastole, especially in the presence of coronary disease. All the above mentioned consequences are amplified by the presence of hypertension.

Age-related changes in renal function are also tightly related to hypertension. In the elderly pulse pressure and arterial stiffness are inversely related to glomerular filtration rate (GFR). On the other side, renal dysfunction is a cause of worsening of hypertension and predispose to resistant hypertension. An age-related reduced renal ability to appropriately excrete a salt load was demonstrated. This feature is implicated in the genesis of salt sensitivity, and thus in development of hypertension in the elderly.

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Obesity and Vascular Abnormalities

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This presentation will look at the effects of obesity on vascular structure and function and in particular the way that adipocytes adapt to a change in phenotype with increased inflammation and release of pro-inflammatory cytokines and the loss of vasodilator activity. There has been increasing interest in the role of the perivascular environment which comprises adipocytes, inflammatory cells and neural tissues in various populations dependent upon the phenotype of the individual. Healthy perivascular tissue appears to release relaxing factors such as adiponectin. These appear to be agonist dependent but in obesity this property of PVAT is lost. The cause of the change appears to be an increased oxidative stress and local inflammation which occurs as a result of a change in macrophage phenotype and a down-regulation of eosinophil population. The changes in contractile function would be sufficiently large to increase peripheral resistance and raise blood pressure as well as contribute to insulin resistance and glucose intolerance. In larger vessels these alterations may well be atherogenic. Measures which are designed to cause weight loss appear to improve perivascular anticontractile function and new therapeutic measures which change the PVAT environment may well be crucial to preventing the long-term consequences of obesity which is reaching epidemic proportions in our populations.

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Uric Acid, xantino-oxidase and cardiovascular risk

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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 ethological mechanism in the development of gout and is also significantly associated with an increase in the relative risk of CV diseases in addition with the more consolidated CV risk factors (e.g. hypertension, lipid disorders, diabetes, etc). The hypothesis linking uric acid with 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 development of hypertension later in life. Data from observational studies and physiological experiments suggest that there may be a causal relationship between plasma levels of SUA and the incidence of cardiovascular and renal disease. However, definitely convincing evidence remains elusive for many different reasons that complicates the understanding of the relationship between the study of SUA, its determinants and its confounders. In particular among the confounders a prominent role is played by statistical and methodological issues as well as by the counfonding role of co-variates that might be also mediators of biological pathways (e.g kidney) or might variably interact with additional cardiovascular risk factors. In particular 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 an 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 deposition of urate and gout. The prominent role of xantino-oxidase could directly affect the choice of drugs modulating the plasma levels of uric acid ad support a primary role for febuxostat that is characterized by a more selective and persistent inhibition of the enzyme when compared to allopurinol. This would translated in a greater cardiovascular protection that might increase the extent of the benefit of serum uric acid decrease. 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 explained by a mechanistic 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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The Sympathetic Nervous System in Hypertension: Role of Metabolic Alterations

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Several indices of adrenergic drive, such as plasma norepinephrine, norepinephrine spillover from adrenergic nerve terminals and efferent postganglionic muscle sympathetic nerve traffic, have all shown an increase in hypertension as well as in the different clinical conditions associated with elevated blood pressure values, such as obesity, hypertension and metabolic syndrome. This increase: 1) appears to be potentiated in the metabolic syndrome, 2) seems to be related to (and probably dependent on) the insulin resistance state frequently detectable in the above mentioned disease and 2) contributes to a large extent at the cardiovascular structural and functional alterations typical of the disease.
This presentation will provide an overview of the main neuroadrenergic alterations occurring in hypertension, particularly when this condition is complicated by metabolic abnormalities involving glucose control. It will also examine the reciprocal relationships between sympathetic activity and insulin resistance, and their relevance for the sympathomodulatory effects of non-pharmacological interventions aimed at improving metabolic cardiovascular homeostasis, such as body weight reduction and regular physical exercise.

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Round Table on "New Aspects of Organ Damage"

Microalbuminuria

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Albuminuria reflects impaired permeability of the glomerular membrane in the kidney. Increased transition of albumin molecules from the blood to the interstitial i.e. urine side is caused by impaired endothelial function, increased intraglomerular (filtration) pressure and inflammatory processes among others. Ideally albuminuria should be measured from the early morning spot urine and related to urinary creatinine concentration (UACR, urinary albumin creatinine ratio). Similar to blood pressure measurements, standardization of measurements conditions for UACR is required to obtain reliable values with low variability (e.g. avoidance of exercise 12 to 24 hours prior to sampling, exclusion of any kind of infection). Low grade albuminuria and micro-albuminuria indicate vascular damage of the renal and systemic vasculature. Abundance of evidence exists that elevated albuminuria predicts renal and cardiovascular morbidity and total mortality in various populations independent from other traditional risk factors. However, albuminuria is a risk marker, serves as a diagnostic tool and redefines the individual risk, but albuminuria is not directly involved in the pathogenetic processes leading to the morbid events, unless severe albuminuria develops.

Most intriguingly, change in albuminuria predicts the cardiovascular and renal risk. In diabetic patients, change of albuminuria was superior to predict the change in renal and cardiovascular events than change in blood pressure and blood glucose. Thus, albuminuria indicates more precisely the individual risk (since it reflects vascular damage and not the potential risk of that like blood pressure) and serves as a valuable subclinical organ damage for individualizing antihypertensive treatment.

Round Table on "New Aspects of Organ Damage"

Stable vs unstable plaque

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Atherosclerosis is a chronic inflammatory disease of large and medium-sized arteries leading to the development of intimamedia thicknening and plaques. Acute clinical events usually represent the consequence of plaque stability loss rather than of an increase in size.
Plaques with an unstable phenotype are prone to fissure and rupture, causing the occurrence of a myocardial infarction, stroke, and/or of sudden death. The major criteria for the definition of a vulnerable plaque include active inflammation; a thin cap with a large lipid core (>40% of the plaque's total volume); endothelial denudation with superficial platelet aggregation; fissured cap, which may indicate a recent rupture; or severe stenosis, which would make the plaque more prone to shear stress or may be a marker of other less stenotic but vulnerable plaques.
Other characteristics of a vulnerable plaque are the presence of a large lipid core (usually taking > 30–40% of total lesion area), a high number of inflammatory cells (mostly macrophages) and neovascularization, increasing the risk of intraplaque hemorrhages and enlargement of the vessel wall .
Low local endothelial shear stress triggers the increase lipid uptake and catabolism, induces plaque inflammation and oxidation, downregulates the production and upregulates the degradation of extracellular matrix, and increases cellular apoptosis The either low or high endothelial shear stress may increases in blood thrombogenicity , thus contributing to plaque destabilization.
In experimental models plaque rupture occurs only sporadically, after a long period of time, or is associated to a mechanical injury; moreover, reproducibility is low and events as seen in humans are rarely observed.

Recent studies have underscored the importance of elastin fragmentation in the vessel wall as key factor involved in plaque destabilization with enhanced inflammation and increased neovascularization, promoting the development of unstable plaques, associated with an increased prevalence of cardiovascular and cerebrovascular events.

Another major challenge in cardiac and cerebrovascular research is the development of new techniques for the identification of vulnerable plaques and the clinical use of treatment for the vulnerable plaque stabilization.

New sophisticated techniques have been introduced in the last years for a more accurate evaluation of the typical features of an unstable plaque in different vascular beds. Multidetector computer tomography, cardiovascular magnetic resonance and position emission tomography may provide information on coronary anatomy and myocardial perfusion. Three dimensional ultrasound has emerged as a precise and reproducible method for the assessment of atherosclerosis in large arteries, with high accuracy for the measurement of plaque volume. New bioimaging techniqes may also give relevant information on plaque vulnerability: videodensitometric analysis has been proposed for the non-invasive assessment of plaque composition; novel systems based on echotracking technologies may give relevant information on the multiaxial mechanical properties of carotid plaques. The use of contrast-enhanced ultrasound may enable the assessment of neovascularization of plaque shoulders in vivo real time, and may help stratify plaque vulnerability. Multislice CT scanning and MRI may give accurate measures of atherosclerosis noninvasively *in vivo*, and may also provide information on plaque composition.

Nuclear imaging, and in particular PET, appear particularly promising in identification of plaque composition and in the quantification of macrophage-activity.

Further research will better clarify in the next years the possible clinical applications of these new bioimaging technologies.

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Round Table on "New Aspects of Organ Damage"

Microcirculation

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The presence of structural alterations in the small resistance vessels microcirculation may be considered an important link between hypertension and ischemic heart disease, heart failure, cerebral ischemic attacks and renal failure. It is now widely accepted that structural abnormalities of resistance vessels are common alterations associated with chronic hypertension. An increased arterial wall thickness together with a reduced lumen may play an important role in the increase of vascular resistance, and may also be an adaptive response to the increased haemodynamic load. In the last years, many experimental studies have indicated that changes of small artery structure in hypertension are the consequence of either eutrophic or hypertrophic remodeling (re-arrangement of the same amount of wall material around a narrowed lumen or smooth muscle cell hypertrophy/hyperplasia, respectively). The increased media to lumen ratio was demonstrated to be a powerful predictor of cardiovascular events in a high risk population of patients with primary and secondary hypertension. The prognostic importance of structural alterations of subcutaneous mall resistance arteries was extended to patients with essential hypertension at low-moderate cardiovascular risk, and to major cardiovascular events (myocardial infarction, stroke and sudden death). The possible regression of vascular alterations is an appealing goal of antihypertensive treatment. A complete normalization of small resistance artery structure was demonstrated in hypertensive patients, after prolonged and effective therapy with dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. No effect was observed with beta-blockers and diuretics despite similar blood pressure reduction. Recent data suggest also the presence of a prognostic relevance of the extent of the regression of vascular structural alterations.

However, prospective studies, possibly with less-invasive approaches, are needed in order to clarify whether structural alterations in small resistance arteries may be definitely considered a surrogate endpoint in the evaluation of the effects of antihypertensive treatment. Recently, a non invasive evaluation of retinal arteriolar morphology by Scanning Laser Doppler Flowmetry was proposed. The information provided seems to be similar to those obtained with invasive assessments, thus opening interesting clinical perspectives in terms of risk stratification in hypertensive patients.

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Round table on "New Aspects of Organ Damage"

3D Echocardiography

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Current Hypertension Guidelines emphasize the importance of assessing the presence of preclinical organ damage. In fact, an extensive evaluation of organ damage may increase the number of patients classified at high CV risk and therefore strongly influence the clinical management of patients. Left ventricular hypertrophy (LVH) remains to date the form of hypertensive organ damage for which there is the greatest amount of evidence of a strong independent prognostic significance. In the presence of a chronic pressure overload, a parallel addition of sarcomers takes place with an increase in myocyte width, which in turn increases left ventricular wall thickness. In the development of hypertensive heart disease, myocyte hypertrophy is also associated with apoptosis, collagen deposition and ventricular fibrosis with an impairment of coronary hemodynamics as well, thus profoundly influencing functional properties of the left (and right) ventricle. Thus, the development of LVH represents a step toward the development of clinical cardiovascular diseases, such as congestive heart failure, ischemic heart disease, stroke and sudden death. Therefore, accurate assessment of cardiac anatomy and function might be of help for a prompter identification of early alterations that may predispose hypertensive patients to cardiovascular events. The recent Guidelines of the European Society of Hypertension and of the European Society of Cardiology include echocardiography among the recommended techniques to be considered in hypertensive patients. In fact, echocardiography is a relatively easy method, is repeatable, is specific and more sensitive measure of LVH than electrocardiography; the relationship between LV mass and incidence of cardiovascular events has been demonstrated in various subsets of patients, is continuous and independent of other cardiovascular risk factors.

Despite this, some disadvantages must be recognized. In fact, LV mass reproducibility represents one of the major technical limitations of echocardiography. Furthermore, LV mass estimation by ultrasound is based on a mathematical formula assuming a prolate ellipsoid shape for the LV and in patients with previous myocardial infarction or with asymmetrical hypertrophy this may represent a limitation. For this reason LV mass measurement with cardiac magnetic resonance imaging, which is indubitably more accurate and reproducible, has been proposed, but with obvious limitations related to availability and costs of the technique. Three-dimensional echocardiographic (3DEcho) imaging represents a relevant innovation in cardiovascular imaging. At the beginning of year 2000 the development of fully sampled matrix-array transducers, together with significant improvements in hardware and software of ultrasound systems, has made possible excellent real-time imaging of the beating heart in 3 D. Continuous improvements in semiautomated volumetric analysis, has allowed 3DEcho to evolve from a very complicated and time-consuming research tool into a more simple and relatively fast imaging modality. Available data seem to indicate that 3DEcho provides better estimation of LV mass than 2-dimensional echocardiography, providing better correlations that 2-dimensional echocardiography with MRI measurements. Several studies have suggested that 3DEcho might underestimate LV mass as compared to MRI. However a recent metaanalysis has shown that the underestimation was more evident in studies performed before 2004, and tended to progressively disappear with time. The results of studies published after 2008 were more homogenous and showed excellent accuracy, possibly related to the technical improvements of 3-dimensional echocardiographic technologies. Globally, the analysis of the available data indicates that a larger degree of variability may be observed in patients with overt cardiac disease, possibly owing to the greater distance of the LV walls from the transducer in dilated hearts; furthermore, asymmetric dilation in severe ischemic cardiomyopathy may make the endocardial border difficult to trace accurately. Three-dimensional ultrasound also offers the opportunity for a more sophisticated assessment of LV function.

An established advantage of 3D imaging over cross sectional slices of the heart is the improvement in the accuracy of the evaluation of left ventricular volumes and ejection fraction by eliminating the need for geometric modelling. Furthermore, speckle tracking echocardiography (STE), a technique which allows the derivation of multiple parameters of myocardial function, may be performed in 3 D. In fact, 2D STE has the intrinsic limitations of 2D imaging, such as the use of foreshortened views that affect the accuracy of the quantification of individual components of myocardial motion. In addition, the assumption that speckles remain within the 2D imaging plane and can be adequately tracked throughout the cardiac cycle may not always be valid, because of the complex 3D motion of the heart chambers.
In conclusion 3DEcho is a promising tool for the diagnosis of heart disease and in hypertensive patients it has the potential of providing more accurate measures of cardiac structure and function for a more timely identification of preclinical organ damage. At the present time however the three dimensional approach with ultrasound mainly represents a promising research tool; further advances in ultrasound systems technology and in dedicated software for image analysis will hopefully allow the clinical implementation of real time 3DEcho in clinical practice.

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Cardiometabolic risk factors, cognitive disturbance and dementia

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The benefits of blood pressure lowering on stroke, ischemic heart disease, heart failure, and kidney disease are widely recognized. High blood pressure has also been implicated in the development of cognitive dysfunction and vascular dementia 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 BP and WML and cognitive function in the elderly. Recently, data from the Ohasama study show that increased home systolic blood pressure and increased day-to-day systolic blood pressure 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 microbleeds 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 or vascular dementia 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 white matter lesions progression and cognitive decline by lowering blood pressure 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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Old and New Pharmacological Treatment in Hypertension

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The first outcome trials comparing "old" or *standard* drug treatment with "new" pharmacological treatment in hypertension were published about 15 years ago (STOP-2, CAPPP, NORDIL, INSIGHT, ALLHAT). For all practical purposes treatment based on thiazides and beta-blockers were compared with treatment with ACE-inhibitors, calcium antagonist and alpha-blocker, and no study showed difference in primary cardiovascular CV) endpoint (1). However, though comprising about 54 000 patients these studies were individually mostly underpowered like several other studies published since then (e.g. second leg of ALLHAT, ANBP-2, SCOPE, CASE-J).

Outcome trials in hypertension with individual statistical power were LIFE, VALUE, ASCOT and ACCOMPLISH. LIFE comprised more than 9000 patients aged 55-80 years with ECG-LVH and showed reduction in composite primary CV endpoint favoring the ARB losartan over the beta-blocker atenolol for the same level of BP control. The outcome results in LIFE were related to stronger regression of LVH on the ARB and taken together with secondary analyses of other studies the LIFE data defend including a RAAS-blocker when treating patients with hypertension and LVH. Two studies in hypertensive patients with diabetic nephropathy (IDNT, RENAAL) defend similar assumptions that RAAS blocker should be included in the treatment of hypertensive patients with cardiac or renal impairments.

VALUE was powered for non-inferiority for combined primary cardiac endpoint plus stroke in comparison of ARB with calcium-antagonist in high risk hypertensive patients and was neutral. ASCOT compared outcomes on combined *standard* treatment (atenolol + thiazide) with new drugs (calcium antagonist + ACE-inhibitor) and showed benefit on prevention of most CV endpoints by new treatment but analyses were confounded by an untoward difference in BP between treatment arms (like in VALUE). ACCOMPLISH used a forced titration protocol and achieved BP control in 80% of

participants and showed CV benefits of the combination of ACE-inhibitor + CCB vs. ACE-inhibitor + thiazide. ACCOMPLISH data have not been confirmed in other studies; neither in an underpowered Japanese study published quite recently. Whether ARB is as powerful as ACE-inhibitor in combination with calcium antagonist is currently being investigated in an ongoing study (CHIEF) but preliminary data have been released and show low endpoint rate and no difference between arms.

The overall impression is still that all drugs, both "old" and "new" are needed, and the most important aspect is to control the high BP without introducing side effects. Some data support including RAAS blocker in hypertensive people with end organ damage like LVH and proteinuria. Many other concomitant conditions may favor certain choices among all drugs available based on studies of hypertensive people with establish CV disease.

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Meta-analyses of randomized trials in hypertension

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The large body of data provided by the very numerous randomized controlled trials (RCTs) of antihypertensive drugs and the problems still to be properly addressed in this field, have been recently reappraised by our group through a set of meta-analyses.
Sixty-eight blood pressure (BP)-lowering RCTs (defined as RCTs comparing active treatment with placebo, no treatment or less active treatment, achieving a BP difference, carried out in the period 1966 to end 2013 in cohorts with at least 40% hypertensive patients, and exclusive of trials in acute myocardial infarction, heart failure (HF), acute stroke and dialysis) were identified, and meta-analyzed grouping the RCTs on the basis of clinically relevant questions: 1) Does BP lowering reduce all types of cardiovascular outcome? 2) Is prevention of all outcomes proportional to the extent of systolic, diastolic and pulse BP? 3) Have all classes of BP-lowering drugs been shown capable of reducing all types of cardiovascular outcome? 4) Is BP lowering beneficial when intervention is initiated at any grade (or stage) of hypertension? 5) Do BP-lowering RCTs provide evidence about the systolic (SBP) and diastolic (DBP) blood pressure targets of treatment? 6) Should BP-lowering treatment be preferentially addressed to patients in higher risk categories promising larger absolute treatment benefits?
The results of these meta-analyses appear to provide relevant information for current hypertension guidelines recommendations.

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