HYPERTENSION IN CHILDREN AND ADOLESCENTS: A Consensus Document From ESC Council on Hypertension, European Association of Preventive Cardiology, European Association of Cardiovascular Imaging, Association of Cardiovascular Nursing & Allied Professions, ESC Council on Cardiology Practice and Association for European Paediatric and Congenital Cardiology

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ACRONIMS:

AAP = American Academy of Pediatrics

ABPM = Ambulatory Blood Pressure Monitoring

ACEi = Angiotensin Converting Enzyme Inhibitors

AHA = American Heart Association

BMI = Body Mass Index

BP = Blood Pressure

CCB = Dihydropyridine Calcium Channel Blockers

CKD = Chronic Kidney Disease

CMRF = Cardio-Metabolic Risk Factors

CoA = Aortic Coarctation

CV = Cardiovascular

ESC = European Society of Cardiology

ESH = European Society of Hypertension

FBG = Fasting Blood Glucose

GFR = Glomerular Filtration Rate

HbA1c =Glycated Hemoglobin

HBPM = Home Blood Pressure Monitoring

HDL = High Density Lipoproteins

HCGC = Hypertension Canada Guideline Committee

HMOD = Hypertension-Mediated Organ Damage

LDL = Low Density Lipoproteins

LVH = Left Ventricular Hypertrophy

LVM = Left Ventricular Mass

MetS = Metabolic Syndrome

NHBPEP = National High Blood Pressure Education Program

OBP = Office Blood Pressure

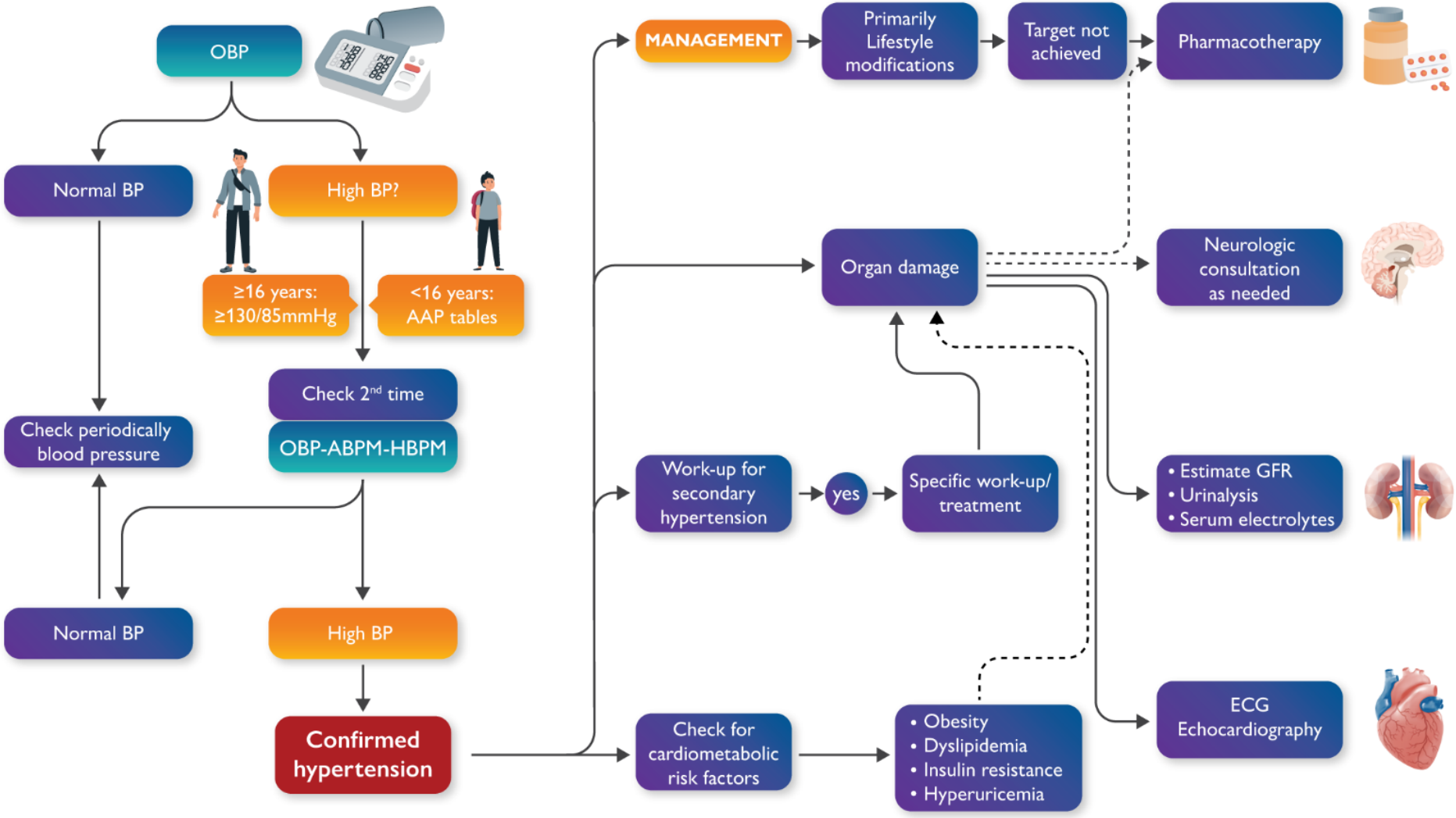
OW/OB = Overweight/Obesity

RWT = Relative Wall Thickness

TG = triglycerides

WC = Waist Circumference

WHO = World Health Organization



Legend: BP=Blood pressure; OBP=Office blood pressure; ABPM=Ambulatory blood pressure monitoring; HBPM=Home blood pressure monitoring; GFR=Glomerular filtration rate; ECG=Electrocardiography

ABSTRACT

Definition and management of arterial hypertension in children and adolescents are uncertain, due to different positions of current guidelines. The ESC task-force, constituted by Associations and Councils with interest in arterial hypertension, has reviewed current literature and evidence, to produce a Consensus Document focused on aspects of hypertension in the age range of 6-16 years, including definition, methods of measurement of blood pressure, clinical evaluation, assessment of hypertension-mediated target organ damage, evaluation of possible vascular, renal and hormonal causes, assessment and management of concomitant risk factors (with specific attention for obesity), and anti-hypertensive strategies, especially focused on life-style modifications. The Consensus Panel also suggests aspects that should be studied with high priority, including generation of multi-ethnic sex, age and height specific European normative tables, implementation of randomized clinical trials on different diagnostic and therapeutic aspects, and long-term cohort studies to link with adult CV risk. Finally, suggestions for the successful implementation of the contents of the present Consensus document are also given.

Introduction

Identification of arterial hypertension (HTN) is challenging in children and adolescents, as standards and definitions are complex during body growth, and outcome cardiovascular (CV) studies cannot be designed. Therefore, a statistical definition of childhood/adolescence hypertension is necessary[1].

Three current guidelines propose different definitions[2-4]. Table 1 summarizes recent criteria for definition, compared with the 4th Report from the National High Blood Pressure Education Program (NHBPEP)[5], which has been a standard reference, because of the adoption of normative tables, based on age, sex, and height, renewed by the American Academy of Pediatrics (AAP)[2].

In addition to the differences in hypertension definition (Table 1), the 2017 AAP guidelines excluded youths with overweight/obesity (OW/OB) from normative tables.

Due to these different indications, ESC Associations and Councils, together with the affiliated Association for European Paediatric and Congenital Cardiology, produce this document to try to reconcile these different views, also suggesting measures to be undertaken in the near future to better clarify discordant points.

Chapter 1: Definition and Classification

Compared to NHBPEP[5], the 2016 ESH guidelines recommended adult cut-points for adolescents starting at age 16 (≥140/90 mmHg)[3,6], more consistent with the physiological body growth[7]. Adopting the NHBPEP's normative tables, however, ESH guidelines did not exclude OW/OB (BMI ≥85th percentile), which could influence the range of normal BP values, and misclassify as normotensive youngsters who are in fact hypertensive[8,9]. The subsequent modification of the normative tables was consistent with the rising evidence of the link of OW/OB with both higher blood pressure (BP), and hypertension-mediated organ damage (HMOD), also in children and adolescents[10,11]. The change in the normative reference tables caused increase in the prevalence of hypertension in this range of age [8,9], at the possible cost of decreased specificity.

Excluding OW/OB from the normative tables, 2017 AAP guidelines[2] used new American adult cut points (≥130/80 mmHg, consistent with the 2017 adult American Guidelines[12]), starting at age 13, a decision contrasting the evidence that complete maturation occurs between 13 and

16 years[7]. A recent position paper endorsed by the Italian Society of Hypertension and the Italian Society of Pediatrics expressed an opinion in favor of maintaining the NHBPEP nomograms[1].

The Hypertension Canada Guideline Committee (HCGC)[4] also endorsed the new AAP tables, but the attempt to provide a simpler method based on fixed cut points also in children, in alternative to BP percentiles, resulted in increasing confusion. Simplification should involve the classification system and, especially, the clinical procedure to confirm diagnosis of hypertension.

Overall, evaluation of prevalence of hypertension in this range of age is made very difficult on a global scale, due to the variety of different definitions.

1. BP measurement. At the present, all current guidelines suggest repeated office measurements (details can be found in Chapter 2), to confirm clinical observations of the first visit. The three guidelines recommend at least 3 different office visits, a challenging protocol that may cause dropout, and therefore, rarely adopted in the real world. Even one single BP assessment done by a doctor, or a nurse, can help identifying children with high BP, though diagnosis of hypertension should always be confirmed by a second visit [13].

The Consensus Panel agrees that once hypertension is detected, just a second visit is needed to confirm HTN, as already previously recommended[14,15]. Advice should be given to favor home BP measurements (HBPM), recommending automated devices validated for children (see Chapter 2), as recommended by all pediatric guidelines and adult European guidelines.

Since the commonly suggested ambulatory BP monitoring (ABPM) uses a Caucasian German pediatric reference database, the Consensus Panel strongly supports the generation of a broad multi-ethnic European reference population for ABPM in children and adolescents, to optimize the use of this important diagnostic tool (see Box 1).

2. Definition of HTN. HTN should be defined according to the modified AAP tables[2] up to age 16, but, clearly, Europe needs specific normative standards to be as accurate as possible (see Box 1). For adolescents 16 year old or older, the suggested office values of ≥ 130/85 mmHg are adequate cut points to align older youths to the adult cut-off for high-normal values[6].

The Consensus Panel agrees that the value of ≥ 130/85 mmHg be sufficient to diagnose hypertension. Rarely, systolic BP exceeding normal adult cut-point is found between 13 and 16 years, especially in particularly tall boys, but this phenomenon can be explained with the peripheral amplification of the pulsatile wave that is greatest in this range of age (up to 20 mmHg

and more)[16]. More research is needed on effect of peripheral pulse wave amplification in this range of age.

The Consensus Panel agrees that echocardiography can be an important add-on to confirmed diagnosis, when it is likely to influence decision making (see Chapter 3 and 4). Table 2 summarizes the points of agreement of the Consensus Panel.

Chapter 2: How to Measure BP in Children and Adolescents

BP can be recorded by office measurement (OBP), ABPM and HBPM[17]. However, while for OBP nomograms created from large reference populations are available, albeit with limitations[2,3,5], the reference values for ABPM and HBPM are generated from single studies.

Whatever measurement is adopted, a pivotal issue is cuff dimension, because too small cuffs overestimate and too large cuffs underestimate BP values. The width of the optimally sized cuff should be approximately 40% of the circumference of the arm at its midpoint between acromion and olecranon, and the cuff bladder length should cover 80% to 100% of the circumference of the arm[2] (Figure 1).

1. Sphygmomanometers. All current guidelines refer to the same database obtained from measurements made with mercury sphygmomanometers (see Chapter 1), which have been recently discontinued because of concerns about mercury toxicity. This has opened the way to automated electronic sphygmomanometers, mostly based on oscillometric technique. However, only a limited number of automated oscillometric devices have been validated for the pediatric age, and their cost is not negligible[18]. Since oscillometric devices do not measure but rather estimate BP, their accuracy might be considered uncertain. However, a recent meta-analysis has confirmed their strong measurement validity, when compared with mercury sphygmomanometers, supporting their appropriateness also for use in children and adolescents, in clinical and epidemiological studies[19].

The Consensus Panel agrees that generation of global BP pediatric reference nomograms obtained by oscillometric devices is a high priority for future studies (see Box 1), though few regional BP standards have already been proposed[20,21]. Only validated oscillometric devices should be used in children. To confirm diagnosis of HTN, oscillometric BP values should be confirmed with auscultatory method, using calibrated (every 6 months) aneroid sphygmomanometers[2,3].

2. Office Blood Pressure (OBP). OBP should be measured with the subject sitting quietly for a few minutes, with the arm resting on a support at heart level[2]. In the case of auscultatory methods, systolic BP corresponds to the appearance of the tone (1st Korotkoff's) and diastolic BP to the disappearance of the tones (5th Korotkoff's).

In office, BP should be measured three times, 1-2 minutes apart[2,3,6] (averaging the last two, discarding the first). At initial visit, BP should be also taken in both arms and one leg in the supine position to rule-out aortic coarctation (CoA, see Chapter 4). For diagnosis of HTN, confirmation is required in a second outpatient visit after some time, the interval depending on the concern about the level of BP.

The Consensus Panel agrees that automated unattended oscillometric BP measurements in children and adolescents should not be used for diagnosis, because no studies are available in children and adolescents to demonstrate better diagnostic value than conventional OBP.

3. Ambulatory Blood Pressure Monitoring (ABPM)

Consistent with recommendations in adult individuals, in children and adolescents, available guidelines acknowledge the importance of 24h ABPM. However, due to the paucity of reference values for interpretation in this range of age[22], clinical interpretation of ABPM values is at present limited. The scarce compliance of children with ABPM measurements, especially during night, makes interpretation of 24h and, more specifically, of nocturnal BP difficult. It seems reasonable that children/adolescents hypertension guidelines recommend an approach to ABPM data interpretation which is based on definition of hypertensive phenotypes identified using both OBP and ABPM values[23]. Because the normative values that are used were derived from a homogeneous population of Caucasian German children, last updated in 2002[22], an effort to create new European ABPM nomograms for age, sex and height, in a larger multi-ethnic, normal-weight population, is critically important (see Box 1).

As suggested by AAP[2], ESH[3], and AHA[24], ABPM can be useful in selected cases (suspected white coat, secondary hypertension, diabetes, monitoring of antihypertensive therapy and clinical trials), and should be performed in secondary or tertiary centers, with specific skills in the diagnosis and treatment of hypertension in pediatric age, to minimize the risk of misdiagnosing HTN.

An age stratified approach has been suggested for ABPM in children and adolescents to classify APBM[3,25]. It is important to take into consideration that ABPM values are often higher than the corresponding office values in children and adolescents, a difference that is function of age[26]. According to available European reference values of ABPM for children[22], based on the 95th percentile, ABPM values might be even higher than ABPM hypertension thresholds for adults[26,27]. To avoid this apparent paradox, due to the higher peripheral amplification of pressure wave in this range of age[28,29], as well as to the greater physical activity especially during day-time[26], application of adult ABPM norms has been suggested for pediatric age[27,30].

The Consensus Panel agrees on the following points for ABPM:

a) Day-time measurements should be scheduled every 20 minutes and night measurements every 30 minutes.

b) It is important to explain the reason for the exam to the young patient to minimize anxiety and maximize cooperation.

c) The ABPM measurements should always be interpreted on the background of OBP evaluation[24] .

4. Home Blood Pressure Monitoring (HBPM)

Also for HBPM, reference nomograms are derived from a single population in which only one HBPM device, validated in children, was used[21]. There are limited data on the association between HBPM and HMOD in children and adolescents, and, as observed for ABPM, the relation between HBPM and OBP varies with children's age[31]. Additional difficulties for use of HBPM in children and adolescents include limited research on clinical application, lack of data on nocturnal BP and current uncertainty on its diagnostic role[32].

The Consensus Panel agrees that European age-sex-height nomograms should be generated (Box 1).

The Consensus Panel agrees that HBPM should be recorded as recommended for adults in the ESC/ESH guidelines[6]. HBPM would be most useful when diagnosis is uncertain, especially when reliable reference values will be available. HBPM can be very useful to monitor effects of therapy.

When using HBPM, parents should be instructed on how the measurements must be performed.

Chapter 3: Clinical evaluation and assessment of hypertension-mediated target organ damage (HMOD).

1. Clinical evaluation. When hypertension is suspected, careful history and physical examination are needed. Table 3 presents the key historical points to collect as recommended by pediatric and adult European guidelines[3,6].

The Consensus Panel agrees that body mass index (BMI) and waist circumference (WC) should be measured according to consolidated methods[33,34]. Since no validated pediatric European tables on WC are available, based on age and sex, the Panel agrees that WC should be normalized for height (waist-to-height ratio) with a suggested cut-off value of 0.50[35].

Routine laboratory tests should be always requested (Table 4, row **Blood chemistry**), with additional tests to exclude secondary causes, when clinical suspicion exists (see Chapter 4).

Based on recent evidence, the Consensus Panel agrees that ECG can be useful also in this range of age[36].

2. Assessment of hypertension-mediated organ damage (HMOD). Assessment of HMOD has been recommended in pediatric guidelines.

The Consensus Panel agrees that three main areas should be explored, kidney, cardiovascular (CV) system and brain.

2.1. Kidney

Kidney function should be evaluated independently of known chronic kidney disease (CKD), to:

a) Identify and stage preclinical kidney disease;

b) Monitor the impact of hypertension and/or therapy on glomerular function.

Enzymatic method should be used rather than colorimetric, to measure serum creatinine for estimation of glomerular filtration rate (GFR); cystatin may be also used.

Microalbuminuria should be measured as a marker of HMOD[3,4]. Even considering that data are limited[37], values >30 mg/g creatinine on a spot urine specimen should be considered abnormal.

The Consensus Panel agrees that two equations for GFR estimation should be adopted (Box 2[38,39]). When GFR is <90 ml/min/1.73m^2, and/or significant microalbuminuria is present, annual controls are appropriate.

2.2 Heart and blood vessels

All pediatric guidelines suggest echocardiography at the time of confirmed HTN, though with different indications and objectives.

The Consensus Panel agrees that echocardiography should be undertaken when the results can impact on decision making.

Allometric normalization of left ventricular mass (LVM) for height should be used. Commonly, indexation in meters raised to the power 2.7 is proposed, with the adoption of either adult prognostically validated cut-points [5], or specific partitions for children and adolescents [3,11]. An age-specific exponent has been proposed, which eliminate residual regression of LVM index with age and height[40, 41]. The Consensus Panel is aware that this remains a controversial issue, and, possibly, more than one single approach should be adopted.

The Consensus Panel agrees that the proposed cut-point of **≥45 g/m$^{2.16}$** is the most reasonable partition value for identification of LVH by echocardiography in this age-range[41] . Alternatively, LVH may be also defined by 95th percentile of height$^{2.7}$-normalized LVM for age and sex, a method that revealed excellent sensitivity[11,42].

Because also relative wall thickness (RWT) correlates with age, the Consensus Panel agrees that RWT be age-adjusted (RWT$_a$) and that **RWT$_a$≥ 0.38** be diagnostic for concentric LV geometry[43].

There is no evidence that more advanced ultrasound techniques are clinically useful.

Depending on the clinical conditions and progression, and possible changes in clinical presentation, echocardiograms may be repeated, especially to evaluate changes in LVM in response to treatment.

Current guidelines do not recommend routine carotid ultrasound, even when other CV risk factors are present. The Association for European Paediatric Cardiology (AEPC) provided important methodological suggestions, but no cut points for any parameter[44].

The Consensus Panel agrees that there is no evidence that carotid ultrasound provides further refinement of cardiometabolic risk in this age range.

2.3. Brain

Hypertension in childhood and adolescence is a risk factor of cognitive impairment earlier in life [45]. hypertension in youths is also associated with lower performance in neurocognitive testing [46].

The Consensus Panel agrees that further research is needed in this area and that indications for neuropsychiatric exam in hypertensive children and adolescents are uncertain, although it might be considered whenever it may influence the clinical management.

Chapter 4: Secondary Hypertension.

Secondary causes of hypertension are more common in children than adults. However, due to increasing prevalence of obesity-related primary HTN, the proportion of secondary pediatric hypertension has been decreasing from 85% to 9%[47] and is mostly seen in tertiary pediatric hypertension clinics[48].

The common causes of secondary hypertension in children and adolescents are renal (parenchymal and/or vascular), cardiac (CoA) or endocrine (primary hyperaldosteronism, congenital adrenal hyperplasia, pheochromocytoma and hyperthyroidism).

In the general population, prevalence of renal fibromuscular dysplasia is 400 cases per 100,000, accounting for about 10% of all renovascular hypertension, with female predominance and usual clinical presentation between 15 and 50 years.[49,50] Unfortunately, no specific data are available for the 6- to 16-year-old age group.[51]

CoA presents in 25 -44 individuals per 100,000 children, representing approximately 5-8% of congenital heart disease[52,53]. CoA is mostly diagnosed and treated during infancy or early childhood. Among hypertensive children older than 6 years, CoA has been reported in 5 cases per 1,000 idividuals[54]. Following treatment, hypertension might persist or return later in life, with or without evidence of relapsed CoA.

Only 1% of adrenal tumor are diagnosed in children[55] and <3% of pheochromocytomas is found under 16 years[56]. Primary aldosteronism likely represents an under-recognized cause of secondary hypertension in the pediatric age group[57]. It is estimated that as many as 4% hypertension cases in this range of age exhibits aldosterone/renin ratio levels >10[57].

Despite some differences about prevalence and suggested diagnostic pathways, all major current guidelines agree on the importance of promptly identifying and treating secondary causes of hypertension in pediatric age[2-4,6]. Table 4 gives indications on when a focused clinical assessment of secondary causes of hypertension is appropriate. Particular attention should be paid to age of detection, as secondary hypertension is more frequent <12 years[58]. Hyperuricemia (>5.5 mg/dL) is reported as a marker of primary hypertension[59].

The Consensus Panel agrees that the first approach for the differential diagnosis between primary and secondary hypertension should include the following steps:

1. Detailed family history;
2. Physical examination including 3-extremity BP measurements and assessment of brachial and femoral pulses, to screen for aortic coarctation;
3. Laboratory test including assessment of:
    - renal function (estimate of glomerular filtration rate - see Chapter 3);
    - serum electrolytes;
    - urinalysis for proteinuria, micro-hematuria and urine sediment;
    - Aldosterone/Renin ratio, considering that interpretation might be difficult, because values vary with gender, age, and effects of possible ongoing pharmacological treatment [60];
    - Thyroid Stimulating Hormone and free thyroid hormones.

In case of abnormal lab tests or Stage 2 / severe hypertension that does not respond to non-pharmacologic lifestyle interventions, the Consensus Panel agrees that further diagnostic investigations may be conveniently undertaken, including;

1. Renal ultrasound to check for structural kidney disease;
2. Echocardiogram;
3. Nuclear magnetic resonance or computed tomography of the adrenal glands
4. Twenty-four-hour urinary or blood metanephrines and normetanephrines
5. Renal digital subtraction angiography for detection of renal artery stenosis

Table 4 displays the main clinical and laboratory differences between primary and secondary hypertension in children and adolescents.

Chapter 5: Treatment of hypertension.

The most recent guidelines agree that management of hypertension begins with non-pharmacological interventions[2-4]. Lifestyle changes are recommended as the initial action, an important strategy to delay drug treatment, or complement BP lowering effect of antihypertensive treatment.

Hypertension in children should be primarily managed by improving their adhesion to a healthy lifestyle, as shown in table 5.

The decision to begin pharmacological therapy is recommended in the presence of signs and/or symptoms attributable to HTN, HMOD, stage 2 HTN, concomitant comorbidities (see Chapter 7), and when there is unresponsiveness to lifestyle modifications[2,3]. Recommended first-line of antihypertensive agents includes angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), dihydropyridine calcium channel blockers (CCB) and diuretics, considering that children and adolescents of African ancestry exhibit reduced antihypertensive response to ACEi/ARB monotherapy[61]. Beta-adrenergic blockers are not recommended, except in specific conditions, due to potential side-effects. A stepped-care approach is strongly and unanimously suggested (Figure 2)[2-4].

1. Lifestyle modifications. The Consensus Panel agrees with the lifestyle suggestion of current guidelines[2,3], as displayed in Table 5, from 2016 ESH guidelines[3].

2. Drug selection. Most antihypertensive agents currently approved for pediatric use are limited to children 6 years of age or older. Legislative efforts, including new pediatric drug regulations in Europe[62] have facilitated ongoing attention to this area. Choice of initial medication is often unclear, some experts use a pathophysiologic approach, but in general the choice of agent is left up to the individual prescriber[2,3,63].

The Consensus Panel agrees that, due to the heterogeneous nature of childhood HTN, drug choice should be based on:

1. Presumed underlying pathophysiology,
2. Presence of concurrent disorders,
3. Availability of appropriate med formulations.

Pharmacologic treatment should be limited to agents licensed for use in children. Figure 2 displays a stepped-care approach on which Consensus Panel members agree.

The benefits and likelihood of response are important in choosing a specific medication. However, it is equally crucial consider potential adverse effects prior the initiation of selected antihypertensive therapy.

Resistant hypertension requires a careful search for adherence and/or screening for secondary HTN. Acute severe hypertension requires urgent intervention and exclusion of hypertensive emergency[64,65].

Similar to adult suggestions[66], the Consensus Panel agrees that hypertension emergency requires admission in Pediatric Intensive Care Unit and should be treated with intravenous drugs with appropriate doses, giving priority to labetalol, nicardipine and sodium nitroprusside.

3. Goal of treatment. There is an ongoing debate on BP targets in children and adolescents. Guidelines propose different BP goals and targets[2-4], in line with the BP thresholds for hypertension diagnosis (see Chapter 1). The ESH and AAP Guidelines also suggest more strict BP goals in case of chronic kidney disease (CKD), mainly in the presence of proteinuria, using ABPM-based criteria[67].

The Consensus Panel agrees that in children with primary hypertension without organ damage, achievement of BP values <95th percentile is acceptable, aligning with the cut-off for diagnosis of HTN. In the presence of HMOD or secondary HTN, the Consensus Panel agrees that BP threshold <90th percentile is preferable.

Children with CKD, without proteinuria, should be targeted to a 24-hour ABPM <75th percentile, while for CKD with proteinuria, the target should be 24-hr ABPM <50th percentile.[3,68].

Consistent with the adult guidelines criteria[6], and recommendations from 2016 ESH guidelines[3], in adolescents aged 16 years or older, the first objective should be lowering OBP to <130/85 mmHg in all patients, with the goal of achieving a target OBP of 120/75 mmHg in patients with HMOD and/or CKD, pending careful follow-up of GFR and electrolytes. The Consensus Panel agrees with the KDIGO recent guidelines[69] that systolic BP should not go below 120 mmHg in adolescents with CKD.

The Consensus Panel promotes HBPM as a useful strategy to follow response to antihypertensive treatment. Repeated ABPM is mandatory to optimize treatment in youth with CKD[68] using devices certified for pediatric use (see Chapter 2).

4. Consensus Panel suggestions for filling gap in knowledge. The Consensus Panel agrees that data about treatment of hypertension in youth are limited and the lack of studies hampers evidence-based management.

Unmet needs and procedures to advance in knowledge are suggested in Box 3. The results of much needed research will help ensure that the young receive safe, effective and age-appropriate antihypertensive drugs.

Chapter 6: Assessment and management of concomitant risk factors.

Cardiometabolic risk factors (CMRF) often coexist with primary hypertension also in children and adolescents [3,70], with a common denominator represented by unhealthy lifestyle behaviors, insulin resistance and low-grade inflammation. Thus, early recognition and management of concomitant CMRF in hypertensive children and adolescents is important to prevent CV disease later during adulthood.

There is no unified definition of CMRF across the most recent guidelines[2-4]. Concomitant CMRF (dyslipidemia, diabetes, even obesity) are sometimes indicated as “comorbidities” and listed together with surrounding conditions, such as CKD or obstructive sleep apnea, which might be rather causes of secondary hypertension (see Chapter 4).

The Consensus Panel agrees that in children and adolescents a clear-cut distinction should be made between co-morbidity factors that might have causative effect (see Chapters 4) and CMRF that often coexist with hypertension and are mostly modifiable by lifestyle changes (Table 6).

Obesity is the most important CMRF to consider in childhood, due to the high prevalence early in the life, the high odds of clustering with other CMRF and the high rate of persistence in adults[71]. Clear-cut overweight and obese children (Table 6)[72,73] exhibit 5.0% and 15.3% prevalence of HTN, respectively compared to 1.9% in normal-weight children[10]. Table 6 also lists recognized definition of all CMRF. Childhood obesity and hypertension are “insidious siblings”, gradually becoming a serious health hazard with an increasing global prevalence associated with unhealthy, sedentary lifestyle among children[74-76]. Since both obesity and hypertension are independently associated with increased LV mass, obesity status should be considered when deciding for therapy based on the presence of cardiac HMOD[77,78].

CMRF need to be targeted alongside treatment of high blood pressure. CMRF are associated with premature atherosclerosis, often referred to as early vascular aging, and are tied with unhealthy lifestyle, insulin resistance and low-grade inflammation.

The Consensus Panel agrees on the following points:

1. There is a research gap on how to score "CV risk" in children and adolescents.
2. Given the young age, doubts remain about the utility of diagnosing metabolic syndrome (MetS) as a CV predictor in children and adolescents[79], despite some evidence of association with target organ damage[80]. Insulin resistance, lipid profile and BP levels show fluctuations during puberty, and might influence the strength of associations between CMRF and outcome in adults[75]. Longitudinal studies could not demonstrate superiority of MetS over BMI or obesity in the prediction of subclinical atherosclerosis, type 2 diabetes or MetS in adulthood[76].
3. Obesity during childhood and adolescence tends to persist in adults[81] and represents a strong predictor of adult CV risk factors and adverse outcomes[82].

Childhood physical inactivity is a critical link among obesity, hypertension, inflammation, insulin resistance and late atherosclerosis in adulthood[83].

The Consensus Panel strongly agrees that the most important step in management of CMRF is lifestyle modifications, as indicated by current guidelines and recent position from American Heart Association[2,3,70] (see Table 5). Physical activity interventions alone or in combination with diet are effective in reducing risk of childhood obesity[84].

General institutional intervention should be promoted with respect to socio-economic and environmental factors[85,86], especially those that promote life-space mobility and access to healthy food markets[86,87]

The Consensus Panel agrees that if a good control of CMRF is not achieved by lifestyle modifications, additional pharmaceutical therapy may be considered, namely in selected cases with high CV risk profile[3,70].

In children aged 10 years or older, high LDL-Cholesterol may be treated with statins and/or additional cholesterol absorption inhibitors, if well tolerated. High triglycerides may justify treatment with fenofibrates, after consideration of their side effects, or supplementation of omega-3 fatty acids. Metformin is recommended in overt type 2 diabetes. When multiple CMRFs coexist, a multidisciplinary approach is needed.

It is impossible to study adverse CV end points in children and adolescents, which necessitates considering the association between CMRF and markers of preclinical CV disease as surrogate end points (e.g. left ventricular geometry)[88].

The Consensus Panel agrees that future research will have to determine whether combination of CMRFs with HMOD in childhood and adolescence can be used to address early therapeutical strategies.

Chapter 7: Implementation of suggestions in the real world.

The standard recommendations for hypertension screening in childhood and adolescence are often neglected[89,90] and efforts at different levels are required for successful implementation in clinical practice[91].

The Consensus Panel noted that publication of guidelines and evidence-based indications do not necessarily imply adherence to them in day-to-day clinical practice. The engagement of major stakeholders such as scientific societies, associations, and public health agencies, are critical to promote implementation of suggestions given in this document, to improve detection and treatment of hypertension in younger people.

1. **International Scientific Societies** should:
    a) Inform national professional societies, both in the clinical (e.g. general practitioners [GPs], pediatricians, cardiologists, pediatric nurses) and those in preventive arenas (e.g. school nurses, adolescent health professionals) about guidelines and other expert evidence-based documents to improve the detection and treatment of hypertension in children and adolescents.
    b) Stimulate national societies to inform and instruct their members.
    c) Organize surveys for GPs, cardiologists and pediatricians at the international level to evaluate the adherence to guidance in daily practice.
2. **National societies** should:
    a) Develop national strategies to implement guidance in clinical practice and prevention programs.

b) Inform and instruct the members on why, when and how to correctly measure BP in children and adolescents, and what to do when hypertension is diagnosed. This task can be accomplished in courses, national congresses, society journals and other media.
c) Partner with public health agencies to design strategies to engage and inform general public.
d) Integrate key performance indicators on hypertension management in children and adolescents, in quality of care monitoring and benchmarking.

3. **Public health agencies** should:
a) Ensure that prevention and management of hypertension in children and adolescents are given greater prominence in the public health agenda.
b) Make aware and inform the general public on risks of hypertension in children and adolescents, using lay-press, social media or integration in large-scale public health campaigns.
c) Establish information campaigns regarding the impact of lifestyle changes on BP, such as high levels of physical activity, healthy nutrition, low salt intake, low free-sugar intake, and non-smoking.
d) Guarantee protected time for children on TV and social media without any promotion of junk food or potentially deleterious lifestyle habits.

Conclusions.

This document highlights the discordant positions of the main current guidelines for hypertension in children and adolescents and identifies the limited information available for clinical daily practice. The Panel of this consensus document tried to reconcile different positions and highlighted needed actions to reduce our knowledge gap.

Among the main measures that need to be undertaken, the Panel strongly suggest:

1. to implement the development of appropriate multiethnic European normative tables for OBP, ABPM and HBPM, through the organization of longitudinal registries, with the prospective to link with adult CV risk;
2. to develop randomized clinical trials, using surrogate end-points to document specific benefits and disadvantages of BP lowering agents and behavioural lifestyle strategies**.**

512 The Consensus panel strongly encourages the implementation of international world-wide
513 initiative to generate normative tables for children and adolescents from all continents, to have
514 general rules on identification of arterial hypertension in this range of age.
515

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Table 1: Guidelines definition of arterial hypertension in children and adolescents.

Releaser	**Year**	**Method**	**Cut points**
National High Blood Pressure Education Program (NHBPEP)[4]	2004	Age-sex-height nomograms	≥95th percentile (<18 yrs) / ≥140/90
European Society of Hypertension (ESH)[3]	2016	Age-sex-height nomograms (NHBPEP)	≥95th percentile (<16 yrs) / ≥140/90
American Academy of Pediatrics (AAP)[2]	2017	New age-sex-height nomograms **only in normal weight**	≥95th percentile (<13 yrs) / ≥130/80
Hypertension Canada Guideline Committee (HCGC)[4]	2020	New age-sex-height nomograms **only in normal weight** Simplified fixed cut-off under and above 12 years	≥95th percentile ≥120/80 (<12 yrs) ≥130/85 (≥12 yrs)

Table 2: Consensus Panel's agreement summary on definition and classification of hypertension in children and adolescents.

BP measurement	1. Two visits to confirm diagnosis. 2. Recommend HBPM.
Definition of HTN	1. Use tables by sex, age and height up to age 16[1]. 2. ≥130/85 mmHg for over 16

Table 3: Anamnestic information for clinical evaluation in children/adolescents with hypertension.

1. Family history of HTN (namely pregnancy hypertension), CVD, familial hypercholesterolemia
2. Birth weight and gestational age
3. Environmental factors: smoking habit, salt intake, alcohol consumption
4. Physical exercise/leisure time
5. Possible symptoms (headache, epistaxis, vertigo, visual impairment, strokes, low school performance, attention defects, dyspnea, chest pain, palpitations and syncope)

Table 4: Clinical differences between primary hypertension and the more frequent secondary forms in pediatric age.

	PRIMARY HYPERTENSION	**SECONDARY HYPERTENSION**
Age of onset	Children and adolescents	**Infants** (aortic coarctation) **Young children** (renal disease, congenital adrenal hyperplasia, thyrotoxicosis, iatrogenic) **Adolescents** (renovascular hypertension, pheocromocitoma, primary hyperaldosteronism, thyrotoxicosis, iatrogenic)
Family history	Frequently positive	Generally negative
Symptoms	Generally absent	Sometimes present and associated with severity
Clinical signs	Absence of murmurs	Cardiac and/or abdominal murmur (aortic coarctation)
	Normal femoral pulses	Upper limb hypertension and weak or absent femoral pulses
	Excess weight frequent	Excess weight rarely present
Blood chemistry	Normal K+	Low/high (rare) K+
	Normal serum creatinine and Normal glomerular filtration rate	Creatinine can be high and low glomerular filtration rate can be present
	Micro / macrohematuria absent	Micro / macrohematuria can be present
	Urine sediment normal	Possible blood cell casts in urine sediment
	Thyroid Stimulating Hormone can be high in the presence of obesity	Thyroid stimulating hormone can be low/suppressed
	Hyperuricemia frequent	Hyperuricemia infrequent

Table 5: Lifestyle modifications summarized from ref #2

General recommendations 1. Physical activity and tailored diet 2. Encourage parents/family participation 3. Encourage smoke-free environment 4. Provide educational support and materials 5. Establish realistic goals 6. Develop a health-promoting reward system
BMI 1. If needed, graduate weight-loss program (see also Chapter 6)
Physical activity 1. At least 60 min of activity per day, at least moderate 2. More activity = more good health 3. Aerobic mostly, but with resistance components (3 times/week) 4. No more than 2-hour sedentary behavior per day 5. If stage 2 HTN, avoid competitive sports
Diet 1. Avoid free sugar (≤5% of total calories), soft-sweetened drinks, saturated fat 2. Prefer fruits, vegetables, and grain products (ideally, ≥4-5 servings/day) 3. Limit sodium intake (<2300 mg/daily)

Table 6: Modifiable cardiometabolic risk factors

Modifiable cardiometabolic risk factors	**Thresholds**
Overweight and obesity	• BMI > 85th and > 95th percentiles of national reference tables **or** • WHO age-specific normative tables (Obesity and overweight (who.int)) **or** • International Obesity Task Force Reference (Launch of the Diet, Physical Activity and Health – A European Platform for Action (europa.eu)
Dyslipidemia	Total Cholesterol ≥ 200 mg/dL LDL-C ≥ 130 mg/dL non- HDL ≥145 mg/dL HDL <40 mg/dL TG ≥ 100 mg/dL < 9 years TG ≥ 130 mg/dL ≥ 10 years
Hyperglycemia	FBG ≥ 100 mg/dL **or** HbA1c ≥5.7% (≥39 mmol/mol)
Physical inactivity	< 60 min/day moderate/vigorous physical activity; sedentary behavior ≥ 2 h/day [10]

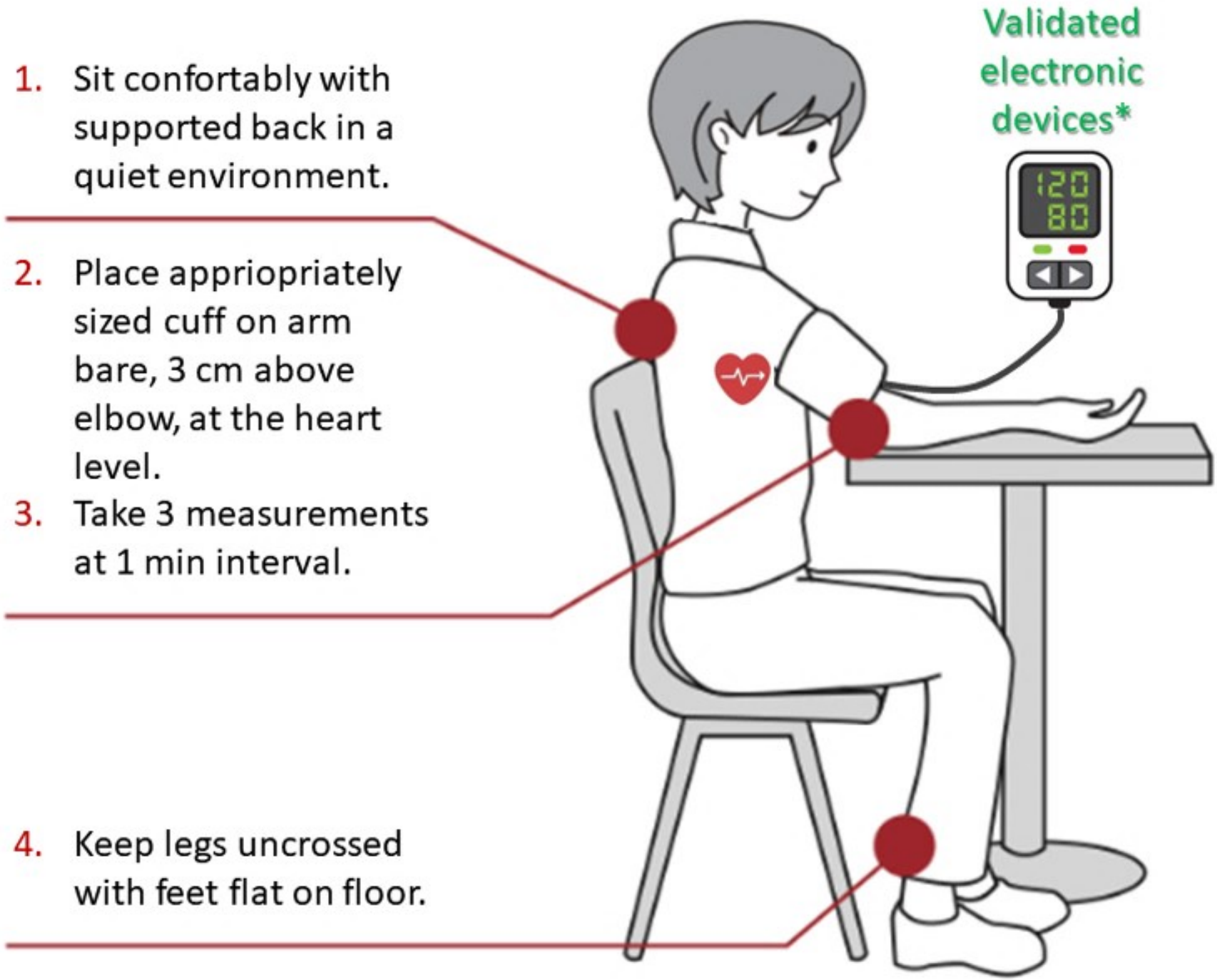
Figure legend.

Figure 1: Correct measurement of blood pressure in children and adolescents.

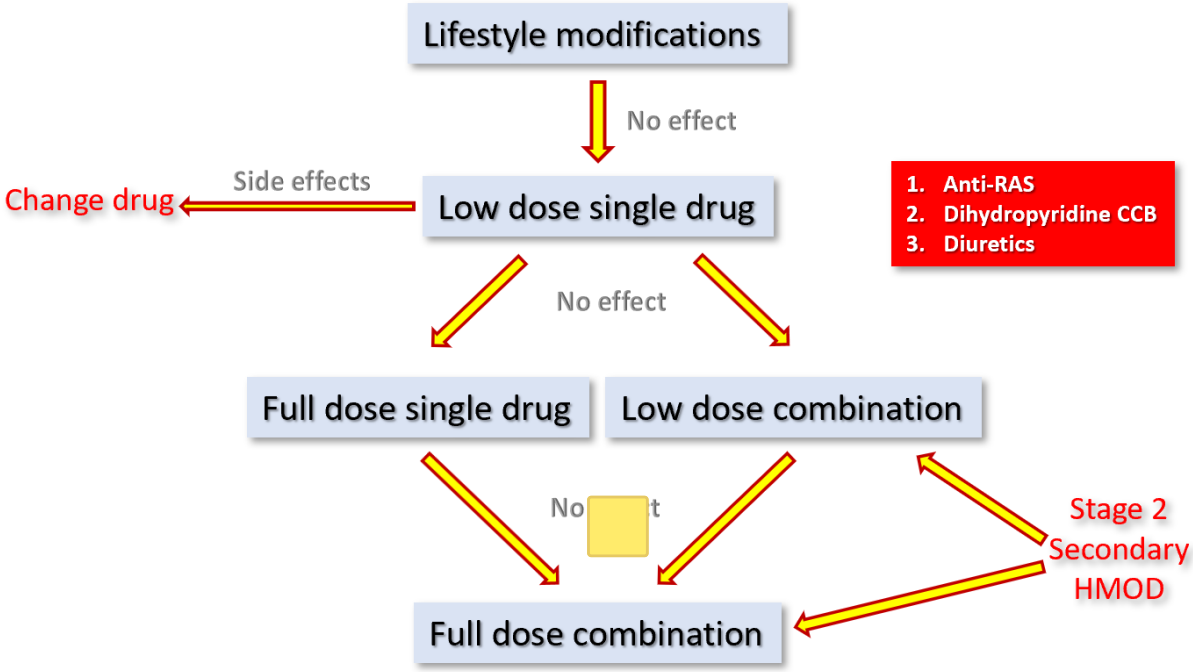
* Validated electronic devices can be found at: https://stridebp.org/bp-monitors/37-pdfs/734-home?format=pdf&tmpl=component&box=children.

Figure 2: Stepped care approach for management of arterial hypertension in children and adolescents.

1. Sit confortably with supported back in a quiet environment.
2. Place appriopriately sized cuff on arm bare, 3 cm above elbow, at the heart level.
3. Take 3 measurements at 1 min interval.
4. Keep legs uncrossed with feet flat on floor.



Hypertension management



BOX 1

Suggestions for epidemiological surveys:
1. Development of multi-ethnic, sex, age and height specific European normative tables and web facilities, in normal-weight children and adolescents. 2. Development of European normative tables for pediatric 24-h ABPM and HBPM, through the EURObservational Research Programme (EORP) of the European Society of Cardiology and the COST Action HyperChilNET of the European Society of Hypertension.

BOX 2

Equations to predict GFR. **Normal values: ≥ 90 ml/min/1.73m^2**
With serum creatinine: *K* × height (cm) / Creatinine (µmol/L). *K* =32.5 in all individuals, *K* =36.5 in boys aged >13 years *With serum cystatin*: GFR= 70.69 × (cysC$^{-0.931}$)

BOX 3

Suggested Actions for treatment
Need of clinical trials to be implemented on specific benefits and disadvantages of BP lowering agents, to establish adequate doses and combinations.
Strong need of clinical trials on 24-hours ABPM, to facilitate assessment of efficacy of antihypertensive strategies and their impact on BP variability.
Need of long-term large cohort studies to link with adult CV risk
Need of specific studies to implementing e- and m-Health