Effects of blood pressure control in cardiovascular prevention

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Abstract

High blood pressure is the main risk factor worldwide for mortality and morbility. Subjects with uncontrolled hypertension increased in the last decades. This narrative review focused its attention on the diagnosis, the pathophysiology, the clinical consequences of arterial hypertension, and on the factors that must be considered for a better blood pressure control. Essential hypertension is caused by a complex interaction of genetic factors, modiulation of homeostatic systems, vessel wall modification, inflammatory mediators. The best therapeutic choice can be, in daily clinical practice, challenging due to the various classes of available drugs, the different individual responses to the same antihypertensive drug, the variability of the phenotypes. The review will also discuss the best strategy to reduce cardiovascular events in hypertensive patients targeting either the overall cardiovascular risk or to blood pressure levels only. This review is based on the material searched for and obtained via MEDLINE and PubMed up to March 2016. The search terms used were "hypertension, blood pressure control" in combination with "pathophysiology, lifestyle, arterial stiffness, antihypertensive drugs, target values and comorbidity".

Introduction

Arterial hypertension (AH) represents the main risk factor worldwide for cardiovascular (CV) and all-cause mortality and is strongly correlated to the risk of stroke, myocardial infarction (MI), renal and heart failure [1]. AH prevalence increases with age involving one third of Western population and 70% of adults ≥ 70 years [2]. Further, despite a series of International Guidelines provides adequate support to the physicians, subjects with uncontrolled hypertension have been increasing over the last years [3-7]. This is in part due to population aging and to the increase in the prevalence of obesity [2]. Aim of this narrative review is therefore to begin with the pathogenetic mechanisms of AH, highlighting emerging issues such as arterial stiffness and inflammation , and understanding how can be individualized excellently antihypertensive therapy, providing a useful tool for the clinician to obtain the therapeutic goal. The control of BP also at a population level will be discussed.

The Prospective Studies Collaboration (PSC) was a large meta-analysis of 61 observational studies on the association between BP and vascular mortality and performed between 1950 e 1990. It was based on 100,000 deaths among 1 million subjects without a history of vascular disease [8]. The main finding was a continuous log-linear association between BP and vascular mortality (coronary artery disease, stroke) irrespective of the baseline BP value, but with a diminishing association with aging: for every 20 mmHg lower systolic BP (SBP), the hazard ratio (HR) for death from CAD declined from 0.49 in subjects aged 40-49 to 0.67 in those aged 80-89 years [8]. The PSC and the Framingham Heart Study also showed that SBP was a stronger predictor of CV events (CVEs) than diastolic BP (DBP) [9]. About pulse pressure (PP) several data showed its predictive role of CVEs, particularly in elderly subjects [10]. Further, about BP as a predictor of CVEs all large epidemiological studies had found no differences between male and female and subjects of different ethnicities [2].

Pathophysiology of hypertension

Hypertension is a very complex disease with a multifactorial pathophysiology, which combine genetic factors, lifestyle, neuro-hormonal disorders, arterial stiffness, low-grade inflammation. In a simplified view, BP may be considered the product of cardiac output (CO) and peripheral resistance (PR). CO is the result of the fluid volume (preload) and the contractility of the heart. Hypertension occurred when CO and/or PR increased. The latter is a simplified version of the pathogenesis but also useful, as we described below, to understand its finer pathogenetic mechanisms.

Genetic factors

One of the aspects to investigate in hypertensive subjects is the presence of AH also in relatives. This fact confirm a genetic contribution to BP levels, with a role of multiple genes. Several studies found the presence of high BP as a part of family history in 60% of subjects [11]. In last years several studies investigated the presence of genetic polymorphism in human hypertension, also with the aim to predict the response to any given therapy. For example, Sciarrone [12] and co-workers showed that subjects with α-adducin Gly460→Trp polymorphism had a brilliant response to diuretic but not the other pharmacological classes. The International Consortium for Blood Pressure Genome – Wide Association Studies provided a genetic risk score based on 29 independent genetic variants. This score is associated with BP levels and TOD [13]. A very recent meta-analysis identified 34 genes associated to high BP levels [14]. Furthermore, some companies sell genetic test to identify individuals with genetic variants associated with, for example, an overactivation of the renin-angiotensin system (RAS) and that can consequently help in choosing the most suitable drug. However, today this is not applied in clinical practice because of the high costs. Currently, the research for hypertension genes is still developing and requires new and complex studies. The hope is to use gene therapy in the management of hypertension as a part of the antihypertensive therapy [15].

Lifestyle: sodium intake and obesity

The sodium restriction in population is an important target for CV prevention, because sodium intake is positively associated with BP [16]. The mechanism involved many pathways, and has not been completely understood [17]. Certainly, a high sodium intake increases sodiemia and the subsequent volume-dependent BP level. Several studies analyze the sodium intake in different population across the world [18, 19]. The INTERrnational study of SALT and blood pressure (INTERSALT) studied salt intake in 52 population samples of 32 countries using 24-urinary specimens [18]. The 24-hour sodium excretion ranged from a minimum of 0,46 grams per day (g/d) in some remote population groups like Yanomami Indians to 5,6 g/d revealed in North China. The INTERrnational study of MAcro/micronutrients and blood Pressure (INTERMAP) confirmed these findings and underlined regional differences in sources of sodium intake: in the United Kingdom and in the United States the most dietary sodium comes from processed food, instead in China the principal source of sodium is the salt added to cooking [19].

Many cohort studies reported a positive association between sodium intake and BP levels [20]. The Prospective Urban Rural Epidemiological (PURE) study showed an increase in SBP for each 1 g increase in sodium intake [20]. Furthermore, the increase in BP values varied depending on the baseline of sodium assumption. In accord with these findings, there was a reduction in SBP associated with a reduction in sodium intake, and this reduction was more significant in patients on high sodium diet [20]. Subjects can be divided in sodium sensitive, those who have with dietary sodium reduction a greater fall in BP, TOD and CVE, and sodium resistant. The first group presented low-renin levels, such as blacks or elderly subjects [21]. Many clinical trials evaluated the effect of sodium reduction on BP. One of the most noticeable, the Trial of HypertensiOn Prevention (THOP), conducted in North America, stressed the difficult to keep a low salt consumption and that over time there is an attenuation of the antihypertensive effect of sodium reduction [22]. However, several studies demonstrated the association between reduction in salt intake and incidence of CVEs and CV mortality. There is a large variability in results coming from prospective cohort studies,

ranged from a positive association between salt assumption and CVEs, null association and an inverse J-shaped association, with an increased risk in population with low sodium intake [23]. However, in Western population, sodium restriction is a key system for reducing BP levels and CVEs, without risk of J-shaped association because of the high content of sodium in processes food. Finally, authors suggest a target of sodium intake of 3-5 g/d. This is the range where subjects reach the better reduction of BP and the lowest rate of CVEs. The 24-hour sodium excretion is useful indicator of sodium intake: above 100 mmol per day indicate an excess of sodium intake. However, authors underlie that the key sources of excess sodium are processed food. The future of a correct sodium consumption is a process that involves food industry, which is the major responsible for the increase in sodium intake in Western populations.

Excess weight gain is a major cause of AH and it is associated with CV and metabolic disease. Several studies conducted evidenced a linear association between BMI, and BP levels [24, 25]. The Framingham Offspring Study showed that overweight and obesity were responsible for 78% of essential hypertension in men and 65% in women [26]. Conversely, weight loss decreased BP levels [27]. Many factors influenced the relationship between obesity and AH. The BP control is much difficult the longer the duration of obesity. Another important aspect is the distribution of the fat. In fact, visceral and retroperitoneal fat are stronger associated with hypertension [28]. Although these clinical evidences, the pathophysiology of obesity-associated hypertension is not completely understood. Visceral adiposity determines a physical compression on the kidneys resulting in an increase in intrarenal pressure with an alteration of renal natriuresis [29]. Visceral obesity is also associated with a RAS iperactivation. Furthermore, in obese patients there is an increase in sympathetic activity and a decrease in parasympathetic tone [30, 31]. Finally, if overweight is maintained during several years, it can cause chronic kidney disease, which worsen hypertension and may eventually cause treatment-resistance [32, 33].

The sympathetic Nervous System activaction

The Sympathetic Nervous System (SNS) has an important role in the regulation of CV homeostasis. Several studies showed the association between SNS activation and increased resting heart rate and CV risk [34.]. Hypertensive subjects with a SNS overdrive presented a higher norepinephrine plasma concentration than normotensive subjects [35, 36]. Further, Mancia and co-workers with the norepinephrine spillover method, which involved the infusion of small doses of radiolabeled norepinephrine, demonstrated the increase in norepinephrine release from the adrenergic nerve terminals of these subjects [35, 36], and allowed to quantify the regional norepinephrine spillover, particularly in the heart and the kidney. Adrenergic mediators are also involved in arteriolar remodeling and are responsible of the increase in peripheral resistance [37, 38]. SNS overactivation is an early event in the history of AH, and may precede the hypertensive state [39]. In addition, the SNS overactivity is more frequent in young hypertensive subjects: this finding supports the concept that adrenergic overdrive may precede the development of the essential hypertension [35, 36]. Hypertensive patients with excessive TOD in relation to their BP levels and hypertension duration often showed a great sympathetic overdrive [40, 41], suggesting that an hyperadrenergic state may accelerate the progression of CVD.

Based on the evidence discussed above, authors underlined that SNS overdrive has a role in the development, maintenance and progression of AH and could represent a primary target of pharmacologic and non-pharmacologic treatments. However, no clinical trial demonstrated the effect on mortality of decreasing adrenergic activity in AH [42].

The renin-angiotensin system

In recent years, the central role of the RAS has been emphasized [43]. The excessive production of renin determines an overstimulation of AT1 receptors, resulting in hypertensive effects. The major action attributed to AT1 activation are vasoconstriction, increase of reactive oxygen species and activation of cytokines and growth factors (see below the section "Role of inflammation in

hypertension") [43]. By contrast, AT2 receptors counteracted these effects [44]. To choose the best drug treatment, some authors suggest to subclassify subjects with AH in RAS-dependent essential hypertensive (high-normal renin levels) and volume-dependent hypertensive (low renin levels) [45]. The distinction between the two subtypes in clinical practice is not carried out by the dosage of renin levels (which may depend on ongoing therapy or other factors), but on the basis of clinical features of the patient. Further, the dosage of renin in essential hypertension is not cost-effectiveness and difficult in clinical practice [46]. However, RAS-dependent hypertension presents an increased sympathetic nervous system tone and is common in anxious young subjects or in people with a medical history of alcoholism, sleep apnea, acute stroke, sinus tachycardia, paroxysmal hypertension [45]. Mann and colleagues suggested in these subjects to add, if high BP levels are still present after a two drugs regimen (a traditional association RAS inhibitor + Anti-volume), as third drug a beta-blocker or an alfa-blocker. Conversely, volume dependent hypertension is presented in subjects with high sodium intake, presence of edema, high body surface area, chronic kidney disease. In these subjects, these author suggested, in addition to the association RAS inhibitor + Anti-volume, to optimize the dose of the diuretic and eventually add as third drug spironolactone [45]. This mechanistic approach has not been transposed by International Guidelines but provides essential ideas at least for drug choice in the treatment of uncontrolled hypertension. In addition, Mann's point of view is useful to underline the importance of the activation of the RAS system in the pathogenesis of hypertension.

Arterial stiffness and central BP: emerging factors to understand the pathogenesis of hypertension
Arterial stiffness, which is emerging as a novel marker of subclinical arteriosclerosis, is expression of hardening (arteriosclerosis) of large arteries (primarily, aorta) due to abnormal collagen production and reduced amount of elastin, with consequent stiffening and thickening of the arterial wall [47, 48]. The gold standard to measure arterial stiffness is carotid-femoral pulse wave velocity (cfPWV), a noninvasive exam that measures aortic stiffness with applanation tonometry [49]. The

relationship between arterial stiffness and hypertension can be very complex: an increased baseline PWV is associated independently with disrupting effects on aortic elastin but, on the other hand, SBP increases aortic wall stress with an accelerated elastin degradation [50]. Although data from the Framingham Heart Study support the hypothesis that aortic stiffness may precede hypertension, other studies have found a relationship between baseline SBP and progression of PWV [51]. Since cfPWV increases with ageing and with higher BP levels, reference values were recently published [52]. The latest 2013 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines for the management of Arterial Hypertension stressed the importance of cfPWV as a marker of subclinical vascular disease and confirmed a threshold value of 10 meter/second [3]. Many studies showed the independent role of cfPWV as a predictor of all-cause and CV mortality also in the general populations [53, 54]. Normally, aorta works as a diastolic pump which ensure a functioning tissue perfusion throughout the cardiac cycle. With stiffness, aorta lose its distensibility, and most of the stroke volume flows through the arterial system and peripheral tissue during systole. As a consequence, the flow becomes intermittent with excessive flow and pressure pulsatility during systole [55]. Further, in AH there are alterations also in small arteries: vasoconstriction, increased wall-to-lumen ratio and vessels rarefaction, with a consequent increase in total peripheral resistance and mean BP [56]. The final result is a large/small artery cross-talk: the higher mean BP increases large artery stiffness which leads to high central BP (CBP) and PP. As a vicious circle, the increased aortic stiffness in turn damages small resistance vessels [57]. With a heart beat a pulse wave travels forward in the circulation and generates multiple reflected waves which travel retrograde toward the heart. The composite reflected wave (sum of multiple tiny reflected waves) impacts the shape of the aortic pressure wave, which is the result of the sum of forward and backward wave. When PWV is elevated, the reflected wave return early in systole and CBP consequently increases [58]. As for cfPWV, even for CBP were validated reference values [59]. CBP seems to be a greater predictor of CVEs events than brachial pressure and some authors proposed the measure of CBP in clinical routine as a guide for therapeutic choice [60]. The Conduit

Artery Functional Evaluation (CAFE) Study first showed the clinical relevance of CBP: subjects randomized to calcium channel blocker (CCB) or to beta-blockers presented the same peripheral BP levels. By contrast, the first group showed a significant reduction in CBP and a significant less number of CVEs when compared to the second group (see also the below section "BP lowering drugs beyond BP targets and role for combination therapy") [61]. In addition, if a large meta-analysis [62] did not show a significant additive predictive value of CBP beyond brachial pressure (P = 0.057), other data demonstrated that the measure of CBP determines a better management of the hypertensive patient [63] and that CBP strongly correlated with TOD than brachial BP [64]. However, up to now, International Guidelines do not recommend routine CBP measurements in clinical daily practice [3, 4, 5, 6]. CBP could exert an important role in isolated systolic hypertension in youth, where an elevated PP amplification could lead to elevated brachial SBP with normal CBP. There is no evidence that these subjects could benefit of antihypertensive treatment [3].

Role of inflammation in hypertension

Recent evidences stress the role of inflammation in hypertension [65]. As mentioned above, one of the effect of AT1 activation is the increase of inflammation with an excess of oxidative stress [65]. Several animal studies provided interesting data. The B7/CD28 T cell costimulation axis, which interacts with CD86 expressed on dendritic cells, is required for full activation of T lymphocytes [66]. The treatment of angiotensin II-induced hypertensive mice with an inhibitor of the axis lowered BP, and B7 deficient mice are resistant to BP elevation in response to angiotensin II [66]. Further, hypertensive mice presented an increased expression of CD86 in dendritic cells [67]. Other authors found in angiotensin II-induced hypertension an increased in aortic monocytes/macrophages and of markers inflammations such as vascular cell adhesion molecule-1, cyclooxygenase 2, nitric oxide synthase [68]. The accumulation of T cells and macrophages in experimental hypertension is predominant in the kidney and in the vessels, anatomic sites critical to the genesis and the

maintenance of AH [69]. Finally, emerging data showed also a role for neutrophils in hypertension [70]: very recently Liu and co-workers showed in a cohort of 28,850 adult Chinese subjects that elevated baseline neutrophil to lymphocyte ratio significantly increased the risk of developing hypertension [71].

Figure 1 schematically summarize the pathogenesis of hypertension.

Blood pressure measurement. Office values, home or ambulatory blood pressure monitoring: which is the best?

One of the major topic discussed in hypertension research is the difference between the different methods for BP measurement. If International Guidelines continue to considered office BP measurements the gold standard for the diagnosis of AH [3, 4, 5, 6], several data and expert consensus provided interesting information on the important role of home BP and of ambulatory BP monitoring (ABPM), also for the prediction of CVEs [72]. In fact, ABPM can give information on the day/night BP cycle, the BP variability, the presence of white coat hypertension (WCH) or masked hypertension (MH) [72]. For these reasons, several trials such as the Systolic Hypertension in Europe (SYST-EUR) study [73], performed in patients with isolated systolic hypertension, the Dublin Outcome Study [74], and the Pressioni Associate Monitorate E Loro Associazioni (PAMELA) Study [75] showed that ABPM had a closer relation to CVEs than office BP values. About the day/night BP cycle, non-dippers subjects, probably for the more load of BP on the heart and the vessels, compared to dippers subjects, presented a more frequent occurrence of TOD and CVEs [75]. Further, Dublin Outcome Study and the PAMELA Study showed that the same increase in SBP values determined an increased CV mortality, when occurred during night, suggesting a superior prognostic role of absolute night-time BP values with respect to day-time BP values [74, 75]. The risk increases even more in riser subjects: as the night-day ratio rises the CVEs increase. In extreme dipper subjects no sufficient data are available to determine a possible prognostic role [3].

BP variability, which increases with age and correlates with the mean BP level, depends on behavioural (for example, anxiety, job stress) and non-behavioural factors. Abnormal BP variability (in particular, nocturnal BP variability) is associated with presence of TOD and with an increased of CVEs and CV mortality [76]. The PAMELA study demonstrated that the short-term erratic or residual BP changes that contribute to overall 24-hours BP variability, in addition to its cyclic component (day-night and postprandial variations) have a significant relationship with CV and all-cause mortality [75].

ABPM and home BP measurement are fundamental for the diagnosis of WCH and MH [77, 78]. WCH is a condition with a prognosis less worse than MH or sustained hypertension but that is important to diagnose and that should not be equated to the condition and the prognosis of normotensive subjects [75]. Both WCH and MH are associated with an increased metabolic risk such as diabetes and overweight and with an increased risk of TOD [77]. WCH has a prevalence of 9-16% and is associated with age, female sex and non-smoking. Subjects with WCH presented an increased risk of developing sustained hypertension and a CV risk greater than normotensives [75]. MH has a prevalence of 13% and is associated with younger age, male sex, smoke, alcohol, physical activity, anxiety, job stress. Subjects with MH present an increases CV risk closer to that of sustained hypertension than to WCH or normotension [78].

Despite these observations, ESC/ESH Guidelines for the managemant of AH consider office BP the gold-standard for screening, diagnosis and management of hypertension and indicate the out-of-office measurement in limited circumstances (for example, suspicion of WCH or MH, suspicious of true and false resistant hypertension) [3]. By contrast, the National Institute for Health and Clinical Excellence (NICE) guidelines suggests, if office BP is high, to offer ABPM to confirm the diagnosis of AH. Further, if a person is unable to tolerate ABPM, HBPM is a suitable method [5]. The 2015 Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension (CHEP) recommends for the diagnosis of hypertension office BP values $\geq$ 180 (SBP) and/or 110 mmHg

(DBP). Out-of-office BP measurements (if possible, ABPM) should be performed if in the first visit mean office BP measurement is 140-179 (SBP) mmHg and/or 90-109 mmHg (DBP) [6].

Authors suggest, for the diagnosis and the management of AH, based on International Guidelines, expert consensus, cross-sectional and longitudinal studies, to add to office BP measurements at least home BP measurements. If there is the suspicious of abnormal night-time values or increased BP variability considering ABPM as soon as possible. However, it is also important to underlie that the reproducibility of ABPM is quite low, and one ABPM is not a sufficient to classify with certainty the night-time BP ratio and/or the BP variability of a subject [72].

Blood pressure lowering drugs: effects beyond target values and role for combination therapy

RAS inhibitors are the recommended first-line drugs in Caucasian subjects [3]. Diuretics played a major role in Afro-American hypertensive subjects, because their AH is generally a volume-dependent hypertension [4]. In elderly subjects with isolated systolic hypertension CCB and/or diuretic are the most effective in reducing SBP [3]. Beyond BP values, in the early 2000s, four trials provided the best evidence in favor of a particular drug-regimen: the Losartan Intervention For Event reduction Trial (the LIFE Trial) [79], the Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE) [80], the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [81] and the Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension trial (ACCOMPLISH) [82]. These trials showed a different number of CVEs in different drug-regimen groups despite no difference in brachial BP values between groups. In the LIFE Trial [79], 9,193 hypertensive patients were randomized to losartan or atenolol. Hydrochlorothiazide was added in the majority of patients to achieve BP control. After an average follow-up of 5 years the composite primary CV endpoint was reduced by 13% in the losartan group. The major benefit was seen in stroke which was reduced by 25%. In the VALUE trial [80], 15,245 hypertensive patients were randomized to either valsartan, or amlodipine. Hydrochlorothiazide was added to each arm in attempting to achieve goal BP targets. Mean follow-up was 4.2 years. BP were

more effectively and more rapidly reduced in the amlodipine-based treatment arm. Although the primary composite endpoint of cardiac morbidity and mortality was similar in the two arms of the trial, MI and stroke occurred less frequently in the amlodipine-based treatment arm (risk reduction 19% and 15%, respectively). In the ASCOT-BP trial [81], over 19,000 hypertensive patients with no prior history of CAD were randomized to amlodipine or atenolol. The ACE-Inhibitor perindopril or the diuretic bendroflumethiazide was added to each arm, respectively, in an attempt to achieve BP targets. After an average follow-up of 5.5 years, the trial was stopped prematurely because of highly significant outcome benefits in favor of the amlodipine-based regimen. All CVEs were reduced by 26%, stroke by 23%, and all-cause mortality by 11% by the amlodipine-based regimen. In the fourth trial, ACCOMPLISH [82], 11,506 hypertensive patients were randomized to a combination of the benazepril, with either hydrochlorothiazide, or amlodipine. Patients were followed for 3 years. CVEs were reduced by 20% (MI by 22% and stroke by 16%, respectively) in benazepril/amlodipine arm compared with the benazepril/hydrochlorothiazide. These different in the primary outcomes are in part due to a better effect on CBP of a specific drug regimen, as the CAFE study (an ASCOT substudy) showed [61]. However, the cumulative evidence from these trials strongly supports the view that, in hypertensive patients, combination therapy with or ARB/CCB is likely to be associated with better CV outcomes and that ACE-I/CCB combinations are preferable to ACE-I/diuretic combinations on major CV endpoints. The above recommendations apply, in general, to those subjects with uncomplicated hypertension. In hypertensive subjects with associated CV disease such as heart failure or CAD, the guidelines are consistent in recommending specific drugs with compelling indications [83, 84].

In resistant hypertension, other trials showed that the addition of spironolactone to the association of RAS inhibitor + CCB + diuretic is more effective than the addition of an alpha-blocker or a beta-blocker [85]. However, in all the cases of essential hypertension, several data suggested to start with a combination therapy [86]. The combination therapy provides an increased achieve of BP target, a synergistic effect of the drug combination, a reduction rate of side effects with also an increased

therapeutic adherence [3]. Further, in recent years a single pill contains two or three antihypertensive drug, with another reason of increased adherence in subjects in combination therapy [87]. A large meta-analysis [88] confirmed these considerations, and recently Gradman and co-workers showed the reduction rate in CVEs in subjects who started a combination therapy [89]. The reduction in CVEs was attributable to a more rapid achievement of target BP.

The results of the main cited trials of this section are summarize in Table 1.

Adherence to therapy and new treatments

Non-adherence to therapy is one of the major cause of inadequate BP control in patients diagnosed with resistant hypertension [90]. The unrecognized of patients with falsely uncontrolled BP (pseudo-resistance) is very important. In fact, in case of noncompliance with the antihypertensive therapy clinician may requests additional expensive diagnostic test [91]. Furthermore, subjects poor concordant with therapy have an higher CV risk [92]. A recent meta-analysis reported a lower adherence in patients treated with diuretics and β-blockers [93]. Also the prescription of a large number of antihypertensive drugs is a possible cause for noncompliance [94]. Several methods have been suggested to evaluate the prevalence of non-adherence to treatment, including self-reporting questionnaires, electronic monitoring systems, pills counting and, in recent years, measurement of serum or urine drug concentration using liquid chromatography-mass spectrometry [95, 96]. Some of them, such as electronic records of pill box opening, do not prove the real drug intake and are less useful in clinical practice [97]. In a recent study [98] authors used the measurement of serum antihypertensive drug concentrations to test the concordance with treatment in two groups of patients diagnosed with resistant hypertension; the first group is composed of hospitalized patients, the second of outpatients. The non-adherence was surprisingly elevated, in particular in the second group in which accounted for almost 50%. Two other studies tested the adherence by toxicological urine analysis on samples collected on the day of the clinical visit [99, 100]. The complete non-adherence was respectively of 30% and 25%. BP values were higher in nonadherent patients. Direct

urine or serum analysis have two important limitations: the technique in not available for all antihypertensive drugs and the method is relatively expensive (about 40-60 euro). However, investigations for secondary forms of hypertension or new interventional treatments have a greater cost. Lastly, even the noncompliance per se has a cost in terms of population's health.

For these reasons, physicians must have lot of attention to the problem of non-adherence, and it may be important to use motivational strategies such as involving patients in making decision, suggesting the use of HBPM, reducing the number of drugs with the single pill associations.

Neprilysin, a neutral endopeptidase, degrades the brain natriuretic peptide (BNP), the urodilatin and the atrial natriuretic peptide (ANP). For these reasons, Neprilysin may be an important target in the treatment of AH [101]. Indeed neprilysin inhibition cause an increase in natriuretic peptides plasma levels and a subsequent vasodilation, natriuresis, reduction of adrenergic overdrive and of RAS activity, antiproliferative and antihypertrophic effects on vasculature and heart [102]. In AH treatment is useful to associate the neprilysin inhibitor with a RAS blocker or an endothelin-converting enzyme inhibitor because neprilysin also degrades vasoconstrictor peptides. This association can lead to vasodilatation and natriuresis by reducing at the same time the vasoconstrictor effects [103]. LCZ696 is the first dual-acting agent composed of the association between neprilysin inhibitor prodrug AHU377 and valsartan. In a randomized, double-blind, placebo-controlled trial, LCZ696 was compared with valsartan and AHU377 in 1328 patients with mild to moderate hypertension. LCZ696 produced a significantly greater reduction in BP values than valsartan; AHU377 produced a BP reduction significantly greater than placebo but smaller than LCZ696. In the Phase III Prospective Comparison of angiotensin receptor-neprilysin inhibitor with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial was compared the efficacy and safety of enalapril and LCZ696 in 8442 patients with class II, III or IV heart failure [104, 105]. This randomized double-blind trial underlined the superiority of LCZ696 in reducing BP, CV death and hospitalization. In the LCZ696 group there was also more reduction in mean SBP. The US Food and Drug Administration approved Entresto (Novartis),

sacubitril plus Valsartan, on July 2015 for the treatment of chronic heart failure [106].

Catheter-based renal denervation (RDN) is an interventional treatment proposed for resistant hypertension, considering the role of SNS activity in elevation of BP [42]. In 2009, the nonrandomized study (Symplicity HTN-1) showed a significant reduction in BP after the RDN [107]. The following Symplicity HTN-2 confirmed these results [108]. The BP reduction was durable, lasting over 36 months of follow-up [109, 110]. However, these two trials had some limitations: they were not blinded (vulnerability to patient and physician related biases), and the evaluation of efficacy, was based on office rather than ABPM [111]. ABPM, as mentioned above, reduces observer bias and minimizes the white-coat effect. Further, drug adherence was not monitored, either at baseline or during follow-up. The subsequent Symplicity HTN-3 was a single-blind randomized trial in order to prove the efficacy of the RDN in resistant hypertension [112]. Otherwise, Symplicity HTN-3 failed to reach the primary end point. Lack of demonstrated efficacy of RDN in Symplicity HTN-3 may be due to lack of statistical power or that the a fraction of African American participants increased their antihypertensive medication, contrary to protocol, which masked a potential BP lowering effect of RDN in contrast to other participants. In addition, as a consequence of the inexperience of the investigators, the denervation procedure was inaccurate in many cases due to insufficient delivery of appropriate energy in the renal arteries. The Prague-15 study was a very recent and rigorous study. This prospective, randomized, open-label multicenter trial evaluated the efficacy of RDN versus intensified pharmacological treatment including spironolactone in patients with true-resistant hypertension. This was confirmed by 24-hour ABPM after and by measurement of plasma antihypertensive drug levels. One-hundred six patients were randomized to renal denervation (n=52), or intensified pharmacological treatment (n=54). Both the arms of the study showed a significant and similar reduction in BP levels [113]. Further studies are needed to better understand the mechanism and the efficacy of renal denervation.

The prospective non randomized DEBut-HT trial studied the early generation of implantable device for the electrical stimulation of the carotid sinus baroreceptors [114]. This trial studied 45 subjects

with resistant hypertension and showed a significant and prolonged reduction in office BP and in ABPM. 8 serious adverse events (7 procedure-related and 1 device-related) occurred. A second-generation system of BAT (Barostim neo™) has been recently designed with the aim to reduce the operating field and hence possible complications. A single (instead of 5) electrode is implanted at one carotid site, and the battery is smaller, with an extended life span (≈3 years). In a single-arm open-label study enrolling 30 patients with resistant hypertension a significant BP reduction was observed after 6 months. Only 1 long-term procedure-related complications occurred [115]. Future studies will better clarify the role of stimulation of the carotid sinus baroreceptors in resistant hypertension.

Blood pressure control: the earlier and the lower are the better? Importance of residual risk

The management of hypertensive subject should be "BP oriented" or "risk factors oriented"? The treatment of the hypertensive patient should be modulated only according to BP levels or in relation to overall CV risk? International Guidelines for the management of AH appear to follow the first approach, providing BP thresholds (generally ≤ 140/90) that the patient must reach [3, 4, 5, 6]. However, guidelines for raised blood cholesterol suggest a "risk factors oriented" approach, and the treatment is based on the overall CV risk, calculated, for example, with the European SCORE charts [116, 117]. Further, in their meta-analysis, the Blood Pressure Lowering Treatment Trialists' (BPLTTC) conclude that the "risk factors oriented" method based on CV risk calculators is more cost-effectiveness than the BP approach [118]. However, Zanchetti and co-workers, in a recent meta-analysis based on 68 randomized controlled trials, provided some interesting considerations [119]. As BPLTTC, they showed that relative reductions of all outcomes did not significantly differ in groups at different CV risk and absolute risk reductions significantly increased with the increasing level of CV risk, suggesting the cost-effectiveness of risk-based approach. However, key appears to emphasize that break down BP levels of high-risk individuals will not prevent the fact that these same individuals, because of their high residual risk, will present a larger number of

CVEs when compared to low-risk subjects [119]. This concept leads to make three important considerations. First, the best achievement in terms of prognosis is obtained by treating the subjects with mild hypertension without risk factors ("the earlier the better"). Second, at any level of CV risk, lower BP levels are better ("BP oriented" approach: the lower the better). Third, it is important to identify the residual risk of subjects by evaluating the presence of TOD to reclassify their CV risk and to modulate the drug therapy. Hence the importance of assess the presence of TOD in subjects with AH. The hypertensive patient should be evaluated for the presence of vascular organ damage (arterial stiffness), carotid damage (increased intima-media thickness (IMT, presence of atherosclerotic plaques), heart damage (left ventricular hypertrophy, systolic dysfunction, diastolic dysfunction, silent ischemia) [3]. However, these exams have costs and is a major challenge for the clinician to select patients for TOD evaluation. Recently, Struthers proposed the B-type natriuretic peptide (BNP) screening as a cost efficient system to identify hypertensive patients with residual risk [120]. The identification of patients with residual risk is important for drug regimen choice. For example, an hypertensive subjects without TOD can benefit (as mentioned in the above section) as a first-line drug of RAS inhibitor [3]. By contrast, the presence of a systolic dysfunction requires the addition of other drug classes such as beta-blockers [121].

Very recently, the Systolic blood PRessure INtervention Trial (SPRINT) convincingly support the concept "the lower the better". The SPRINT study randomized 9,361 hypertensive subjects with at least one CV risk factor (not diabetes) and older than 50 years to a "intensive" treatment group, designed to reach a SBP target < 120 mmHg, and a "protocol" group, designed to reach a SBP target < 140 mmHg. The study stopped early because of the superior benefits of the "intensive" treatment group on CVEs, CV mortality and total mortality, suggesting new SBP target, different from those proposed by International Guidelines [122, 123]. Several data of this study merit to be discussed. The results of SPRINT on "hard" endpoint could potentially change all the future Guidelines on AH. Heart failure was the most common CVE, and by contrast there was no difference between two groups on the incidence of stroke. This is in contrast with all the large

longitudinal trials on hypertension which have been demonstrated that the strongest CV outcome related to hypertension is stroke. This could be attributable to the fact that the study stopped early, and some CVEs such as stroke have not had time to emerge. Hypotension, syncopal episodes, acute kidney injury, and serum electrolyte abnormalities were more commonly detected in the "intensive" treatment group, but certainly not so commonly as to cancel out the major observed benefits.

The limitations of the study were the average run-in BP in SPRINT (averaging, 139.7 mm Hg), with a contingent modest BP fall to-target in the "intensive" treatment group (18 mm Hg) and the exclusion of diabetic and frail patients. For the same reasons this trial did not add knowledge about BP target to reach in high-risk individuals such as diabetics. The Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial (ACCORD BP), which used the same SBP goals used in SPRINT to determine the value of intensive compared with standard BP reduction in 4,733 diabetic adults, showed that the composite CVD outcome was 12% lower in the intensive treatment group, but not statistically significant [124]. Another limitation of SPRINT is that the subjects enrolled in the study were more "fit" than those who, for example, live in nursing homes, so the trial did not provide information on BP thresholds in frail patients with lots of comorbidities [125]. Finally, although SPRINT results probably will radically change the future guidelines, this study has some severe limitations, and the clincian must individualize the BP goals taking into account all the patient's characteristics.

Finally, several studies have identified BP levels below which CVEs increase rather than decrease. In the medical literature, this phenomenon has been called J curve: as above certain levels increase CVEs plungers, this also happens when BP is too low [126]. The attention was especially focused on DBP, the main factor underlying coronary perfusion. However lots of studies included subjects with CV disease, and some of these found a J-shaped curve also for DBP and stroke and for SBP and CAD [127]. In conclusion, up to date, down SBP values between 90 and 114 mmHg and DBP values between 60 to 74 mmHg there is no evidence to suggest a J-shaped. In conclusion, further studies, also performed in diabetic and in frail subjects, are needed to improve medical knowledge

on hypertension and definitel estabilished BP target values in different subgroups of hypertensive patients [127].

The SPRINT and the ACCORD trials are summarize in Table 2.

Blood pressure (un)control? Time for development of algorithms

Despite the increased number of cross-sectional and longitudinal studies, International Guidelines and expert consensus paper, the majority of hypertensive subjects present uncontrolled hypertension [2]. As we mentioned in the introduction of this review, a critical role is probably attributable to population aging and to the increase in obesity. However, is important to stress some consideration. First, the National Health and Nutrition Evaluation Survey (NHANES) showed that the overall prevalence of uncontrolled hypertension was 12.8%. Further, 81.5% of those with AH are aware they have it, and 74.9% are being treated. In addition, only 52.5% are under control, with significant variation across different patient subgroups [128]. Of those with uncontrolled hypertension, 89.4% reported having a usual source of healthcare, and 85.2% reported having health insurance. Second, the direct and indirect costs of AH are enormous, considering subjects and their families impacted and the healthcare money spent on treatment of BP complications [128]. Obtaining an adequate BP control at a population level has remained a challenge. Too often the healthcare provider, who visits of the hypertensive subjects, prescribe an inappropriate antihypertensive therapy. Too often, the hypertension specialist visits essential uncomplicated hypertensive subjects instead subjects with true resistant or secondary hypertension. It is time for an adequate hypertension knowledge at the level of community general medicine. To obtain this, system-level approaches and evidence-based management algorithms can help to standardize the treatment. A virtuous example was the Kaiser Permanente Northern California, a regional American hypertension program which involved a population of 3 million subjects [129]. With a system-level method, this program provided an electronic hypertension registry, tracked hypertensive with regular feedback to providers, developed an evidence based algorithm, promoted single-pill combination therapy, used medical assistants for

follow-up BP checks. The result was a method that facilitates the physician in its therapeutic management and helped the patient in therapeutic adherence. Between 2001 and 2009 the number of subjects with AH increased by 100%, but hypertensive subjects meeting target BP goals improved from 44% to 80%, improved to more than 87% in 2011 [129]. Also the very recent SPRINT trial showed that a large number of subjects can reach the therapeutic target with treatment algorithms and careful monitoring, even with only two or three medicines ("control" and "intensive" group, respectively [122].

Also based on these data, the authors believe that the future of BP control will be based on a systematic approach with evidence based algorithms and a multifactorial coordination that help healthcare provider in the management of hypertensive subjects. The final step of an algorithm which provides simple and complete informations on AH management, in case the healthcare provider has properly executed all the algorithm steps but elevated BP levels perist, must be the visit of an hypertension specialist. In this way, the hypertension specialist would treat only patients with resistant or refractory hypertension, or, in any case, with BP levels complex to control. The global result is a better population BP control, a reduction in BP complications, a reduction in healthcare cost.

Conclusions

Hypertension is the major risk factors in the world for CV and all-cause mortality. Further studies are needed to better understand its complex pathogenesis. The clinician to obtain a BP control for the individual patient should consider several factors such as age, lifestyle, the presence of other risk factors, presence of TOD. Further, recent data showed that start earlier and lower as soon as possible BP values reduce the risk. The combination therapy could be a good strategy to obtain this. Finally, a system level approach to the management of hypertension with the avoid of evidence based algorithms seems to be the best strategy to obtain a good BP control at a population level.

Figure legend

The pathogenesis of hypertension involves several factors such as genetic factors, inadequate lifestyle, SNS and RAS overactivation, inflammation, large artery stiffness, small vessels resistance which interact each other in the genesis of hypertension.

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