**ISOLATED SYSTOLIC HYPERTENSION IN THE YOUNG. A POSITION PAPER ENDORSED BY THE EUROPEAN SOCIETY OF HYPERTENSION**

**Running title: Isolated systolic hypertension in youth**

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**Abstract**

Whether isolated systolic hypertension in the young (ISHY) implies a worse outcome and needs antihypertensive treatment is still a matter for dispute. ISHY is thought to have different mechanisms than systolic hypertension in the elderly. However, findings from previous studies have provided inconsistent results. From analysis of the literature two main lines of research and conceptualization have emerged. Simultaneous assessment of peripheral and central blood pressure led to the identification of a condition called pseudo or spurious hypertension, which was considered an innocent condition. However, an increase in pulse wave velocity has been found by some authors in about 20% of the subjects with ISHY. In addition, obesity and metabolic disturbances have often been documented to be associated with ISHY both in children and young adults. The first aspect to consider when evaluating a person with ISHY is the possible presence of white coat hypertension which has been frequently found in this condition. In addition, assessment of central blood pressure is useful for identifying ISHY patients whose central blood pressure is normal. ISHY is infrequently mentioned in the guidelines on diagnosis and treatment of hypertension. According to the 2013 European Guidelines on the management of hypertension people with ISHY should be followed carefully, modifying risk factors by lifestyle changes and avoiding antihypertensive drugs. Only future clinical trials will elucidate if a benefit can be achieved with pharmacological treatment in some subgroups of ISHY subjects with associated risk factors and/or high central blood pressure.

There is still debate in the literature about the clinical significance of an isolated increase in systolic blood pressure (SBP) detected in the first decades of life. Controversies remain especially about the management of young subjects with isolated systolic hypertension (ISH) because whether ISH in the young (ISHY) implies a worse outcome and needs antihypertensive treatment is increasingly under challenge [1-3]. The lack of a consistent definition of young age for people with ISHY has contributed to the variations in reported outcome. Several issues regarding ISHY werereviewed and discussed in a consensus meeting held under the auspices of the European Society of Hypertension, on June 18, 2017, in Padova, Italy. Specific objectives of the panel of experts were to provide an update on ISHY and to discuss a number of open questions on the clinical significance and the management of this condition. Goal of the present document is to provide updated information rather than guidelines because when evidence is lacking and opinions of experts are not in full agreement, definitive recommendations cannot be set forth.

**Trajectories of blood pressure from childhood to adulthood**

From puberty to mid-life, brachial blood pressure (BP) changes follow a non-linear increase and diverging BP trajectories between SBP and diastolic BP (DBP): whereas DBP displays a cubic trajectory with a plateau-like behavior, SBP age-related changes are characterized by a steep increase during childhood, a plateau phase between 20 and 40 years [4-7], followed by a subsequent increase (Figure 1). Therefore, at the population level, pulse pressure (PP) values decrease in the age range between 20 and 40 years. After 50 years of age, PP increases exponentially as the result of further SBP linear increase and a DBP plateau phase is reached around 60 years, followed by a decrease [8]. Changes in adult life have been attributed to progressive stiffening of large arteries [9].

A number of epidemiological observations described the individual patterns of BP change over time and the associated clinical and prognostic significance. However, most of these studies were limited by cross-sectional design and substantial data from large-scale prospective longitudinal BP evaluations, assessing the effective intra-individual time-dependent BP changes, became available only in recent years. It has been observed that higher baseline SBP is predictive for steeper increases in aortic stiffening, BP and the future risk of hypertension, both in adolescence [10,11] and in adulthood [8,12]. Moreover, sex, ethnicity, smoking status, obesity and diabetes mellitus were significant effect-modifiers of an increased annual rate of change in PP [10,11,13]. Changes in body composition also play an important role in determining the rate of BP changes during adolescence. Variations in body mass index (BMI) after puberty have been related to sex differences in BP values from puberty to the age of 50-60 years, and were also shown to be significant determinants of the future risk of hypertension during adulthood [11]. The evidence of a positive relationship between weight gain and increased SBP in early adolescence should form the basis for future interventional research in this field aiming at evaluating the effectiveness of weight control programs during puberty.

There is uncertainty as to whether BP rate of change during childhood before puberty is associated with future risk of hypertension [5,10,14]. Some studies explored the clinical and prognostic significance of different BP trajectories both in early adulthood and in the elderly. In a group of 1169 adults aged 30 years, steeper PP trajectories until the age of 14 years predicted the development of mild chronic kidney disease [15]. Another study described the BP trajectories associated with an increased risk of developing coronary artery calcifications after 25 years, in subjects aged 18 to 30 years. As compared with subjects with stable BP values, individuals showing increasing values of both SBP and DBP were associated with a nearly doubled risk of coronary atherosclerosis [16]. Steeper increases in SBP and PP during mid-life were also associated with a greater risk of angina [13]. Recently, Tielemans et al, exploring data from two prospective and nearly extinct cohorts of individuals aged 50 years at the first evaluation, found that individuals with steeper BP rises were exposed to 2-to-4-fold higher risk of cardiovascular and all-cause mortality in the subsequent 10 years, independently of baseline BP [17]. This last observation reinforces the concept that longitudinal changes in BP are of importance in predicting the cardiovascular risk of an individual, and highlights the importance of extending the evaluation not only to baseline BP but also to focus the attention to BP changes over time. Further evidence is needed in order to better characterize the risk associated with increased longitudinal BP trends over life.

**Prevalence of ISH and high PP in young subjects**

ISH defined as a SBP ≥140 mmHg and DBP <90 mmHg [18] is the most common form of hypertension in the elderly [18,19]. However, ISH can be present also in young and very young individuals, more commonly in males (table 1).

*Prevalence of ISH in young adults*

The prevalence of ISH in the general adult population follows a typical J-shaped pattern, with a nadir in the fifth decade, a steep increase after 70 years of age and an earlier peak, though of lower magnitude, below 30 years of age [19,20]. In the elderly, ISH is more prevalent in females compared to males, while in subjects younger than 35 years the prevalence is higher in males chiefly in the youngest age classes [19,20]. According to data from the NHANES study [21] it is more common in black than white individuals. ISH is the most common type of hypertension among young males (table 1). Results from the HARVEST study obtained in a population of 18 to 45 year old grade 1 hypertensive subjects have shown that ISH prevalence was higher in men until 37 years of age and was similar between the two genders at 38-41 years [23]. A longitudinal analysis from the NHANES Study [21] showed that the prevalence of ISH in 18-to-39-year subjects slightly increased 5 years later in males (2.4% vs 3.3 %), while among females it slightly decreased (0.9% vs 0.5%), even if these differences did not reach the level of statistical significance.

*Prevalence of ISH in children and adolescents*

ISH may be present also in children and adolescents (table 1). The diagnosis of ISH in subjects <16 years conforms with paediatric conventions, and differs from that adopted for adult and elderly patients being defined as a SBP ≥95th percentile and a DBP <90th percentile [24]. Among children and adolescents, ISH is the most frequent form of hypertension and is often correlated to overweight and obesity. In a Swiss survey of 5207 children with a mean age of 12.3 years, 2.2% of the study participants were hypertensive (diagnosis confirmed after three separate visits) and among the hypertensives 81% presented ISH [25]. Of note, hypertension was associated with excess body weight, elevated heart rate and parents' history of hypertension. Similar results were observed in a recent BP screening program from a US population [26] in which 21,062 young subjects (mean age 13.8 years) were examined. In this study, sustained hypertension was present in 2.7% of the participants of whom 92% exhibited ISH, 6% systolic-diastolic hypertension and 2% isolated diastolic hypertension. Hypertension was more frequent among boys (3.3%) compared to girls (2.1%), and the prevalence increased with increasing BMI, being 2.6% and 6.6% in overweight and obese subjects, respectively [26]. A higher prevalence of prehypertension (14.2%), stage 1 hypertension (15.7%) and stage 2 hypertension (7.3%) was observed in a sample of 2655 Greek schoolchildren (9-13 years) participating in the Healthy Growth Study [27]. Also in this population ISH was the most prevalent phenotype (11.9%) and was positively associated with BMI and waist circumference in both genders and with sedentary behaviors in boys. The relationship between BMI and BP increase was explored in a recent paper by Kropa et al. [28]. Investigating 2700 middle school and high school physically active subjects (mean age 15.7 years) the authors observed that BMI accounted for 19.7% of the variability in SBP and for 8.5% of the variability in DBP. Lurbe et al [29] explored the prevalence of hypertension in a group of 593 overweight and obese young subjects (mean age 12.2 years) and observed that 86.2% were normotensive, 8.1% had high-normal SBP, 4.0% had ISH and 1.7% had systolic-diastolic hypertension. No cases of isolated diastolic hypertension were found.

*Distribution of PP according to age*

In the Third NHANES study (1988–1994) [30], in subjects divided into 3 age classes of 17-44 years, 45-64 years, and ≥65 years, an increase in PP was observed from the first to the second age class (from 42.2 mmHg to 67.7 mmHg) and then it levelled off (67.0 mmHg in the oldest class). In a recent Chinese population-based study [31] participants were divided into four age classes (18-30 years, 30-45 years, 45-55 years, and 55-70 years). PP progressively increased with aging being 37.8 mmHg, 38.7 mmHg, 42.0 mmHg, and 48.0 mmHg, respectively, in the four groups. The distribution of PP in adults younger than 45 years was recently explored in 1241 grade 1 hypertensive participants from the HARVEST study divided into 7 age classes [22]. Among the men, PP was highest in the youngest age group (61 mmHg), then it gradually decreased with aging and reached the lowest values in the two oldest groups (49 mmHg and 50 mmHg, respectively). Among the women, PP decreased from the first to the second age group (from 52 mmHg to 45 mmHg) and then it gradually increased to reach the highest value in the oldest group (52 mmHg). Of note, PP in females was lower than in males until 37 years of age, but after that age it was higher in females.

**Pathogenesis of ISH and elevated PP in the young**

*Hyperkinetic circulation and hemodynamic transition in hypertension of the young*

The hyperkinetic state of increased cardiac output, tachycardia and elevated BP has been documented in about one third of young patients with prehypertension by Julius et al using invasive hemodynamic measurements [32]. The same group of investigators subsequently used a noninvasive measurement method (Echo-Doppler) and found that 14% of 691 study participants (average age 32.6 years) had prehypertension and 37% of them had hyperkinetic circulation [33,34].

Patients with established hypertension characteristically have increased peripheral vascular resistance [32]. It follows that in the evolution from prehypertension to established hypertension there must be in many young subjects a hemodynamic transition from high cardiac output to increased vascular resistance. In his unique Bergen study [35] Per Lund-Johansen followed initially untreated patients with mild hypertension over a period of three decades (1965, 1975, 1982). In the resting state there was a stepwise increase of BP and vascular resistance together with a decrease of cardiac output and stroke volume. The resting heart rate did not change from the first to the third decade. Thus, in Lund-Johansen study the reduction of cardiac output was entirely due to a decrease in stroke volume associated with vascular rarefaction. In a hemodynamic study, Julius et al [36] compared prehypertensives with normal resting cardiac output to age matched normotensive volunteers. There was a marked reduction of stroke volume in the prehypertension group. This decrease was seen at baseline and was even more profound after ‘chemical denervation’ of the heart with propranolol and atropine. There was no difference in cardiopulmonary blood volume between the prehypertension and normotension groups.

In the evolution of established hypertension, the decrease of stroke volume is associated with increased vascular resistance [33,37]. This rise in resistance is best explained by a BP-induced restructuring of resistance vessels. There are two characteristic elements of restructured resistance vessels; they are less capable of dilating and they contract excessively to various constricting stimuli. The fact that restructuring is a secondary effect of higher BP and it is already present in early stages of hypertension supports the notion of early antihypertensive treatment. However, presently there is no evidence that such an early treatment may be useful. Unfortunately, in the Lund-Johansen [35] and Julius et al [38] studies there was no information about whether young people with borderline or mild hypertension had ISH, diastolic hypertension, or systolic-diastolic hypertension.

*Autonomic nervous system regulation in hypertension of the young*

In the early nineteen-seventies it was well known that fast heart rate is a strong predictor of hypertension and adverse cardiovascular outcomes [39]. However, there was a considerable disagreement about the pathophysiology of tachycardia. Particularly interesting was the report from the Cleveland Clinic [40] that some patients with tachycardia and elevated BP are hyper-responders to beta adrenergic stimulation. Another possible mechanism was that individuals with tachycardia may have a pacemaker which inherently induces a faster heart rate. This issue was addressed by Julius et al who used atropine and propranolol to block the cardiac autonomic nervous receptors [41,42]. The basic finding of this study was that in hyperkinetic prehypertension the sympathetic stimulation is increased whereas the parasympathetic inhibition is decreased. This strongly suggested that the abnormality emanated from the medulla oblongata where the sympathetic and parasympathetic tone are regulated in a reciprocal fashion. The autonomic blockade totally abolished the increase of cardiac output and heart rate in the hyperkinetic state thereby proving that the hemodynamic abnormality was neurogenic. Alterations in parasympathetic/sympathetic regulation of the cardiovascular system have been described also in ISHY. The more common finding reported in this clinical condition is the increase in resting heart rate which may be dependent on the alteration of either vagal or adrenergic control of sinus node activity [43]. Indeed, data collected throughout the years confirm that vagal control of heart rate is impaired in this form of hypertension, the magnitude of the alteration being directly related both to the severity and the duration of the SBP elevation [43, 44]. However, it is fair to say that emphasis has been put on sympathetic overdrive and little information exists about the decreased parasympathetic inhibition in hypertension [45]. As mentioned above, data collected in the context of the Tecumseh study have shown that about 1/3 of the young hypertensive patients display a so-called “hyperkinectic circulation”, i.e. an elevation in both resting heart rate and cardiac output, the latter being the factor majorly responsible for the isolated increase in SBP [34]. Interestingly, in the Tecumseh study the patients characterized by this specific hypertensive state also displayed an elevation in plasma norepinephrine levels, a finding which suggests the occurrence of an adrenergic overdrive. This has been later directly documented in young hypertensive patients via the microneurographic as well as the radiolabelled norepinephrine approach [46-48]. The latter technique has shown that in young patients the BP elevation is accompanied by a marked increase in systemic but also cardiac and renal norepinephrine secretion, indicating a pronounced adrenergic activation [48,49]. Given the evidence that ISHY may be associated with alterations in arterial compliance and distensibility [50], the observation that sympathetic neural mechanisms exert a tonic inhibition on both compliance and distensibility of large and medium size arteries is of specific interest [51]. This suggests that the abnormalities in sympathetic cardiovascular control detected in ISHY may have adverse effects on vascular structure and function [52].

*Arterial stiffness and measurement of SBP in the young*

Although one of the most striking features of vascular ageing is the progressive increase of arterial stiffness, as measured noninvasively by arterial pulse wave velocity (PWV) [50,53-56], the rate of arterial stiffening with age is not similar in all arterial districts. The largest change in PWV occurs in the aortic trunk (eg 0.92 m/sec per decade), with much lower rates in the arm (0.48 m/sec per decade) and leg (0.56 m/sec per decade) [53]. This phenomenon translates to a significant change in stiffness gradient between the central aorta and peripheral arteries. The relative stiffness gradient between the arm and the aorta drops from 118% at age 10 years to 87% at age 20, 64% at age 30 and 46% at age 40 [53]. This large discrepancy in stiffness gradient with age has significant implications in the measurement of BP in the brachial artery in the young and its relationship to central hemodynamics for characterisation of central organ damage such as left ventricular hypertrophy.

The relationship between the central aortic PP and the peripheral pulse in the upper limb is described by a transfer function which depends on the properties of the arteries [57]. Since there is a low rate of stiffening in the upper limb arteries [53], this has been approximated to a constant frequency-dependent function after the cessation of body growth (approx. age 18 years) with considerable success in the noninvasive estimation of central aortic pressure [58]. This method has been found useful and reliable down to age 8 years [59,60], presumably because the shorter distance from left ventricle to reflecting sites is offset by lower arterial distensibility. A better method for estimating peak central SBP in youth is from the late systolic shoulder of the radial pressure wave [61]. In the young, the large stiffness gradient is associated with variable effects of wave reflection such that the central and peripheral pressure waveforms differ in spectral power, that is, they have different energy in the harmonic components of heart rate frequency [62,63]. This has pronounced effects on the relationship between central and peripheral SBP. With age, as the stiffness gradient reduces, the differences in energy content of peripheral and pressure wave frequency components also reduce, so that the peripheral and central waves tend to resemble each other. Hence there is less of a difference between central and peripheral SBP, for a relatively constant DBP as occurs in ISH. That is, not only central aortic stiffness but also stiffness gradient between central and peripheral arteries may be a useful measure for evaluating the relevance of ISHY in relation to central organ damage.

*Effects of high heart rate on arterial stiffness*

The frequency dependency of the transfer function between the central aorta and peripheral (brachial or radial) pressure pulse determines the relationship between aortic and peripheral SBP for a constant DBP. With changes in heart rate, harmonic components will be amplified or attenuated to different degrees. Since the brachial transfer modulus function exhibits a monotonic increase up to a frequency of around 4 Hz in adults and fully grown adolescents (age >18 years) [57,58], a high heart rate implies a higher amplification of the fundamental and first 2-3 harmonics. That is, a higher PP will be measured in the brachial artery for a similar central aortic PP due to the heart rate-dependent amplification phenomenon [64-66]. The implication for ISHY is that heart rate plays an important role when comparing effects of high SBP measured in the brachial artery on central hemodynamics and central organ damage.

Recent studies have elucidated the heart rate dependency of arterial stiffness as measured by arterial PWV and underlying mechanisms [67-69]. This has been quantified as an increase of 0.17 m/sec for an increase of 10 beats/min [68]. A high heart rate has been identified as a significant factor of cardiovascular risk [39,70]. If a high heart rate is associated with ISH where there is also an increase in mean BP, this will also increase the overall arterial stiffness. Since arterial stiffness is a significant independent cardiovascular risk factor [71-72], this combined effect will result in a compound increase of overall risk. Specifically, it can also contribute to a preferentially accelerated effect on vascular aging in the young. From the reference values of PWV in the normal population [50] an increase of 10 beats/min, with the associated increase of 0.17 m/sec in PWV, would result in additional 2 years of vascular age at a chronological age of 40, but an additional 5 years of vascular age at age 20.

*Contribution of stroke volume and arterial stiffness to elevated SBP in ISHY*

The arterial BP has two major physiological components, besides the simple extremes of SBP and DBP. The static or steady state component which is represented by the mean arterial pressure is determined, physiologically, by the cardiac output and peripheral vascular resistance. In contrast, the pulsatile component or the PP is determined, physiologically by stroke volume, aortic stiffness and timing of wave reflection. The landmark studies by Lund-Johansen [35] and Julius [34,38], described in the previous sections, demonstrated that young patients in the earliest stages of hypertension were characterised by a hyperkinetic circulation, involving elevations of cardiac output and heart rate. However, and somewhat surprisingly, relatively few studies have examined the contribution of stroke volume and aortic stiffness to ISHY *per se* or whether a hyperkinetic circulation invariably precedes sustained elevation of BP.

In a small study of 32 healthy men aged between 17 and 28 years [73], high brachial PP was positively associated with elevated stroke volume and cardiac output. There was no significant association with heart rate, suggesting that the stroke volume was probably the major driver of the elevated PPs in these young individuals. The same authors had earlier demonstrated that the contribution of stroke volume to high PP in hypertensive men was most marked in younger individuals (those aged <50 years) but became much less important after the fifth decade [74], suggesting that other haemodynamic mechanisms (presumably aortic stiffening and early return of wave reflection) were responsible for the elevated PP observed in older individuals. The Enigma Study [75], which included 1008 young adult university students (mean age 20 years) examined cardiac output and stroke volume using a validated [76,77] non-invasive inert gas re-breathing technique. Carotid-femoral PWV (aortic) (aPWV), a robust measure of aortic stiffness, was also assessed. Increased cardiac output and stroke volume were the predominant haemodynamic disturbances in ISHY in the Enigma Study and, in particular, elevated stroke volume was evident in the majority of cases. However, it was also clear that ISHY is a heterogeneous condition, since ~20% of subjects had normal stroke volume, but increased aPWV. Therefore, at least in some individuals, ISHY might be associated with premature aortic stiffening and a trajectory towards sustained ISH in later life.

*Blood pressure variability in the young*

A number of studies have shown that the cardiovascular risk related to hypertension may not only depend on the magnitude of the BP elevation per se but also on the presence of other associated conditions such as increased BP variability (BPV) (either in the short or the long term) [78,79]. Recent data suggest that high BPV may play an important role also in children and young adults. Data from Fujita et al [80] in 198 children and adolescents, from Kotsis et al [81] in 115 young healthy volunteers, and from Boardman et al [82] in 152 young adults (mean age, 31 years) suggest that increased 24h systolic BPV is associated with increased arterial stiffness. Also long-term BPV has been found to be associated with worse outcome in youth. Using data from the Coronary Artery Risk Development in Young Adults (CARDIA), which recruited healthy people aged 18 to 30 years, Yano et al [83] found that long-term BPV throughout young adulthood was associated with worse cognitive function in midlife. In the Bogalusa Heart Study Chen et al [84] found that childhood visit-to-visit BPV, measured in 1797 subjects, was predictive of adulthood hypertension besides the mean levels. Thus, a large body of evidence supports a pathophysiological role for high BPV in determining hypertension and hypertensive complications also in children and young adults.

Some studies have shown that BP and heart rate variabilities were positively correlated to each other, suggesting a primary role of central nervous mechanisms in regulating these hemodynamic parameters [78,79]. In addition, the genetic background may also play an important role in fluctuations of BP over time [85]. Lurbe et al [86] also highlighted the role of low birth weight as a determinant of future BPV in children and showed that healthy children and adolescents who had lower birth weights tended to have not only the highest BP values but also the highest 24h systolic BPV later in life.

The effect of a comprehensive healthy lifestyle on BPV in healthy populations is largely unknown [87].In a large population-based study of 1999 young healthy adults, Maseli et al [88] showed that a healthy lifestyle and individual health metrics were significantly associated with a lower BPV. These data suggest (but, of course, do not prove) that a decrease in BPV might contribute to the beneficial effect of a healthy lifestyle regarding the prevention of cardiovascular events.

**Characteristics of subjects with ISHY**

As reiterated in this article, ISHY is thought to have different mechanisms than ISH of the elderly.It is thus conceivable that also risk factors for ISH may differ between young adults and elderly subjects. However, findings from previous studies in patients with ISHY have provided inconsistent results. Long ago, Julius et al documented that young subjects with hyperkinetic circulation had overweight and metabolic disturbances [34]. Among 5685 adults aged 18-39 years from the NHANES study, obesity, male sex, smoking, and low educational level were each associated with higher odds of ISHY [89]. In contrast, studies in smaller samples have found that ISHY was more common in tall men, non-smokers, and active in sports [90,91]. These conflicting data suggest that ISHY is a very heterogeneous condition that may include subjects with totally different genetic background and clinical characteristics.

*Association of ISHY with obesity and the metabolic syndrome*

As mentioned above, obesity and metabolic disturbances have often been found to be associated with ISHY both in children [25,26] and young adults [34,89]. In the NHANES study and a study by Asgari et al [89,92], high BMI was a major factor associated with the identification of ISHY. Middelmiss et al [93] found that in young overweight individuals it was the level of peripheral vascular resistance that distinguished between individuals with elevated versus normal brachial SBP suggesting that the mechanisms underlying elevated SBP in young adults depend on body size. In the Olivetti Heart Study [94], among participants aged less than 50 years (n=356) only 3% had ISHY. Subjects with ISHY had higher values of BMI, waist circumference, fasting blood glucose and HOMA index of insulin resistance compared to normotensive subjects. However, none of these differences reached statistical significance, conceivably because of the very small number of subjects with ISHY. Using a lower cut-off (SBP≥130 and DBP<85 mmHg) to define ISHY the prevalence rose to 6% and the differences in blood glucose and HOMA index attained statistical significance (p<0.05). In addition, the prevalence of metabolic syndrome was higher in ISHY than normotensive participants (26% vs 2%, p<0.05). Consistent results were obtained in the MINISAL children program, which was aimed at the assessment of habitual sodium intake in a sample of 1600 Italian children and adolescents aged 6 to 18 years [95]. By stratifying the 97 hypertensive subjects by hypertensive subtype, the group with ISHY had the highest average BMI Z-score and the highest habitual sodium intake [95]. Overall, the results of the Olivetti and MINISAL children study, together with the evidence available from other sources [96] suggest that insulin resistance and high salt intake are two important factors in the pathogenesis of ISHY. These two factors may act synergistically as insulin resistance and the accompanying hyperinsulinemia tend to enhance the sympathetic tone, the renin-angiotensin system activity and the sodium and water reabsorption at the renal tubular level [97] thus contributing to increasing BP salt-sensitivity (Figure 2). Over time these factors may generate a gradual increase in arterial stiffness that further contributes to the increase in SBP. However, other studies of ISHY subjects provided different findings suggesting that ISHY may have different pathophysiologic backgrounds. In the Mahmud and Feely’s observational study [91] or the O’Rourke study [90], it was reported that young people with ISH did not have any additional risk factor and that central BP was normal. Indeed, central BP measurement can help to identify the different phenotypes of people with ISHY and the ISHY subjects at higher risk [98,99].

*Effect of regular physical activity on arterial distensibility and ISHY*

A large number of epidemiologic studies have shown an association between regular physical activity and decline in the risk of cardiovascular and all-cause mortality [100,101]. It is possible that regular exercise training may attenuate cardiovascular disease through a variety of factors, including lower BP, reduced BMI, better lipid profile, etc. [101,102]. In addition, it has been shown that aerobic physical activity can limit the age-related decline in arterial elasticity as measured from carotid-femoral PWV [103] and improve small artery compliance in young adults [104] as well as in children [105]. However, the long term effect of regular endurance exercise training on central BP and augmentation index (AIx) is still controversial, due to contrasting findings between different studies [106-109]. Training induced bradycardia together with the improvement of cardiovascular risk factors can account for the better indexes of arterial distensibility observed in trained individuals compared to their sedentary counterparts [110-112]. However, there is ample evidence that heart rate has a negative relationship with the AIx and central SBP [113,114], due to the delayed return of the reflected wave and the increase in stroke volume at low heart rates. These bradycardia-related mechanisms may account for the conflicting results on central hemodynamics found in athletes [106,107,109,115]. In particular, equivocal data have been published for central BP because in some studies athletes exhibited lower central BP than sedentary controls [27], in other studies no difference was found between athletes and controls [106,107,116] and in some other athletes even showed an increased central BP [108,109]. In summary, training induced bradycardia may have an apparently unfavourable effect on central hemodynamics due to the prolongation of ejection duration so that the reflected wave may return in systole. On the other hand, improved small artery compliance and reduced peripheral resistance can decrease the magnitude of the reflected wave in athletes [117]. Long distance and Olympic marathon runners usually have low body height and attain success at a later age than other athletes. In these persons, a higher degree of aortic stiffness may assist in developing and maintaining an optimal entrainment between heart rate and stride rate [118], so that upward as well as forward motion increases perfusion of the heart [118], and the legs [119] for hours at a time.

The increased stroke volume secondary to bradycardia may explain why peripheral PP is higher and ISHY is more common in athletes than sedentary people [22,75]. High elasticity of the vascular tree may also contribute to the elevation of SBP in trained individuals. So-called spurious systolic hypertension was first described by Mahmud and Freely [91] and O’Rourke et al [90] in small groups of apparently healthy young men who were often participating in sports activities. ISH in these individuals has been attributed by these authors to exaggerated amplification of the arterial pressure wave travelling to the periphery [2,90,91].

**Clinical significance of ISHY**

Although non invasive measurement of central hemodynamics has provided new insights to ISHY, whether this condition implies a worse outcome and needs antihypertensive treatment remains unclear. Only did a few studies assess the association of SBP, PP or ISH with future risk of adverse outcome in young individuals providing inconsistent results. From the analysis of the literature two main lines of research and conceptualization have emerged for ISHY. Simultaneous assessment of peripheral and central BP led to the identification of the above mentioned condition called pseudo or spurious ISH, first described by O’Rourke [90], which was considered an innocent condition. However, an increase in vascular stiffness, assessed by PWV has been documented by some authors in subjects with ISHY [75]. History and evidence in favour of these two different views, whose apparent differences may be a result of categorisation, are reported here below.

*The “innocent condition” view*

Study of wave reflection phenomena show changes in pattern in children during growth and maturation up to the time that maximal height is reached (around 17-20 years of age) [120], then further changes from 30 years onward that can only be attributed to fatigue and fracture of elastin fibres, with degeneration, dilation and stiffening of the proximal, predominantly-elastic thoracic aorta [121-123]. The adverse process of arterial aging in human adults has been widely studied, and is the cause of ISH in adults, and the most common cause of cardiac failure and stroke in the elderly [123,124]. This is entirely different to ISHY [120], where elevation of SBP and PP is caused in many subjects by high amplification of the arterial pulse in the upper limb, and is not associated with high SBP or PP in the aorta, or to high left ventricular SBP [120,122]. Attention was first directed by findings of elevation of SBP in the brachial and radial arteries of young tall males with normal DBP and mean BP in the brachial artery and normal SBP in the proximal aorta. As mentioned above, this was described as “Spurious Systolic Hypertension” [90,120] – when high SBP and DBP were confined to the upper limbs, and not apparent in other arteries or in the central aorta. A good prognosis for such individuals has been shown over a 31- and 12-year period by Yano et al [1] and by Saladini et al [22], respectively.

The Australian Group in Sydney in a long series of studies has shown progressive increase in aortic aPWV in normal subjects aged 18-80 years [53], progressive increase in SBP and PP with age which was greater in central than in peripheral (brachial and radial) arteries, progressive increase in augmentation (height of the second systolic peak) of both central and peripheral pulses and progressive decrease in amplification of the pulse (ratio of radial PP divided by aortic PP) with age [120]. They explained these changes on the basis of differences in aortic stiffness, and hence timing of reflected waves as the aorta stiffens with age. This work concentrated on adults, and was linked with interpretations of brachial arterial pressures with age, typified by the Framingham study [7,8]. This covered a normal population from 25 to over 80 years of age. Initially, no children were studied. In Framingham, there was little increase in SBP with age in the 20s or 30s, but progressive increase beyond, up to the 80s. The “plateau” of the 20-40 year olds was most obvious in males. Data on change in BP with age in the paediatric group was obtained from the U.S. National report on high BP in children and adolescents [125], and linked up with the adult Framingham data to show low SBP of around 60mmHg around 2 years of age increasing progressively to 80 mmHg at 5 years of age, and linking with the adult Framingham data to confirm presence of a relative plateau of brachial SBP between the paediatric and adult populations (Figure 1). A single study linking paediatric and adult populations, and running from neonates to 35 years gave further support for the presence of a plateau of brachial SBP around 20 years of age [14]. The Sydney Group published a longitudinal study from 2-19-year old children [126], and then combined the Framingham with central SBP data of McEniery et al in adults [127] to estimate central SBP from brachial pressure. All are presented in figure 1. These data combined suggest that the “plateau” in change in brachial SBP of the young adult population is due to maximal amplification of the aortic pressure wave to the upper limb at this age. The rise in central SBP with age appears to be linear from age 10-80 years as is the increase in PWV with age [53,122,127] and the progressive increase in augmentation of pressure waves [and (reverse) amplification of the pulse waves] throughout life [120,123]. The relative plateau of increase in brachial SBP from age 10-80 years is seen in all the large studies of arterial SBP that cover this age range; it has not previously been explained, but can be on the basis of variable timing of wave reflection. The same explanation can be applied to the apparently paradoxical finding that, the neonatal invasively recorded radial artery pressure wave shows a prominent “tidal wave” as seen in elderly and hypertensive adults [128]. This is attributable in infants to early return of wave reflection caused by short body length [128]. In fully grown older adults, the same pattern is caused by high aortic PWV.

According to this concept, there would not necessarily be any abnormality in elevated brachial SBP in childhood, adolescence or young adulthood when this elevated SBP is confined to upper limb arteries. It can be explained by physiological mechanisms, and it reverts to the normal range in adult life [1,2,22,129]. This is supported by studies showing that ISH in young male individuals does not carry greater risk than those without [1,2,22], and that the vast majority of persons with this condition revert into the normal range of SBP in later life (“Young Finns” study [129]), and their aortic PWV remains within normal limits with aging.

This review concentrates on changes in the radial pressure waveforms with age. But changes in central BP can be synthesised from the radial artery pulse, using a Generalised Transfer Function, or a Second Systolic Shoulder method. [59,60]. The “benign view” was proposed also by other authors (2) who recognised the limitation of numbers derived exclusively from the cuff sphygmomanometer.

*The “true hypertension” view*

According to other authors, ISHY should be considered a condition of true hypertension associated with increased future cardiovascular risk [75] because data from four separate studies, containing six [90], 174[ 91], 750 [130] and 1008 [131] healthy young subjects, respectively, challenge the view that the condition is spurious. These studies have examined the phenomenon of spurious ISHY with regard to brachial and central pressure, and PP amplification. The SphygmoCor device was used in all studies. Mahmud and Feely [91] observed a greater difference between central and brachial SBP in those with spurious ISHY versus those with normal BP (brachial-central difference of 31mmHg versus 20mmHg). However, pressure amplification was actually lower in the individuals with spurious ISHY compared with gender-matched controls, when amplification was expressed in the conventional manner as the ratio of peripheral to central PP. In the study by Hulsen et al [130], amplification was significantly higher in the subjects with spurious ISHY, denoted as those subjects with high brachial SBP and ‘normal’ central SBP, defined arbitrarily as <90th percentile. However, in The Enigma Study, the largest cohort studied to date [75,131], there was no difference in amplification between individuals with ISHY and matched normotensive controls.

It is widely accepted that PP amplification varies between individuals, depending on a number of factors, including height and heart rate [131], and amplification may well be abnormally high in *some* young individuals with ISHY. However, in contrast to the notion that spurious ISHY arises from exaggerated amplification of *normal* central BP, the proponents of the “true hypertension” view [131,132] contend that further examination of the data from the studies described above reveals that central SBP is actually *higher* in individuals with ISHY versus controls: 116 vs 100 mmHg [91], 120 vs 98 mmHg [130] and 117 vs 105 mmHg [131], for brachial and central SBP, respectively. In the study by O’Rourke et al [90], central SBP was 119 mmHg. Therefore, according to the Cambridge investigators [131,132] these data suggest that individuals with ISHY are simply amplifying an already elevated central BP and that such individuals may be at significantly increased cardiovascular risk.

As discussed in an earlier section of this document, the majority of subjects with ISHY in The Enigma Study were also characterised by higher levels of stroke volume and cardiac output compared to normotensives [75]. Moreover, further data from the Anglo-Cardiff Collaborative Trial in over 4700 individuals demonstrate clearly that while PP amplification is only moderately higher in subjects with ISHY compared with normotensives, stroke volume is markedly higher [132] and is the predominant driver of the elevated PPs observed in young subjects with ISHY. This has important clinical significance, based on the studies by Lund-Johansen [35] and Julius [32-34], which showed that elevations in stroke volume and cardiac output in young individuals represent the earliest phase of essential hypertension and are likely to transform over time into sustained and irreversible essential hypertension. In at least some of the individuals with ISHY in The Enigma Study, aPWV was also elevated, suggesting that ISHY might also be associated with premature aortic stiffening [75]. Thus the Enigma Study investigators concluded that these individuals appear to have the same pathophysiological mechanism underlying their hypertension as older ISH subjects, although it is unlikely that such stiffening is due to age-related elastin degeneration. As discussed in more detail in other sections of this document, we know that BP and PP track throughout life. As such, subjects with ISHY with elevated PP *and* aortic stiffening may be predisposed to sustained ISH and an excess of cardiovascular risk, in later life. Clearly, further long-term, observational studies are required to accurately determine the fate of individuals with ISHY. According to the “true hypertension” view, a large body of evidence indicates that ISHY is associated with increased brachial *and* central BP suggesting that the *majority* of individuals with ISHY are likely to be at increased future cardiovascular risk.

*Prognostic value of elevated PP in the young*

The clinical significance of elevated PP in young individuals remained unexplored for long because of the obvious necessity of a long-term follow-up to collect a sufficient number of events. The first authors that highlighted a different prognostic value of PP according to age were Sesso et al [133] who examined 11,150 men during a mean follow-up of 10.8 years. These authors compared the predictive role of mean BP and PP for the development of cardiovascular disease among adult-to-elderly versus young-to-middle age men. In subjects ≥60 years multivariate Cox analysis demonstrated a graded increase in risk of cardiovascular disease from the first to fourth quartile for both PP and mean BP. In contrast, among younger men (<60 years of age), mean BP preserved its predictive role for unfavourable outcome, whereas PP only showed a marginal and not significant predictive value. Further evidence in young individuals came from the study by Sundström J et al [134] who examined 1,207,141 18-year-old conscripts (mean age 18.4 years) followed for 24 years. These authors observed that only DBP and not SBP was significantly associated with all-cause mortality. More recently, the above mentioned study by Yano et al [1] compared the risk of cardiovascular mortality in different hypertension subtypes. Among men with ISHY the risk of unfavourable outcome was similar to that observed in patients with high-normal BP and lower than that observed in diastolic or systolic-diastolic hypertensive patients. A different trend was observed among the women. In the female gender, ISHY was associated with a greater increase in risk of cardiovascular mortality, only lower than that observed for systolic-diastolic hypertension and higher than that in women with diastolic hypertension. The prognostic significance of PP and mean BP for development of hypertension needing treatment and cardiovascular events was recently tested in 1241 young-to-middle-age participants from the HARVEST study (mean age 33.1 years, mean follow-up 12.1 years) [22]. Participants in the highest PP tertile had a reduced risk of incident hypertension needing treatment and of cardiovascular events compared to those in the bottom tertile. In contrast, participants in the top mean BP tertile had an increase in risk for both outcomes. In summary, the data from the literature indicate that PP has a different prognostic significance in young and elderly individuals. In the elderly, PP is a well established predictor of risk whereas in young men high PP may even have a protective role. More data are needed to better understand the clinical significance of elevated peripheral PP among young women.

**Assessment of subjects with ISHY and role of central blood pressure**

The first aspect to consider when evaluating a person with ISHY is the possible presence of white coat hypertension (WCH) because one of the strongest determinants of high PP in these individuals is a pronounced white-coat effect (WCE) [22,29,34]. The role of the WCE in young patients with elevated SBP was first described by Julius et al. [34] in the Tecumseh study. These authors observed that young borderline hypertensives with hyperkinetic circulation had a marked WCE assessed with home BP measurement, while those with normokinetic hypertension and the normotensive subjects had a very small difference between office and home BP. Similar findings were obtained by Lurbe et al [29] in 593 overweight and obese children (mean age 12.2 years), 24% of whom had ISH. In the ISH group, 75% of the children had WCH versus 10% among the systolic-diastolic hypertension group. Saladini et al. [22] in a cohort of young to-middle age grade 1 hypertensive subjects (mean age 33.1 years) observed that the strongest predictor of high PP in these subjects was the systolic WCE. These data suggest that a pronounced alarm reaction to the doctor’s visit is a strong determinant of increased office SBP in ISHY and suggest that all subjects with ISHY should be assessed with out-of-office measurement to exclude WCH. Detection of sustained hypertension should prompt investigation of whether the patient has other risk factors or target organ damage [2,18] in order to decide whether antihypertensive treatment is needed (figure 3). If ISHY is confirmed by out-of-office measurement, assessment of central hemodynamics and arterial distensibility may provide additional useful information.

Central (aortic) BP represents the direct load determining target organ damage [135,136]. Indeed, a meta-analysis of clinical studies showed that central BP is related to left ventricular hypertrophy, carotid intima media-thickness and albuminuria, independently of peripheral BP [137]. This has been also shown in a cohort of 300 young to middle-aged patients, being central mean BP associated with end-organ damage, even when adjusted for ambulatory 24h BP [138]. In the HARVEST study [99], ISHY subjects with low central SBP had a risk of development of hypertension requiring anti-hypertensive treatment similar to that in the normotensive subjects of control while those with high central SBP had a risk comparable to that observed in subjects with systolic-diastolic hypertension.

However, it should be pointed out that measurement of central BP has to be calibrated with BP values normally obtained by conventional (usually oscillometric) brachial measurements. Another important limitation to the use of central BP in ISHY is the lack of official thresholds values that differentiate normal from high central BP. A possible approach is to calculate central BP value corresponding to the current brachial 140/90 mmHg cut-off, on the basis of BP amplification. Analysis of cross-sectional data in healthy men (n=3603) and women (n=3176) from the Anglo-Cardiff Collaborative Trial, suggested a cut-off value of central BP approximately of 125/90 mmHg [131]. A subsequent study, specifically aimed to derive and validate outcome-driven thresholds of central BP, determined the values of 110/80 mm Hg for optimal central BP and 130/90 mm Hg for hypertension in a derivation cohort (1272 individuals and a median follow-up of 15 years) [142]. Regarding central PP, a value greater than 50 mmHg predicted adverse cardiovascular outcomes in over 2400 participants without cardiovascular disease from the Strong Heart Study [143]. Reference values for central SBP and PP have been published by Herbert et al in healthy populations and patients with cardiovascular risk factors, providing age- and gender-specific reference ranges [66]. For each decade of age, they provided the 10th, 25th, 75th and 90th percentile for central BP values. Although this approach has never been applied to peripheral BP, it may be of help for distinguishing between subjects with spurious hypertension (normal central BP) and those with ISH (central BP in the high-normal range or higher) with possible implications for treatment. Nevertheless, it might be of particular relevance in young subjects to quantify the phenomenon of pressure amplification by comparing measured central and peripheral BP values versus reference PP amplification in the normal population [66]. The reduction of PP amplification or the increase of its reciprocal PP ratio, which has been associated with risk factors or disease [136], will allow the clinician to detect early vascular aging process, possibly providing prognostic information on ISHY. This hypothesis should be supported by future studies evaluating fixed threshold versus age- and gender-specific reference ranges of central BP for the estimation of cardiovascular risk in the young beyond traditional brachial cuff measurement. At any rate, central BP appears as a promising tool for evaluating the overall cardiovascular risk of ISHY subjects and for deciding whether they may need antihypertensive treatment. It is thus the opinion of this panel that central BP should always be included in the assessment of ISHY as summarized in figure 3.

**Management of ISHY according to present guidelines**

ISHY is infrequently mentioned in the guidelines on diagnosis and treatment of hypertension, whose focus remains almost invariably confined to treatment of hypertension in middle-age and elderly people. Little attention is somewhat surprisingly devoted to this condition also in guidelines dealing with the mechanistic aspects, the clinical significance and the need for treatment of hypertension in adolescents and children, an example being the recent guidelines issued by the American Academy of Pediatrics [144] as well as a position paper of two recognized experts in this area [145]. An exception is the guidelines on hypertension in children and adolescents of the European Society of Hypertension published in 2016 [24] which, as mentioned above, included ISHY in a Table classifying the hypertension phenotypes in these age categories. The European guidelines on children and adolescents mention the case of young individuals in whom an isolated brachial SBP elevation is accompanied by a normal central SBP. Although recognizing the peculiarity of this condition, they refrain from reaching any firm conclusion on its clinical significance because of 1) the limitation of available prognostic data and 2) the uncertain prognostic superiority of central vs brachial BP in general, and even more in younger population strata. This is in line with the position taken by the 2013 guidelines of the European Society of Hypertension and the European Society of Cardiology [18] on hypertension in the adulthood in which specific mention was made of the possibility that this condition reflects mechanistically regional discrepancies of arterial distensibility and has no adverse prognostic significance, as argued and reported by the pioneer studies of O’Rourke et al [90,120]. However, given the large number of studies currently devoted to ISHY and the growing evidence on its mechanistic and clinical aspects, it is the opinion of this panel that these young individuals should receive recommendations on lifestyle modification (particularly cessation of smoking), and that they require long-term follow up because some will develop sustained hypertension . In subjects who present with other risk factors and/or have high central BP pharmacological treatment may be considered.

**Future research directions**

Given the present lack of data on the prognostic significance of ISHY and the consequent uncertainty about whether this condition should also be managed with drug treatment, there is a need for a placebo-controlled clinical trial in the near future to elucidate if a benefit can be achieved with treatment at least in some subgroups at higher risk. Due to the young age of the participants and the consequent long time necessary to accumulate a sufficient number of hard events, organ damage might be used as an intermediate endpoint for assessing the benefits of antihypertensive therapy. Particular emphasis should be put on the prognostic role of central BP.

**Conclusions**

Epidemiological, pathophysiological and clinical research has removed ISHY from being one of the Cinderella of the hypertension world. Epidemiological research has shown that in childhood, adolescence and young adult life an elevation of SBP with no concomitant increase of diastolic values is by no means rare, and that this is particularly the case in the male gender and in overweight or obese subjects. Mechanistic research has additionally documented that in these people an isolated SBP elevation may be associated with, and caused by, not just one but, to a variable quantitative degree, multiple factors that can operate in isolation or interact to determine this BP phenotype: a hyperkinetic heart (as demonstrated decades ago by the pioneer work by Julius and colleagues) [32-34], a selective increase in heart rate or stroke volume, and an increase in arterial stiffness above the values regarded as normal for young age ranges.

This review has addressed an aspect of ISHY which can be legitimately defined as a clinical dilemma regarding ISHY pathophysiology and appropriate patient’s management. The ISHY condition identified by O’Rourke and colleagues [90,120] is characterized by an isolated SBP elevation at the level of the brachial artery with normal central BP. These subjects did not exhibit a greater cardiovascular risk or progression to systolic-diastolic hypertension, which made this condition appear as clinically innocent, a conclusion favoured by its attribution to an excessive peripheral pulse wave amplification attributable to higher harmonic content of aortic waves at the generalised transfer function frequencies of greatest amplification (about 4Hz), and where aortic impedance modulus is very low [122]. However, the clinical innocence of ISHY with a normal central SBP has not been unequivocally supported by the results of other investigations [131,132], and it is also somewhat weakened by the persistent uncertainty on whether central BP is prognostically superior and overcomes the predictive value of peripheral BP. In addition, ISHY is often associated with sympathetic activation, which may play a mechanistic role because of its ability to increase arterial stiffness by increasing heart rate [67-69,112] but also by acting directly on the elastic modulus of the vessel wall [110,146-148] as well as by determining and supporting a hyperkinetic performance of the heart.

The most appropriate conclusion seems thus that the issue remains open to future research and to additional mechanistic and epidemiological contributions that might clarify the clinical nature of an ISHY that presents a high brachial but normal central SBP i.e. with spurious systolic hypertension. Although the above mentioned findings suggest that ISHY may not be clinically innocent, all major prospective studies now available [1,22,133,134] are substantially negative. Cross-sectional studies have shown that in ISHY subjects concomitant metabolic risk factors (insulin resistance, metabolic syndrome, overweight, diabetes, etc) may be more frequent than in the control population. For this reason, the 2013 European guidelines on arterial hypertension [18] recommended to only follow these people closely, modifying risk factors by lifestyle changes and avoiding antihypertensive drugs. Hopefully, future studies will clarify whether a benefit can be achieved with pharmacological treatment in ISHY subjects who present with other risk factors and/or have high central BP.

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**Legend to figures**

**Figure 1.** Schematic representation of tracking of peripheral systolic and diastolic blood pressures (pSBP, pDBP, black lines), and central systolic pressure (cSBP, gray line) in the general population. The gray area indicates pulse pressure; bright gray area represents pulse pressure amplification. Data are extracted from references 4, 7, 126, 127.

**Figure 2.** Pathophysiological aspects of isolated systolic hypertension in the young. The sketch

illustrates the pathogenetic mechanisms that can account for the relationship between obesity

and isolated systolic hypertension in young individuals.

**Figure 3.** Proposal for a diagnostic flow-chart for young subjects with isolated systolic hypertension.

**Table 1**. Prevalence of ISH in children, adolescents, and in young-to middle-age adults.

|  |  |  |  |
| --- | --- | --- | --- |
| **Author** | **Population** | **Age (years)**  Mean±SD or Age range | **Prevalence %** |
| **Children and adolescents** | | | |
| Chiolero A (2007) [24] | General Swiss population (n=5207) | 12.3±0.5 | 1.6 |
| Cheung EL (2017) [25] | General US Population (n=21062) | 13.8±1.7 | 2.5 |
| Karatzi K (2017) [26] | General Greek Population (n=2655) | 9-13 | 11.9 |
| Lurbe E (2016) [28] | Spanish overweight and obese (n=593) | 12.2±2.3 | 4 |
| **Young-to-middle age adults** | | | |
| Staessen J (1990) [18] | General Belgian population (n=4202) | 10-30  30-40  40-50 | 2.8  0.1  0.8 |
| Mallion JM (2003) [19] | French working population (n=27,783) | 15-19  20-24  25-29  30-34  35-39  40-44  45-49 | 5.8 (M) <1 (F)  9.3 (M) <1 (F)  6.8 (M) <1 (F)  6.2 (M) <1 (F)  6.3 (M) <1 (F)  5.8 (M) 2.1 (F)  7.8 (M) 3.7 (F) |
| Liu X (2015) 20] | General US population (n=24,653) | 18-39  40-59 | 3.3 (M) 0.5 (F)  6.6 (M) 5.4 (F) |
| Saladini F (2009) [22] | Italian Stage I hypertensives (n=1141) | 18-21  22-25  26-29  30-33  34-37  38-41  42-45 | 48 (M) 13 (F)  28 (M) 15 (F)  14 (M) 11 (F)  15 (M) 4 (F)  12 (M) 8 (F)  5 (M) 5 (F)  1 (M) 0 (F) |

M, male; F, female.

Figure 1

Figure 2

Figure 3