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Antihypertensive Treatment: Past, Present and Future

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The definition of hypertension: systolic and diastolic blood pressure or both?

The development of a mercury sphygmomanometer for practical usage by Riva-Rocci in 1896-97 opened an era in which blood pressure became a quantity in which blood pressure (BP) became a quantity measurable at the bedside and therefore an object of clinical and scientific investigation [1]. The Riva-Rocci method only allowed measurement of systolic blood pressure (SBP), but even after diastolic blood pressure (DBP) could be measured by the introduction of Korotkoft's auscultatory method in 1905, the definition of hypertension remained predominantly based on SBP. However, around the 1950s, perhaps because of the interest in so-called "malignant" hypertension characterized by markedly increased diastolic values, DBP came to call predominant clinical and research attention, to the point that in 1968 George Pickening's most famous book "High Blood Pressure" was all centered on diastolic hypertension, and the case of systolic hypertension was dismissed in a few lines [1]. SBP came back as an important component of hypertension only during the 1990s after the completion of the first trials of isolated hypertension in the elderly. The publication in 2002 of a large meta-analysis of observational studies definitely established the role of both SBP and DBP as risk factors [2] and, subsequently, all guidelines use SBP and DBP values to define hypertension.

Should hypertension be treated? The successful story of BP lowering

In spite of the availability of BP measurement devices and the increasing awareness of the cardiovascular risk of high BP, antihypertensive treatment was delayed until the 1950-60s not only because of the lack of effective BP lowering drugs, but particularly because medical thought was dominated by the prejudice that

hypertension was a compensatory mechanism "not to be tampered with" [1].
With the development of several classes of effective and well tolerated antihypertensive drugs during the second half of the 20th century, this prejudice has been disproved by a series of randomized controlled trials (RCTs) that have shown BP lowering, independently of the drugs used, is accompanied by greater benefits than harms. In a recent systematic review we have identified 68 RCTs in which BP lowering by drugs has been compared with placebo or less intense BP lowering, and a meta-analysis of these data has shown all major types of cardiovascular (CV) events as well as mortality are significantly reduced by antihypertensive treatment [3].

Are all BP lowering drugs equally beneficial?
The relative effectiveness of different BP lowering drug classes has also been investigated by head-to-head comparison of different drugs in the same RCT. Fifty trials have been identified by our survey, and their meta-analysis has shown that, for similar BP reductions the effect of all antihypertensive drug classes on most outcomes are similar. A few differences, particularly in the prevention of stroke and heart failure, do not contradict the conclusion that the benefits of antihypertensive drugs can be predominantly attributed to BP lowering *per se* [4].

Unanswered issues of antihypertensive treatment: initiation and goals
As can be understood from the contradictory or vague recommendations given by most hypertension guidelines, uncontrovertible trial evidence on the issues at what BP and CV risk levels antihypertensive treatment should be initiated and to what levels BP should be brought by treatment is not available.
However, some useful information on both these issues, is provided by our recent meta-analyses. When a meta-analysis was done of RCTs with baseline (untreated) mean BP values within the grade 1 hypertension range and with an average CV risk within the low-moderate range, the risks of stroke, coronary events, major CV events and all death were significantly reduced by BP lowering treatment [5].

Further evidence in favour of treating hypertension before CV risk becomes excessively high also comes from another meta-analysis of our group that at higher levels of CV risk, although the absolute benefit of treatment is greater, greater also is the residual risk of patients [6].
As to the SBP target to be achieved by treatment, our meta-analysis indicate that in RCTs where SBP was brought below 130 mmHg there was some further significant reduction of stroke, whereas reduction of other outcomes, such as coronary events, heart failure and cardiovascular mortality did not reach statistical significance. Point estimates, however, were still on the side of reduction, indicating that, when achieved SBP is just below 130 mmHg there is no risk of a J-curve effect. Further information on SBP target will come from the SPRINT trial [7] to be published soon and the ongoing ESH-SHL-SHOT trial [8].

The future: goals and expectations
The major goal of hypertension research and management in the next decades is finding realistic solutions to the worldwide problem of insufficient BP control. While an earlier treatment initiation, a wider use of fixed association preparations and, hopefully, new drugs will certainly be helpful, the major obstacles to successful control are physicians' inertia and patients' lack of adherence. The future challenge for hypertension research is finding new means, new solutions to overcome these obstacles, common, in general, to chronic disease control.

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The impact of hypertensive large arteries damage in cardiovascular disease

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Increased arterial stiffness has emerged as a faithful marker of the severity of target organ damage in hypertension and in many other clinical conditions. Carotid to femoral pulse wave velocity has been associated with the occurrence of cardiovascular events and cardiovascular death in numerous epidemiological surveys [1]. High blood pressure and increased arterial stiffness are closely related [2, 3]. Although the most obvious reason for it is that the relation between strain and stress of the arterial wall is non linear. Because of unbuckling of collagen fibers caused by the progressive stretching of the wall, the arteries become stiffer as blood pressure increases. Beside this well know phenomenon, more active ones also contribute to make the wall stiffer when blood pressure increases, such as tridimensional changes in connections between smooth muscle cells and fibrous components or the wall, but also mechanical properties of the cells themselves [4]. Interestingly, the relation between arterial stiffness and blood pressure goes two directions, and high arterial stiffness has been shown to predict the transition from normotension to hypertension [5, 6]. On the other hand, blood pressure is not the sole determinant of arterial stiffness. Beside genetic factors, many cardiovascular risk factors affect arterial stiffness, so that at a given age, the range of values between two individuals may vary by 2 or 3 folds [7, 8]. This is considered as the best index of early vascular aging (EVA) [9-11]. Independently of traditional cardiovascular risk factors, arterial stiffness is predictive of major outcomes such as cardiovascular events and death, but also all cause death and non cardiovascular death [1]. Recent insights into other situations such as cancer and chronic kidney disease show that these associations cover complex mechanisms [12, 13]. Arterial stiffness is also a target for treatment [14].

An overview of the different treatment options will be presented, together with the ongoing SPARTE study [15], which aims at demonstrating that targeting arterial stiffness provides additional benefit to the patient.

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How Can Antihypertensive Treatment Modify Arterial Structural Damage?

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Endothelial dysfunction, carotid intima-media thickness (CIMT), arterial stiffness and high central blood pressure are considered markers of arterial damage increasing the risk of cardiovascular events.

Effect of antihypertensive drugs on endothelial function (1)
ACE-inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and aldosterone antagonists improve endothelial function (EF), while thiazides and thiazide-like diuretics and nonvasodilating betablockers (BBs) did not. Some antihypertensive drugs have a differential effect on the macro- and microcirculation: while calcium channel blockers (CCBs) improve EF at the microcirculatory level, the vasodilating BB nebivolol improves EF predominantly at the macrocirculation. Vasodilating BBs like nebivolol and carvedilol may have a beneficial effect on EF through preservation of NOsynthase activity by reducing asymmetrical dimethylarginine and by enhancing the bioavailability of NO because of their anti-oxidant properties. In addition, nebivolol activates NO synthase.

Effect of antihypertensive drugs on CIMT and atherosclerotic plaques (1, 2)
In randomized clinical trials CCBs were superior to other antihypertensive drugs like ACEIs, ARBs, diuretics, BBs and alpha blockers in reducing CIMT. However, with vasodilation the arterial IMT decreases without decreasing the intima-media wall area. Since no intima-media wall area has been measured in those studies, it cannot be excluded that the larger decrease in CIMT with CCBs - the most potent vasodilating drugs – does not represent a superior real decrease in intima media mass.
Early studies showed that particularly after myocardial infarction BBs may prevent cardiovascular events.

It has been suggested that the negative inotropic and chronotropic properties of BBs could decrease the risk of plaque rupture by decreasing not only the stress (blood pressure) but also the stress frequency (heart rate) on the arterial wall and plaque. It also appears that stabilization of the vulnerable plaque may be associated with a reduction of plaque volume and or area. Since only a few small studies have been published, robust data are lacking.

Effect of antihypertensive drugs on arterial stiffness (1, 3-5)
Many antihypertensive drugs decrease arterial stiffness. But, it is not always clear whether this decrease is only a 'passive' effect due to the decrease in blood pressure (BP), or whether also a direct effect of the drug is present. Despite a decrease in BP, a substantial amount of studies with diuretics and nonselective beta-blockers did not show a decrease in arterial stiffness. In comparative studies, for a similar decrease in BP, ACEI decreased arterial stiffness more than CCBs and the combined diuretic amiloride-hydrochlorothiazide (6). In short-term trials, arterial stiffness can be improved by functional changes (vascular smooth muscle relaxation) and to some extent also by structural changes. In long-term trials with antihypertensive drugs, structural changes are likely to be more prominently present. In long term trials, CCBs, BBs, diuretics, ACEIs and ARBs reduced arterial stiffness, suggesting that the decrease in BP per se can already improve arterial stiffness (7). Although ACEIs tended to have a larger effect than diuretics, BBs and CCBs, meta-analytical approaches could not identify differential efficacy of classes of drugs. However, in long-term studies different doses of ACEI and ARB showed no further decrease in BP at higher doses, but a clear lower arterial stiffness compared to lower doses, showing a BP independent effect of the ACEI and ARB on arterial stiffness.
RAS blockers may be very effective in reducing arterial stiffness because the RAS system is a potent pro-fibrotic system. (8)

Effect of antihypertensive drugs on central blood pressure and wave reflection (1, 3, 8, 9)

Central BP can be boosted by early wave reflections.

Apart from cardiac function, the timing of the arrival of the reflected wave at the ascending aorta depends on the pulse wave velocity (determined by arterial stiffness) and the distance of the major reflection points to the heart. With vasodilation these major reflection points move to more distal arterial sites decreasing the risk of early arrival of the reflected wave. A structural decrease in media-to-lumen ratio of small arteries may have a similar effect. ACEIs, ARBs and CCBs decrease media-to-lumen ratio more than diuretics, while the effect of BBs is small. A decrease in wave reflections will translate in a more pronounced decrease in central BP compared to peripheral BP. This was observed with ACEIs, ARBs, direct renin inhibitors, aldosterone antagonists, CCBs, nitrates and phosphodiesterase type 5 inhibitors. The opposite was found with BBs, while diuretics had a neutral effect. While nonvasodilating BBs showed an increase in wave reflection, this did not change or decreased with vasodilating BBs.

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Defining Left Ventricular Hypertrophy: Why is it so difficult?

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The purpose of scaling organ dimensions has rationale in the possibility of comparing individuals with different body size, a potent determinant of organ size (1).

Human heart size has been a major target for studies of this type. The attempt to normalize left ventricular (LV) mass (LVM) for body size has strong clinical implications, since, with the exception of age, LV hypertrophy (LVH) is the most potent (and possibly reversible) marker of cardiovascular risk. The computation of LVM index is indeed increasingly included in echo-reports.

A strong tradition makes body surface area (BSA) the indexing variable most often used to normalize for body size LVM, LV dimensions and volumes in adults. BSA has been used ratiometrically (i.e. assuming that LVM values are linearly proportional to BSA values). However, a three-dimensional parameter (such as LVM) cannot be a linear function of a two-dimensional measure (such as BSA). This geometric mismatch was nicely represented in a simulation, demonstrating that the power regulating the relation between LVM and BSA is not 1 (linear) but 1.5 (exponential), as it would be expected (2). In other words, to make linear the relation between LVM and BSA, BSA needs to be raised to the power of 1.5, resulting in a cubic function, compatible with the three-dimensionally shaped LVM (i.e.: m^2 raised to the power of $1.5 = m^{2\times1.5} = m^3$).

The relations between measures of body size and organ size are in fact allometric (3) and are regulated by power regressions, of the type $Y = a \times X^b$, where the coefficient of regression b is the allometric scaling factor also called the "allometric signal".

The most practical procedure for scaling, therefore, would be to normalize organ size using body weight (Kg), which is a three-dimensional parameter. This is what has been done for heart weight in a series of 104 mammalian species (4).

The allometric regression regulating this relation across the species was the following: Heart Weight = $5.8 \times Kg^{0.98}$

The allometric signal of BW is very close to 1 because both terms of the equation share a common three-dimensional shape. As we know that the normal left ventricle represents 40-45% of the total weight of the normal heart, LV weight in a healthy man of 80 Kg should be 170-190 g. Table 1 shows that this holds true only in the presence of normal body proportions, while substantially overestimating the observed LVM in the presence of abnormal body shape.

The reason of the overestimation relies in the different body composition of the three subjects. Both the obese and the anorectic patients carry a deficit of fat-free mass, which is relative in the obese patient and absolute in the presence of anorexia. Thus, normalization of LVM for body weight or variables derived using weight, such as BSA produce errors. And, in fact, the use of normalization for BSA underestimated the prevalence of LVH and the population risk attributable to LVH, when applied in a population with high prevalence of obesity (5).

Ideally, since the LV is a muscle, LV mass should be normalized for fat-free mass. A surrogate of fat-free mass is body height. In mammals, height (or length) is a measure of the skeletal size, the architecture supporting the muscle mass. The skeleton, therefore, is genetically linked to given amounts of muscle (6) and skeletal length (or height) is biologically linked to a genetically programmed ("ideal") fat-free body mass. Thus, body height is an acceptable surrogate of what should be fat-free mass in normal conditions. Because of the geometric disproportion between height (a linear measure) and LVM (a three-dimensional variable generated by a cubic function), the relation cannot be linear, because LVM should approach a cubic function of height. And, in fact, when examining a very large body-size range, encompassing near the entire life span (between 3 months and 70 years of age) and maintaining normal proportions between weight and height (i.e. in normal weight individuals), the allometric signal found to linearize the relation between LVM and height is 2.7, therefore close to 3 (7).

However, this allometric signal changes when reducing the age range and confining the analysis to childhood or adulthood. In the Framingham Heart Study, the allometric signal was 2.0 (8), close to the 2.1 in our adult reference subpopulation (9) and a recently reported 1.7 (10). These disparities suggest that the age-range of the reference population is important to generate the allometric signal of height (11).

We postulate that consideration of the full age range might incorporate information on changes of the relations between heart dimension and body size with aging.

In the Strong Heart Study (5), the performance of the lower allometric signal of height (2.1) is not significantly better than the allometric signal obtained using the entire age-span (2.7): in either condition the population risk attributable to LVH is 17%. However, when using even lower allometric signals (1.7) the performance is clearly reduced (10), suggesting that even small differences might impact our ability to identify harmful conditions.

Eventually, we suggest using methods of normalization that maximize population-attributable risk, which is the most important measure of incident disease for programs focused on disease prevention.

Table 1 (from ref #1): Examples comparing echocardiographic LVM and value predicted by body weight, using the equation from ref #4.

	Normal	**Obesity**	**Anorexia nervosa**
Sex	Male	Male	Female
Age (years)	39	48	17
Weight (kg)	81	151	34
Height (m)	1.80	1.72	1.58
BMI (Kg/m^2)	25	51	14
Blood pressure (mmHg)	118/64	126/82	92/60
Observed LVM (echo)	188 g	220 g	43 g
Predicted LVM (based on BW)	194 g	356 g	83 g
LVM, difference from observed (g[%])	6 g (3%)	136 g (62%)	40 g (93%)

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From left ventricular hypertrophy to heart failure: new advances

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Pathologic left ventricular hypertrophy (LVH) and heart failure with preserved ejection fraction (HFPEF) are prevalent and frequently encountered in cardiac diseases such as hypertensive heart disease, aortic stenosis and diabetic cardiomyopathy. How LVH is related to abnormalities of LV diastolic function (namely, increased LV passive stiffness) found in HFPEF remains incompletely understood. In order to advance in this issue seems convenient move from the macroscopic view of LVH as increased muscle mass to a microscopic view in which the alterations of the histologic constituents of the myocardium are altered. In fact, cardiomyocyte hypertrophy, accumulation of collagen leading to interstitial fibrosis, and microvascular rarefaction are typical changes in pathologic LVH. Recent experimental and clinical studies have revealed that despite adequate treatment of the underlying cardiac disease, changes in both cardiomyocyte and collagen matrix occur during the development of HFPEF and that these changes combine to cause a major increase in LV passive stiffness that contributes to diastolic dysfunction. In fact, some studies have emphasized the role of changes in titin (the giant molecular spring protein that is one important factor responsible for cardiomyocyte passive stiffness); specifically, changes in its phosphorylation. In addition, other studies have remarked the contribution of changes in the composition and structure of collagen fibers; particularly, changes in collagen phenotype (e.g., with a relative excess of collagen type I over collagen type III fibers) and organization (e.g., an excess of cross-linking among collagen microfibrils) that result in a more stiff collagen matrix. Once proven operative in large samples of HFPEF patients, these mechanisms can serve as targets for successful therapy aimed to interrupt the progression from LVH to HFPEF.

In this regard, it has been reported that some therapeutic interventions may reduce either titin-dependent or collagen-dependent myocardial stiffness in animals and patients with HFPEF.
In addition, imaging and circulating biomarkers that reflect these changes in titin and collagen could be used to detect the earliest transition from LVH to HFPEF, to improve diagnostic criteria for HFPEF and prognostic assessment, and to monitor treatment efficacy before changes in myocardial structure and function or clinical status are evident.

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Management of heart failure with preserved systolic function

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Heart failure with preserved ejection fraction (HFpEF) currently represents almost one half of all heart failure patients and, with the growing elderly population, is projected to become the predominant form of heart failure in the future.

HFpEF is characterized by a complex pathophysiology, encompassing multiple etiological mechanisms and exhibiting a diversity of clinical presentations.

In general, outcomes in HFpEF are similarly poor as those in patients with heart failure with reduced ejection fraction (HFrEF) with respect to hospitalization and mortality risk.

Despite the therapeutic advances for patients with HFrEF through landmark clinical trials on neurohormonal modulation and device therapy, clinical trials in patients with HFpEF have been challenging, and results have been neutral. To date, no therapy has proven to improve survival in HFpEF. The mainstays of treatment are diuretics and guideline-directed management of comorbidities.

Promising new therapeutic options on the basis of sound scientific rationale and observational data, such as the recently-published study on angiotensin-neprilysin inhibitors , may prove to benefit patients with HFpEF.

To optimize clinical trial effectiveness, trials in patients with HFpEF should consider inclusion of patients with the common comorbidities that drive HFpEF's underlying pathophysiology through the balanced use of the following key inclusion and exclusion criteria: universal EF cutpoint; appropriate NP-level thresholds; limited number of patients with atrial fibrillation; and use of a clearly-defined history of heart failure and diagnosis of previous heart failure. Attaining hemodynamic measurements related to HFpEF through the use of echocardiography, cardiopulmonary exercise testing, and invasive hemodynamics may complement or validate challenging patients.

Thoughtful clinical trial design that incorporates the lessons learned from previous and ongoing clinical trials in patients with HFpEF will provide the trial landscape necessary to determine if future therapies actually improve the outcomes and/ or quality of life in patients with HFpEF.

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How to manage blood pressure in the acute stage of stroke

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Elevated blood pressure (BP) is commonly observed in the acute period of stroke. During the first 24 hours from stroke onset, up to 80-90% patients with ischemic and hemorrhagic stroke, respectively, are hypertensive (supine BP ≥ 140/90 mmHg). Moreover, the alteration of circadian rhythm of BP, as well as high BP variability are frequent findings in patients with acute stroke. Raised BP tends to decline spontaneously in the first few hours and days following stroke. Only less than one half of stroke patients will remain hypertensive after 10 days, even without treatment. High BP predicts a poor outcome when present in the first 24 hours after the onset of both ischemic and hemorrhagic stroke. Of note, early recanalization of occluded cerebral artery responsible for ischemic stroke is associated with more rapid BP decline than in patients with persistent arterial occlusion. Furthermore, in the first 24 hours after stroke, BP decreases usually much more after intracerebral hemorrhage than after major ischemic stroke.

The pathomechanisms responsible for the elevation of BP in acute stroke are complex and poorly understood, but undiagnosed and untreated chronic hypertension is probably the main contributor. Up to 50% of stroke patients are taking antihypertensive drugs before the acute event. Other factors affecting hypertensive response in acute stage of stroke possibly include transient stimuli like stress of hospitalization, pain, urine retention, infection, activation of neuroendocrine systems, as well as more brain-specific contributors like raised intracranial pressure, and damage of brain regions that regulate the activity of the autonomic nervous system.

Although debated more than 30 years, the best strategy to manage raised BP in acute stroke remains unclear and seems to mainly depend on the underlying stroke subtype.

In ischemic stroke, transiently elevated BP may be needed to maintain the collateral perfusion and thus to prevent the salvageable tissues from necrosis, whereas in hemorrhagic stroke subtype, high BP may

accelerate both early re-bleeding with hematoma expansion and early recurrent stroke. Nevertheless, in both stroke subtypes, very high, especially sustained high BP, as well as more variable BP values are associated with the poor outcomes.

Rapid identification and control of all factors, that temporarily alter the BP level, is the first step in the strategy of BP management in acute stroke. Careful examination and continuous monitoring should precede any BP medical treatment. The timing of the potential antihypertensive therapy is largely dependent on stroke subtypes.

In ischemic stroke, the most critical is to save the vulnerable tissue surrounding the infarction, and thus decreasing of BP during the first 24 hours from stroke onset, when collateral flow in penumbral area is a concern, should be avoided. However, extremely high BP may potentiate hemorrhagic transformation of cerebral infarct, and facilitate progression of peri-lesional edema with further decrease of cerebral perfusion pressure and subsequent extension of tissue damage. Available evidence, in summary, suggest a neutral or harmful effect of early (within 24 hours) BP lowering on the prevention of unfavorable outcome (death or dependency), as well as on recurrent vascular events in patients with acute ischemic stroke. Current guidelines caution the BP reduction in acute ischemic stroke. Generally, BP evaluation should be frequent and preferably continuously monitored, especially in the first 24 hours, and its reduction should be gradual and controlled, if BP is over 220/120 mmHg. Despite natural history of spontaneous BP normalization, some clinical situations have been identified, where BP reduction during the first 24 hours after acute ischemic stroke is warranted: BP levels over 180/110 mmHg in case of eligibility for reperfusion therapy, and acute end-organ damage like acute heart or renal failure, aortic dissection.

By contrast, in intracerebral hemorrhage the critical point is to stop bleeding.

Current evidence suggests that in patients with acute (within 6 hours of onset) intracerebral hemorrhage intensive antihypertensive therapy (systolic BP target below 140 mmHg within 1 hour) is safe and may be superior to a more conservative guideline-recommended regimen of systolic BP target of 180 mmHg.

Furthermore, the benefits of early treatment to reduce systolic BP might be enhanced by smooth and sustained BP control. Reduction of BP may also be important in subacute phase of hemorrhagic stroke at the time of progression of peri-hematomal edema.
Of note, to date, no specific agent can be recommended in management of hypertension in the acute phase of both ischemic and hemorrhagic stroke subtype. More clinical studies are needed to further investigate the early BP interventions in the hyperacute phase of stroke.

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Hypertension and Cognitive Decline

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A better understanding of the role of vascular factors contributing to the onset and progression of cognitive decline with advancing age is becoming a top priority for research and public health. Hypertension is a very common condition in older individuals in whom it represents the major cardiovascular risk factor. A large number of studies have reported strong relationships between indices of vascular aging and either cognitive impairment or silent cerebral small vessel disease.

Hypertension is known to be the most important factor for developing macrovascular cerebral complications such as stroke and, consequently, vascular dementia[1]. Hypertension may also predispose to the development of more subtle cerebral processes based on arteriolar narrowing or pathological microvascular changes. It has been suggested that cerebral microvascular disease contributes to the development of vascular cognitive impairment. The mechanisms underlying hypertension-related cognitive changes are complex and not yet fully understood[2]. Correlations between cerebral white matter lesions and elevated blood pressure (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. In addition, there is some evidence that antihypertensive drug treatment may play a role in the prevention of cognitive impairment or vascular dementia through BP control[3].

Results from cross-sectional and longitudinal studies have shown a correlation between blood pressure and cognitive function in elderly people[2,3]. Moreover, the association between large artery stiffening and cognitive impairment has been reported by several cross-sectional studies and has been confirmed in longitudinal studies[4,5]. The mechanism of such association has not yet been firmly established.

Exposure of small vessels to highly pulsatile pressure and flow may explain microvascular damage and resulting intellectual deterioration[4].

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How to Assess Cognitive Decline in Routine Clinical Practice

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Assessing and stratifying the risk is a way to predict (a possible future) and its aim is to develop preventive strategies. For stratifying it is necessary to know the damage that arterial hypertension causes in the target organs because, the progression in the continuous of the vascular disease is determined by the damage of a target organ and not by the presence of a risk factor.

However, when assessing the damage of a target organ our evaluation is not complete. The heart and kidney are evaluated systematically but not the brain. The 30% of hypertensive patients have lesions in the cerebral white matter, lacunar infarctions or microbleeds, which are not investigated. These patients have an incorrect stratification if we ignore the evaluation of the brain.

The "burden" and progression of the vascular brain injury increase the risk of stroke and cognitive impairment. This damage, silently, precedes the clinical expression of the disease (stroke or cognitive impairment) for many years. However, performing a magnetic resonance image (MRI) of the brain in all hypertensive patients for risk stratification is impracticable and economically impossible.

The approach of the cognitive state of the hypertensive patients is a way of infering vascular injury of the brain. Identifying patients with cognitive impairment is critically important, particularly if one can implement other therapeutic strategies, to stop the progression of the disease.

Between 70-80% of people with mild cognitive impairment or in the initial stage of a dementia syndrome, who attend a routine practice, are not detected. There is not a simple test considered as gold standard. The Minimal Mental Statement Examination (MMSE), described by Folstein in the 70s, is the most widely known and widespread tool.

However, it is limited because of its low sensitivity and specificity, because it depends on the age and the level of education and because it does not evaluate the executive functions, which are the most cognitive domain affected in patients with vascular brain injury, are not evaluated. Despite this, the MMSE has been useful and it's in continuous use.

Planning, working memory, visual-spatial, decision-making are some of the most important executive functions. This cognitive domain depends on the integrity of the white matter that connects the dorsolateral prefrontal cortex to the basal ganglia. The Verbal fluency, the Trial Making Test (Part B) and the Stroop test, all evaluate aspects of executive function, but the Clock Drawing test is the simplest, fastest and most feasible to perform in a routine clinical practice. The Clock Drawing test evaluates the planning, the visuo-spacialty and some aspect of semantic memory and the result can be interpreted quantitatively (cut-off) or qualitative.

This test does not try to establish a diagnosis. It is a screening test that detects which patients have a cognitive impairment. Only, a complete neuropsychological assessment together with MRI of the brain will establish the diagnosis.

According to our data, 28% in a sample of hypertensive patients attending the practice-office of cardiology, had cognitive impairment and 8.9% early dementia. In another epidemiological study conducted in our country hypertension increased 5 times the chance of presenting alterations in the executive domain. This means that the patients suffering a non-amnestic cognitive impairment (dis-executive) double the risk of developing dementia

So, in patients with hypertension or vascular damage, especially in the population over 60 years old, we should know the impact or damage that the vascular disease has caused in the target organ brain, using neurocognitive test, specifically evaluating the affected domains (executive function). A complete neuropsicological test batteries and neuroimaging should be used when the screening was positive.

In 2007, with an update in 2013, the *Argentine Federation of Cardiology* published the guidelines for the assessment of cognitive disorders in patients with any vascular disease.

They included the state of knowledge on these topics as well as the most useful tests and the ways of the implementation in detail. We reinforced the importance of thinking neurocognitive about the consequences of hypertension and we recognized the need of an interdisciplinary approach to the problem. Clinicians and cardiologists, should to detect early neurocognitive diseases in hypertensive patients, in the routine clinical practice.

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Impact of chronic kidney disease in cardiovascular disease

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Chronic kidney disease (CKD) has reached epidemic proportions. The most comprehensive information on its prevalence in developed countries comes from the National Health and Nutrition Examination Surveys (1). Based on the presence of albuminuria and decreased estimated glomerular filtration rate (eGFR), the prevalence of CKD stages 1-4, as defined by the National Kidney Foundation (2), increased from 10.0% in the period 1988-1994, to 13.1% between 1999 and 2004 (1).

The concept of a continuum of pathophysiological changes mediated by angiotensin II was first conceived for the progressively increasing severity of cardiovascular disease (CVD) in the presence of risk factors (3). A similar gradual transition takes place within the renal vasculature, resulting in kidney disease of increasing severity. The initial, subclinical damage to glomerular endothelium is induced by such risk factors as hypertension and/or diabetes, and the consequent endothelial dysfunction. Subsequent glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis lead to incipient disease, identified by high albuminuria. Further damage occurs in the absence of pharmacological intervention, with the emergence of overt nephropathy, defined as the presence of very-high albuminuria or proteinuria. Thereafter, there is a gradual decline in the GFR and an increase in serum creatinine levels that culminates in end-stage renal disease (4).

Because of the similarity between the pathophysiological effects of angiotensin II on the cardiovascular system and the renal vasculature, it seems logical to suppose that CVD and CKD progress simultaneously. Most individuals with CKD die of coronary heart disease before end-organ damage occurs in the kidneys. Similarly, patients with CVD often exhibit varying degrees of CKD.

The presence of high albuminuria has long been identified as a marker of CKD, and it is also acknowledged as a predictor of cardiovascular morbidity and mortality. Even low-grade microalbuminuria (i.e., >30 mg/24 hours) is associated with increased cardiovascular risk in apparent healthy patients (4).

In CKD, it is useful to consider 2 subtypes of arterial vascular disease, namely, atherosclerosis and large-vessel remodeling or arteriosclerosis. Atherosclerosis is an intimal disease characterized by the presence of plaques and occlusive lesions. There is a high prevalence of atherosclerosis in CKD. Atherosclerotic lesions in kidney failure are frequently calcified, as opposed to fibroatheromatous, and have increased media thickness compared with lesions in the general population. Clinical presentations of atherosclerosis include ischemic heart disease, namely, angina, myocardial infarction, and sudden cardiac death, which is common in CKD, and cerebrovascular disease, peripheral vascular disease, or heart failure. Patients with CKD also have a high prevalence of arteriosclerosis and remodeling of large arteries. Remodeling may be due either to pressure overload, which is distinguished by wall hypertrophy and an increased wall-to-lumen ratio, or flow overload, which is characterized by a proportional increase in arterial diameter and wall thickness. Remodeling often accompanies a reduction in arterial compliance, which can be detected through measurement of aortic pulse wave velocity and characteristic impedance. Noncompliant vessels may result in increased systolic blood pressure, increased pulse pressure, left ventricular hypertrophy, and decreased coronary perfusion. Both decreased aortic compliance and increased pulse pressure have been found to be independent risk factors for CVD in CKD patients (5).

According these evidences, the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Working Group recommend that all people with CKD should be considered at increased risk for cardiovascular disease (6).

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The Kidney in Obesity

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Overweight and obesity which have reached epidemic levels worldwide are a widespread condition with an ever-increasing prevalence. In Westernised societies, it is currently estimated that 35% of the population, and 50% of those over 50 years of age, are overweight or obese. Over the last years, besides the importance of obesity in the prevalence of CV risk factors and in the risk for cardiovascular disease, the impact on the kidney has received attention. This was in part due to the recognition that the presence of chronic kidney disease (CKD), in which obesity seems to be play an important role, increases morbidity and mortality beyond the traditional CV risk factors. The impact of obesity on the kidney includes a wide spectrum, from characteristic pathologic lesions to increment in urinary albumin excretion (UAE) and proteinuria/or decrease in glomerular filtration rate (GFR), what today is considered chronic kidney disease (CKD). After proteinuria, body mass index was found to be the second most important contributor to relative risk for developing ESRD. Two relevant elements emerge as central in the pathology of kidney in the presence of obesity. The first is the presence of a characteristic lesion in the glomerulus, the obesity-related glomerulopathy, and the second is the relevance of fat deposit in the kidney with impact on the renal hemodynamics and intrarenal regulation. Likewise, lipid loading of tubular cells also produces functional alterations and predispose to renal scarring.

The mechanisms leading to the structural abnormalities are complex and in part related to effect of obesity-associated cardiometabolic risk factors and their final effector mechanisms. Hypertension, diabetes, dyslipidemia and insulin resistance alone or in clusters, largely contribute to renal damage through multiple effectors, adipokines, lipids, RAAS, SNS, inflammation, oxidative stress,

apoptosis and finally renal scarring. However, the local hemodynamic factors also play an important role.

The final goal of interventions is to reduce the rate of decline of eGFR, delaying the ESRD and in parallel the reduction in cardiovascular morbidity and mortality associated to CKD. The protection of kidney damage needs to combine weight reduction with the proper control of the cardiometabolic risk factors associated, hypertension, metabolic syndrome, diabetes and dyslipidemia. Additional salt intake reduction should be implemented if proteinuria is present. Even a small reduction in weight can to contribute to achieving control in hypertension and diabetes. Losing weight reduces the UAE or proteinuria. Dietary restriction-induced weight-loss, reduced proteinuria or microalbuminuria by half, with no significant changes in the GFR but no data exist about the impact on the rate of GFR decline overtime (88). After bariatric surgery, reduction in GFR is much higher than in dietary-induced weight loss, reducing the hyperfiltration (88,89).

The potential role of different classes of drugs in to reduce proteinuria and to protect about glomerular filtration decline it is far to be established. The protective effect of drugs blocking the RAAS, such as angiotensin converting enzyme inhibitors, angiotensin II receptor blockers or antialdosterone compounds is controversial. Although all of the RAAS blocker agents reduce albuminuria at short term beyond the BP lowering effect, the long-term impact in to reduce the rate of GFR decline is a controversial matter.

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Renal protection in the diabetic patient

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Diabetic nephropathy is today the leading cause of end-stage renal disease in developed countries. Thus, the percentage of patients on dialysis who suffered from diabetes ranges between 25 and almost 50% depending on the regions. Therefore, renal protection in diabetes is a major public health issue around the world. Today the renal protection of diabetic patients is based essentially on a good glucose and blood pressure control. Control of body weight and smoking cessation are also to important measures that should be implemented in all diabetic patients.

Regarding the control of blood pressure, the prescription of blockers of the renin-angiotensin system such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers or even renin inhibitors is one the recommended first step in the management of patients with chronic kidney diseases including diabetes. The recent data of the ACCOMPLISH have also demonstrated that the combination of an ACE inhibitor with a calcium channel blocker is very effective and better than an ACE inhibitor combined with a diuretic in reducing renal events in patients with a high cardiovascular risk such as diabetics.

Despite these effective treatments, many patients with diabetic nephropathy continue to progress towards end-stage renal disease. Therefore, efforts should be done to develop new therapeutic being investigated one can mention the selective blockade of aldosterone receptors which has been found to lower blood pressure and proteinuria. New agents of this type such as finerenone are being investigated in the prevention of diabetic nephropathy and large clinical trials with renal and cardiovascular endpoints are ongoing. Another class which could be considered in the future is endothelin receptor antagonists if one can demonstrate that their efficacy is superior to their side effects in particular peripheral edema which may sometimes be severe.

In this domain, although the first studies were disappointing, new trials are being conducted and should provide interesting results in the next years.
Today, many efforts are being done to develop new agents to retard the progression of diabetic nephropathy more effectively. New strategies will probably be available in the near future.

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How to improve adherence and persistence with treatment

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Blood pressure (BP) is poorly controlled in all hypertensive populations worldwide. This is not due to ineffectiveness of available treatment because in proper environmental conditions (e.g. clinical trials) antihypertensive drugs can lower BP < 140/90 mmHg in more than 80 percent of the patients. It is due to a variety of factors that range from 1) deficiencies of health care structures in the area of cardiovascular prevention 2) physicians' reluctance to step up the doses or the number of antihypertensive medicaments (therapeutic inertia) when BP is found to be uncontrolled or 3)low adherence to or persistence with the prescribed treatment regimen by the patient. This presentation will focus on the last factor, which is believed to play the most important role on the low rate of a BP < 140/90 mmHg, i.e. the target recommended by current guidelines in hypertensive populations. Based on the analysis a large Italian data-base it will be shown that adherence to non-pharmacological measures that lower BP is extremely low, but also that this is the case for drug treatment. It will then be shown that adherence to drug treatment is closely related to the rate of BP control as well as to the incidence of cardiovascular morbid and fatal events, high adherence being accompanied by a much lower risk of coronary heart disease, cerebrovascular disease and heart failure both in middle age and in elderly patients.
Finally, the factors responsible for low adherence to treatment will be reviewed together with the measures that may allow adherence to be improved. It will be emphasized that increasing knowledge on adherence is a fundamental step to improve cardiovascular prevention, but also that research in this area is difficult. First, measures of adherence are either fallible or too complex to be used in large scale studies. Secondly, within individuals adherence may vary over time which means that continuous measures are needed. Thirdly, subjects need to be unaware of being under observation in order for their behaviour to reflect the usual one.

What is new in the interventional therapy of resistant Hypertension

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Developing additional approaches to the current management of RHTN, that consists of lifestyle modifications combined with polypharmacotherapy is a clinical priority. Percutaneous catheter-based transluminal renal denervation (RDN) by delivery of radiofrequency energy is emerging as a new approach to achieve sustained BP reduction in this setting. The pathophysiological background as well as the efficacy and safety data from many non-randomized trials favoured RDN as a promising therapy for RHTN. However, SYMPLICITY HTN-3, the first prospective, randomized study to include a sham-control group failed to meet its primary effectiveness endpoint at 6 months firing up scientific concerns regarding the extent of RDN effects on BP. Currently, more than 1.5 year after this publication, many potential causes have been suggested to explain the HTN-3 failure, beyond the regression to the mean phenomenon, the placebo effect and the Hawthorne effect: a) Procedural aspects related to the reduced number of completed ablation attempts, non-circumferential pattern of energy delivery especially with the use of a single electrode mono-polar catheter and the fact that most of the participating and very experienced interventionalists in USA, were yet unfamiliar with the RDN procedure b) The studied patient population. The patients were over-treated (50% were on central sympatholytics, 22% on aldosterone antagonists, 36% on peripheral vasodilators) with a long history of hypertension and the accompanied advanced arterial remodelling may limit any reduction in BP after RDN. C) Antihypertensive drugs may have been maximized, but not stabilized since 40% of the patients changed their medications. The variable adherence to antihypertensive medications may also explain the huge reduction of BP in the sham ablation arm in African Americans.

What we have learned in the meantime

Human and other preclinical observations suggest that asymmetric and most probably distal renal artery targeting is required to achieve effective ablation of renal sympathetic nerves. Maximum procedural efficacy would also mean the achievement of ablation in all four quadrants, or 'circumferentiality', of both renal arteries. There appears to be a 'dose-response' dependency between the number of ablation attempts and the efficacy of renal nerve ablation.

What is needed to be determined

a. Reliable markers of procedural success to establish on time whether denervation has been completely achieved in a specific patient
b. The *appropriate patient population* with high chance of response, (i.e. younger patients with hypertension in earlier stages, even without treatment).
c. The appropriate design and methodology of the clinical trials (ambulatory BP instead of office BP as the primary endpoint, measurement of adherence with antihypertensive therapies, the necessity of a sham procedure) .
Towards this direction, 2 studies including sham ablation arm, in USA and Europe start enrolling patients hypertensive patients with and without medications in order to test whether RDN really reduces high BP.

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Epidemiology of Cardiovascular Risk Factors in Latin America

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The burden of cardiovascular diseases (CVD) and specifically the absolute number of cases and deaths continue to rise in Latin America (LA). CVD is responsible for 1.6 million deaths annually and approximately 30% of these deaths occur before age 70 years. Overweight and obesity are independent risk factors of CVD and plays a crucial role in the development of diabetes mellitus type 2 (DM2). In the last two decades the obesity prevalence in LA has increased by more than 20% and nowadays his prevalence in most of the LA countries is over 40%. The INTERHEART study demonstrated that abdominal obesity (AO) is the most frequent risk factor for an acute myocardial infarction (AMI) in LA, with a population-attributable risk (PAR) of 48.5%, while in the rest of the world was 30.2%. Recently, the INTERSTROKE study also demonstrated that in the LA countries AO has a high PAR to ischemic and hemorrhagic stroke.

At present the mean prevalence of DM2 in LA is around 10% with the number varying between 14% in Mexico and above 12% in Dominican Republic to under 5% in Peru. There is a big difference within countries between urban and rural settings. A recent study in Peru showed a more than twofold difference between the prevalence of diabetes in the coastal urban population (8.2%) and the people living in suburban areas in the sierra and the jungle (4.5% and 3.5% respectively). These differences may be attributed to lifestyle changes occurring with urbanization, such as a more sedentary life with loss of physical fitness and dietary modifications towards more elaborated products with higher sugar content (particularly sweet beverages) and less fiber content, as well as increased weight. The indigenous population is another group at risk.

For example, the Mapuches and Aymaras in Chile had the lowest prevalence of T2D in the world (less than 1%) but increased to 8.2% and 6.9% respectively in those who were transferred from a rural to an urban environment.

There are a number of physiological and metabolic changes associated with overweight that may contribute to an increased risk of CVD and DM2. Increased visceral adipose tissue disturbs the adipocytokine secretion and leads to a low-grade chronic inflammatory state by the infiltration of macrophages in adipose tissue. It is noteworthy that the LA population seems to have a higher sensitivity to develop systemic low-degree inflammation as a response to AO. This inflammatory state is found to be associated with peripheral resistance to insulin-mediated glucose uptake and atherosclerosis. The above metabolic alterations might lead to vascular endothelial dysfunction, abnormal lipid profile, hypertension, and vascular inflammation, and all these factors could favor the development of T2D and CVD. Hypertension is considered the leading cause of cardiovascular death, stroke and myocardial infarction worldwide. The prevalence of hypertension in LA varying between 37.5% in Colombia to 52% in Brazil. However the awareness, treatment and control of hypertension are far from adequate, with 57% of hypertensive respondents aware of their diagnosis, of whom about 53% were treated; only 33% of those treated and 18% of those affected had controlled blood pressure. The smoking rates vary between 20.8% and 48.1%, and the rates of increased levels of cholesterol is around 6.9-11.4% and LDL-cholesterol between 5.8-12.2%. However, the risk factors associated to insulin resistance (IR) are the most prevalent: 53.3% of the population in LA has low levels of high-density lipoprotein cholesterol (HDL-C), and 49.7% has high levels of triglycerides (TG). Moreover, low handgrip strength (HGS) that has been associated to IR, has been identified as a predictor of premature mortality, of similar magnitude value as the well-established risk factors BMI and blood pressure. There is substantial evidence, that low muscle strength is a risk factor for chronic disease and predictor of CVD and all-cause mortality both in initially healthy adults and those with disease, including hypertension.

Furthermore, we recently showed in an international cohort DM2 and pre-DM2 patients, which included people from LA and other low-middle regions, that lower HGS, a widely used index of whole body muscle strength, was a powerful predictor of cardiovascular and all-cause mortality over 6 years of follow up. While the precise mechanism by which muscle strength and or mass are protective against cardio-metabolic diseases is not clear, it is suggested that this may be mediated by the inverse association between strength and classic risk factors such as HOMA index, triglycerides and blood pressure, positive associations with markers of vascular function and lower arterial stiffness and/or its inverse associations with inflammatory markers such as CRP and TNF-α. While there is little data regarding these interactions in LA countries, we recently demonstrated in the ACFIES study of fitness and cardio-metabolic risk factors in Colombian schoolchildren, that handgrip strength was inversely associated CRP, as well with SBP, diastolic blood pressure (DBP), HOMA index and a composite metabolic risk score. Despite the increased adoption of westernized, obesogenic lifestyles in LA, these populations are still burdened by maternal under nutrition. These early life insults, which may manifest in lower birth weight offspring, appear to accentuate the relative risk of chronic disease at lower levels of adiposity. Thus LA populations may be more vulnerable to the pathogenic consequences of obesity than individuals with similar lifestyles in high-income countries. While epidemiological studies show a strong association between low birth weight and adult chronic disease, evidence that these individuals also show higher level of pro-inflammatory markers and lower levels of muscle mass and strength, suggest potential contributory pathways.

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How to Face the Inequities

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Cardiovascular disease (CVD) is no longer just a health issue, but a major economic burden. Non-communicable diseases (NCDs) account for two thirds of all deaths in the world. CVD alone, including heart disease and stroke, makes up nearly 50% of all NCD deaths. By 2030 the total global cost of CVD is set to rise from approximately US$863 billion in 2010 to a staggering US$1,044 billion.1 More than 80% of CVD occurred in low- and middle-income countries (LMIC). In these regions, CVD occurs at a much younger age than in high-income countries, thereby contributing disproportionately to lost potential years of healthy life as well as lost economic productivity. 2 According to WHO, "the social determinants of health are mostly responsible for health inequities-the unfair and avoidable differences in health status seen within and between countries" 3The social determinants of health as well as race and ethnicity, sex, sexual orientation, age, and disability all influence health disparities.

Health disparities are differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups, and health inequities are differences in health, which are not only unnecessary and avoidable but, in addition, are unfair and unjust, in a broad concept are actually differences that could be resolved and are not. Health inequalities can also be present between different ethnic groups or geographic locations. CVD is one of the conditions most strongly related to health Inequalities:
Although in the last 20 years, the prevention and treatment of cardiovascular diseases has prolonged in average the life of citizens in developed countries by around two years inequalities remain: This benefit has not happened in the same way in the developing countries moreover there are variation in life expectancy between the wealthiest and most deprived neighborhoods living in the same country.

Deaths from CVD have fallen, but the decline has been smaller in the poorest communities, there appears to have been no narrowing of the relative difference between the most deprived and the least deprived socio-economic groups. These differences or inequalities in cardiovascular health also persist between ethnic groups and geographic areas.

Equity is defined as achieving something for everyone at all times and is a problem that concerns the economy which is the science that studies how best to distribute insufficient resources (health needs are unlimited and resources are limited).

Tackling health inequalities in CVD is an integral part of creating a fairer and healthier society, and improves the health of the population as a whole.

Inequalities in health outcomes arise because of the conditions in which people are born, grow, live, work, and age – the social determinants of health.

Often the issue of equity and efficiency in health care focuses only on access to health systems and this is an incomplete concept of the process leading to the preservation or restoration of the healthy state. To succeed, quality health care services are required, equitable access to them, appropriate prescribing of medications and procedures and patient adherence to directions. To this we must understand that stakeholders in this process are not only the patient and health providers, but are also decision makers, family, and society as a whole.

How they should allocate resources for health, it is a difficult decision, because often the efficiency and equity cannot be fulfilled simultaneously, because if you want to increase the effectiveness often have to reduce the equity and if you want to achieve equity often need to less effectiveness. For example, if there are 10 patients requiring each 20 monetary units to solve their own problems and the system has only 200 units, if shared equally giving 10 units to each subject, the equity is 100 but effectiveness is 0 and if you decide to deliver 20 units to 5 subjects, equity is 0 but the efficiency rises to 50%.

Although the burden of CVD is already enormous in LMIC, there exists a window of opportunity for preventing the epidemic from reaching its full potential magnitude.

This requires the rapid deployment of strategies already proven to be effective in high-income countries. Such strategies need to be tailored for LMIC for them to be affordable, effective, and accessible to disadvantaged groups.
Ideally, the control of CVD in LMIC would involve a dual approach in which evidence-based clinical strategies for CVD prevention and treatment are complemented by evidence-based population level strategies
Suitable efficient strategies to reduce inequities must meet the following characteristics

1. Strengthen communities where people live, work, play, socialize, and learn;
2. Enhance opportunities within underserved communities to access high-quality, culturally competent health care with an emphasis on community-oriented and preventive services;
3. Strengthen the infrastructure of the health system to reduce inequities and enhance contributions from public health and health care systems; and
4. Support local efforts through leadership, overarching policies, and through local, state, and national strategy.

The Government should consider the possible impact on health inequalities when developing its domestic policies.
The Government should consider whether implementing legislation that incentivizes good practice within the food industry may help reduce the root causes of CVD risk factors.

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