Consensus Document

Management of the hypertensive patient with elevated heart rate: Statement of the Second Consensus Conference endorsed by the European Society of Hypertension

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In June 2015, a panel of experts gathered in a consensus conference to plan updating recommendations on the management of the hypertensive patient with elevated heart rate (HR), previously released in 2006. The issues examined during that meeting and further discussed by the participants during the following months involved the assessment of HR, the relevance of HR as a cardiovascular risk factor, the definition of tachycardia and the treatment of the hypertensive patient with high HR. For the measurement of resting HR the panel experts recommended that scientific investigations focusing on HR should report information on length of resting period before measurement, information about temperature and environment, method of measurement, duration of measurement, number of readings, time interval between measurements, body position and type of observer. According to the panellists there is convincing evidence that HR is an important risk factor for cardiovascular disease and they suggest to routinely include HR measurement in the assessment of the hypertensive patient. Regarding the definition of tachycardia, the panellists acknowledged that in the absence of convincing data any threshold used to define tachycardia is arbitrary. Similarly, as there are no outcome studies of HR lowering in tachycardia hypertension, the panellists could not make practical therapeutic suggestions for the management of such patients. However, the experts remarked that absence of evidence does not mean evidence against the importance of tachycardia as a risk factor for cardiovascular disease and that long-term exposure to a potentially important risk factor may impair the patient's prognosis. The main aims of the present document are to alert researchers and physicians about the importance of measuring HR in hypertensive patients, and to stimulate research to clarify unresolved issues.

Keywords: cardiovascular, heart rate, hypertension, measurement, mortality, prognosis, risk, sympathetic nervous system

Abbreviation: HR, heart rate

INTRODUCTION

In 2006, the European Society of Hypertension published an Expert Consensus Document titled 'Identification and management of the hypertensive patient with elevated heart rate' [1]. This document summarized the available data on the association between high heart rate (HR) and the cardiovascular risk in hypertension. During the 9 years, since the publication of the 2006 Consensus paper, research on HR in hypertension and other clinical settings has actively been pursued. The results of many new important studies, including several large cohort studies and re-analyses of clinical trials in hypertension focusing on the association between high HR and adverse outcome have been published. These studies have widened the information available in 2006 and have reinforced the evidence about the importance of high HR as a risk factor for cardiovascular diseases. Several issues were reviewed and discussed during a consensus meeting held under the auspices of the European Society of Hypertension, on 18

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June 2015, in Padova, Italy, and further discussed between the experts during the following months while a consensus statement was elaborated. Specific objectives of this consensus document were to agree on methodological standards for assessment of HR and to give an answer to a number of open questions on the clinical significance of office and out-of-office HR. An extensive literature review was used to provide the scientific evidence that supports the panel's consensus statements. Although many subjects relevant to high HR were initially identified, the experts addressed four issues as currently being the most important and controversial points, mainly using the information coming from the studies published in the last 10 years. The issues examined involved the assessment of HR, the relevance of HR as a cardiovascular risk factor, the definition of tachycardia, and the possible advantage of reducing high HR in hypertension. The goal of the present document is to provide updated information rather than guidelines because when evidence is lacking, recommendations are based on the opinions of the experts, which might be wrongly perceived as prescriptive. Individual doctor's judgement will thus retain a key position in terms of diagnostic and therapeutic decisions.

HOW TO MEASURE HEART RATE

Office heart rate

Most information on the prognostic capacity of HR for cardiovascular events and mortality has been obtained from studies that measured HR in resting conditions. However, many sources of variability, including physical factors, psychic stimuli, environmental factors and body position, may affect the assessment of HR measured by healthcare personnel [2,3]. Therefore, to minimize the effect of these confounding variables, the measurement of resting HR should be strictly standardized. Recommendations on how to measure resting HR based on the available evidence are presented in Table 1. All scientific investigations focusing on HR should report the following information: length of resting period before measurement, information about temperature and environment, method of measurement, duration of measurement, number of readings, time interval between measurements, body position and type of observer (doctor, nurse, technician and automatic device).

Recommendations for the clinician are roughly the same as those used for blood pressure measurement which is usually made during the same session. Patients should relax for at least 5 min before the measurement to make sure that stable haemodynamic conditions are achieved. In patients with strong alerting reaction, a long period of adaptation may be necessary. Care is recommended to standardize the conditions of measurement. Factors which can alter patient's haemodynamics, such as exercise, alcohol, smoking and coffee consumption, should be avoided in the hours preceding measurement. Room temperature should be comfortable and sources of noise should be avoided. Thus, the patient should be instructed to relax as much as possible and not to talk during the measurement. The individual should be comfortably seated, with the legs uncrossed. Usually, HR measurement follows each blood pressure reading. There was some debate among the experts about whether electrocardiography should be preferred to pulse palpation. A good correlation between the two measurements has been found in healthy men [4] and in patients with stable coronary artery disease [5] with correlation coefficients more than 0.9 in both studies. Electrocardiography allows a more precise estimation of HR and has been used in many epidemiologic studies and clinical trials. However, the use of electrocardiography implies an increase in costs and whether electrocardiographic measurement may actually be advantageous for research purposes is still unknown. In addition, electrocardiography is performed in the lying posture, whereas HR measurement from pulse palpation can be obtained in the sitting position together with blood pressure. The panel felt that the sitting position should be preferred because in epidemiologic studies blood pressure has been more frequently measured in that position and HR can be measured at the end of each blood pressure measurement. For these reasons, electrocardiographic measurement is allowed but is not recommended even for research. The panel agrees that a 30-s period is an optimal length for the palpatory method.

TABLE 1. Recommendations for the measurement of resting heart rate

Exercise, smoking, alcohol and coffee consumption should be avoided before measurement
The patient should be allowed to relax for at least 5 min
A longer period of adaptation may be necessary
Background noise and talking should be avoided
Room temperature should be comfortable
The sitting position should be preferred
The individual should be comfortably seated with legs uncrossed
HR should be measured by pulse palpation over a 30-s period
Electrocardiographic measurement is acceptable but not recommended
HR should be measured after each blood pressure reading
At least two measurements should be taken and averaged out
The result may vary according to the type of observer

HR, heart rate.

Out-of-office heart rate

Both HR and blood pressure are influenced by the doctor's visit and office measurement often overestimates the usual level of these haemodynamic variables with obvious diagnostic and therapeutic consequences [6]. Measuring blood pressure out of the office by ambulatory and self-measurement techniques is increasingly used in clinical practice. Both modalities proved to be of relevant clinical use as they provide prognostic information over and above office measurement. The same concept can be applied to HR and indeed recent studies have shown that ambulatory HR may have greater prognostic accuracy than office HR.

Self-measured heart rate

Little information is available on the relationship between home HR and adverse outcome. In the Ohasama study, Hozawa *et al.* [7] found a 17% increase in the risk of mortality for a 5-bpm increase in home HR, but that study failed to compare the predictive power of self-measured HR with that of clinic HR. The panel acknowledged the paucity of prognostic data, but felt that for hypertensive individuals who measure their blood pressure at home with automatic monitors, reporting of HR data together with blood

pressure may provide useful information. The measurement protocol should be the same as that recommended by the European Society of Hypertension guidelines for home blood pressure using a 7-day schedule [8]. HR should be measured four times per day, twice in the morning and twice in the evening. Although no comparative data for office versus home HR are available, results from the Ohasama study [7] suggest that home-measured HR is lower than office HR. In that study, the lower limit of the top HR quintile was 74 bpm for morning HR and was 75 bpm for evening HR.

Ambulatory heart rate

Recent data suggest that as for blood pressure, HR measured with ambulatory monitoring provides more meaningful clinical information than office measurement [9–11]. Among the ambulatory HRs, average night-time HR has shown a greater predictive value than daytime HR for cardiovascular events and mortality [9–11]. In addition ambulatory HR has been found to be more reproducible than office HR. In the Hypertension and Ambulatory Recording VEnetia STudy, a small decrease in average daytime (−1.0 bpm) and virtually no change of night-time HR (−0.3 bpm) were observed when two 24-h recordings were performed 3 months apart [12]. This attests to a negligible reaction when HR is measured with ambulatory monitoring and may account for the better prognostic value found for ambulatory than office measurement.

The aforementioned data suggest that intermittent HR measurement, which is provided by the oscillometric devices currently used for recording blood pressure non-invasively, is reliable and of clinical use and raise the issue of whether HR data should be included in the ambulatory blood pressure–monitoring report. It is opinion of the panel experts that ambulatory HR data should be used chiefly for research purposes. However, in patients with high HR in the doctor's office, ambulatory HR may provide additional useful information. HR recorded during the 24 h is probably more representative of the overall haemodynamic load on the arteries and the heart because it better reflects cumulative arterial injury from mechanical stress on the arterial wall. This is attested to also by the greater impact of ambulatory HR on target organ damage than office HR [13–16]. In these studies, nocturnal HR had a greater prognostic accuracy for outcome than diurnal HR.

RISK FACTOR OR RISK INDICATOR?

A large body of evidence indicates that high HR can be considered as an important determinant of atherosclerosis and a strong predictor of death from cardiovascular and non-cardiovascular causes. However, because of the complex interaction with other risk factors, it is still unclear whether HR should be considered a true risk factor for cardiovascular disease or simply a marker of autonomic imbalance. A large number of studies have shown that high HR is correlated with many other risk factors for atherosclerosis and cardiovascular events including high blood pressure, dyslipidemia, hyper-insulinemia, hyper-glycaemia, obesity and increased haematocrit [3]. Numerous studies have demonstrated that increased adrenergic tone may produce a state of insulin resistance via various mechanisms, which may account for the relationship between HR and the components of the insulin-resistance syndrome. However, in most studies of resting HR, the association with adverse outcome persisted when all other traditional risk factors were taken into account. In many studies also, a physical activity score, an index of physical fitness, indices of pulmonary function, level of haemoglobin and parameters derived from analysis of HR variability were included in the regression models. In all models, high HR remained an independent predictor of mortality or cardiovascular events. These analyses ruled out the possibility that the risk related to high HR was because of poor physical fitness or to some underlying chronic disease unrecognized at the time of baseline assessment. It should be pointed out that in many of those studies the predictive power of HR for mortality was higher than that of cholesterol and/or blood pressure and the clinical onset of cardiovascular disease was evaluated after a long period of observation of up to 20 years and over. The above considerations suggest that HR can be used to establish independent risk relations in different clinical settings including general populations, hypertension, diabetes, coronary artery disease and congestive heart failure [1,17,18]. The evidence was particularly strong in hypertension [18]. As of today, 12 studies conducted in hypertensive patients have been published (eight after the publication of the previous consensus document) and all invariably showed a positive association between resting HR and adverse outcome [19–30] (Table 2). A positive association with outcome has been found in one cohort study which enrolled participants with prehypertension [19] and five cohort studies which recruited participants with hypertension [20–22,25,30]. In the Glasgow Blood Pressure Clinic Study [25] a combination of baseline and follow-up HRs was evaluated. Hypertensive patients with a HR persistently >80 bpm had an increased risk of all-cause and cardiovascular mortality. The highest risk of all-cause mortality was found for a final HR of 81–90 bpm. An association between HR and mortality was found also in people with prehypertension. In the Atherosclerosis Risk in Communities study [19], prehypertensive individuals with HR of at least 80 bpm had 50% higher all-cause mortality rate than people with lower resting HR. Analysis of data, even though unrandomized, of six clinical trials in hypertensive patients provided consistent results [23,24,26–29]. Three trials were done in high-risk hypertensive individuals [27–29], one trial in elderly patients with systolic hypertension [23], one in hypertensive patients with coronary artery disease [24], and one in hypertensive patients with left ventricular hypertrophy [26]. In the Losartan Intervention for Endpoint Reduction (LIFE) study a 10-bpm increment in HR was associated with a 25% increased risk of cardiovascular mortality and a 27% greater risk of all-cause death [26]. Follow-up HR contributed additional prognostic information to baseline HR. Persistence or development of a HR of at least 84 bpm was associated with an 89% greater risk of cardiovascular death and a 97% increased risk of all-cause mortality. Also in the patients with hypertension and coronary artery disease from the INternational VErapamil-SR/trandolapril STudy (INVEST) [24], follow-up HR after treatment with atenolol

TABLE 2. Cohort studies and clinical trials showing the association of resting heart rate with adverse outcomes in prehypertension or hypertension

Study	Patient number	Age (years)	Follow-up length (years)	Type of study	Definition of tachycardia
ARIC [19]	3275	45–64	10	Cohort of prehypertensive patients	HR $\geq$ 80 bpm (arbitrary)
Framingham [20]	4530	Mean = 56	36	Cohort of hypertensive patients	No definition
French study (Benetos) [21][a]	19 386	Mean = 51.5	18	Cohort of hypertensive patients	No definition
French study (Thomas) [22][a]	60 343	Adult and elderly	14	Cohort of hypertensive patients	HR > 80 bpm (arbitrary)
Syst-Eur [23]	2293	Mean = 70	4	CT in elderly patients with ISH	HR $\geq$ 80 bpm (upper quintile)
INVEST [24]	22 192	Mean = 66	2.7	CT in hypertensive patients with CAD	No definition
Glasgow Clinic [25]	4065	Mean = 52	2.5	Cohort of hypertensive patients	HR >80 bpm (arbitrary)
LIFE [26]	9190	Mean = 67	5	CT in hypertensive patients with LVH	HR $\geq$ 84 bpm (upper quintile)
ASCOT [27]	12 159	Mean = 63	5	CT in high-risk hypertensive patients	No definition
VALUE [28]	15 193	Mean = 67	4	CT in high-risk hypertensive patients	HR of 79 bpm or more (upper quintile)
ONTARGET/TRANSCEND [29][a]	31 531	Mean = 66	5	CT in hypertensive patients with CVD	No definition[b]
Cooper Clinic [30][a]	53 322	Mean = 44	15	Cohort of hypertensive patients	HR > 80 bpm (arbitrary)

ARIC, Atherosclerosis Risk in Community; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial;bpm, beats per minute; CAD, coronary artery disease; CT, clinical trial; CVD, cardiovascular disease; HR, heart rate; INVEST, INternational VErapamil-SR/trandolapril Study; ISH, isolated systolic hypertension; LIFE, Losartan Intervention for Endpoint reduction in hypertension study; LVH, left ventricular hypertrophy; ONTARGET/TRANSCEND, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/ The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease; Syst-Eur, Systolic Hypertension in Europe; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.
[a]Data have been extrapolated from the subgroup with hypertension within the study population.
[b]In this study, the lower limit of the upper HR quintile was 79 bpm. The reference number is reported for each study.

or verapamil showed an even stronger association with outcome than baseline HR. Of particular interest are the results obtained in a recent analysis of the Valsartan Antihypertensive Long-term Use Evaluation study [28], in which patients were stratified according to whether they had high HR (top quintile) or lower HR during treatment and whether their blood pressure was controlled or not by antihypertensive treatment. The highest risk of the primary outcome was found in the patients with elevated HR and uncontrolled blood pressure. However, the risk also remained elevated in the patients with blood pressure well controlled by treatment but with persistently elevated HR. A much lower risk was found in the patients with blood pressure uncontrolled and a low HR. These results indicate that cardiovascular risk in hypertensive patients with tachycardia is lowered less effectively by antihypertensive treatment if their HR remains elevated. In conclusion, the data from the literature consistently demonstrated that resting HR is a potent risk factor for mortality and/or cardiovascular disease in hypertension. Generally, follow-up HR when available showed a better association with outcome than baseline HR.

An association with adverse cardiovascular outcome in hypertension was found also for ambulatory HR. In the hypertensive segment of the Ambulatory Blood Pressure-International (ABP-International) study, a large database including 7600 hypertensive patients from six countries, there was a significant 13% increase in risk of events for a 10-bpm increment of the night-time HR [9]. In this study, office HR was a weaker predictor of outcome than ambulatory HR. An association between night-time HR and cardiovascular and/or total mortality was found also in smaller studies [31]. Also blunted nocturnal HR decline was an independent predictor of cardiovascular events in hypertension [9,31–33] but in some studies the association did not remain significant when other variables were taken into account [9,33]. In the Systolic Hypertension in Europe study, the positive relationship between clinic HR and the incidence of fatal end points found in the main study was confirmed in the ambulatory monitoring subgroup, although ambulatory HR did not provide prognostic information over and above clinic heart rate [23]. Finally, in a prospective study of patients with resistant hypertension both slow HR (<60 bpm for clinic or <55 bpm for night-time HR) and fast HR (>75 bpm or >70 bpm, respectively) were associated with worse outcome in comparison with the reference group (60–75 bpm) [34]. Ambulatory HRs were more significant risk markers than office HR. Thus, in this study on resistant hypertension, there was a U-shaped relationship between HR and prognosis, particularly for HR measured with ambulatory monitoring.

It should be pointed out that in many studies, the association of HR with mortality persisted after excluding events occurring during the first years of follow-up (from 2 to 6 years), thereby weakening the possibility that a higher HR was the consequence or a symptom of an underlying disease [9,20,28,35]. In almost all studies performed on patients free of cardiac diseases, the relationship between HR and mortality was linear. In some studies, a flattening of the relationship was found in the individuals of the lower HR quintiles [21,22], but a real upturn in risk for a HR less than 60 bpm was reported only in a minority of studies [36–38]. In many studies, the association between HR and outcome was evaluated after a long period of observation being the follow-up length generally more than 5 years and in some studies even more than 20 years [20,39]. The association between HR and mortality appeared to be equally strong in patients with or without cardiovascular complications and persisted into old age [1,3,22,23,35]. The HR –mortality association was generally found to be stronger among men than women [40]. However, in an analysis of a very large cohort of postmenopausal women (N = 129 135), resting HR was a strong independent predictor of myocardial infarction and coronary death [41]. In almost all studies of resting HR, the association with outcome persisted when other risk factors and comorbid conditions were taken into account. In many studies also, a physical activity score, indexes of physical fitness, level of

haemoglobin and use of β-blockers were included in the survival models [1,30].

To confirm the clinical validity of an epidemiologic association in cardiovascular disease, there should be a pathogenetic plausibility for that association [42]. Plausibility for the HR-outcome association has been proved in a number of pathogenetic studies that have shown that not only is it a marker of sympathetic predominance of high HR but also has a direct detrimental effect on the arterial wall and target organs [43–45]. Animal studies have shown that HR reduction with cardiac-slowing drugs [46] or by ablation of the sino-atrial node [47] can retard the formation of atherosclerotic lesions in the coronary arteries. Tachycardia produces a chronic tensile stress on the arterial wall, which, in the long run, can facilitate the development of atherosclerotic lesions [43]. Changes in the direction of shear stress have been considered particularly important in this respect [48]. Tachycardia shortens the diastolic phase, and causes longer exposure to low endothelial shear stress [43,44]. This will promote vascular smooth muscle cell growth and collagen deposition facilitating the development of atherosclerosis and vascular stiffening. Indeed, an atrial pacing-induced HR increase has been shown to produce progressive reduction in carotid distensibility in rats [49]. This phenomenon was observed also in sympathectomized animals suggesting that arterial stiffening was independent from sympathetic activation [49]. An association between fast HR and large artery stiffness has also been documented in humans with either cross-sectional or longitudinal studies [45,50–52]. Vascular stiffness measured by pulse wave velocity correlates strongly with adverse events. In a recent meta-analysis of the usefulness of pulse wave velocity in predicting cardiovascular endpoints after adjustment for numerous confounders, the aortic pulse wave velocity continued to be a highly significant predictor of strokes, coronary artery disease and cardiovascular disease events [53]. In addition to this promoting arterial wall lesions high HR also facilitates the progression of an early atherosclerotic plaque to a high-risk vulnerable plaque. Minimum HR recorded during a 24-h period predicted the rate of progression of coronary atherosclerotic lesions in individuals with myocardial infarction [54]. In patients who underwent two coronary angiograms within 6 months, a high HR facilitated coronary plaque disruption [55]. HR is an important determinant of myocardial oxygen consumption and of blood flow supply to the coronary arteries. The energy expended by the heart is, in fact, used mainly to achieve isovolumetric ventricular contraction [56]. When the number of iso-volumetric contractions per unit time increases, cardiac work will obviously become uneconomical. As a consequence, high HR increases oxygen demand even when the external work performed by the heart is kept constant.

Tachycardia can facilitate arrhythmias and sudden death not only as a marker of increased sympathetic tone [57] but also directly: an elevated HR may facilitate de-synchronization of ventricular muscle cells, especially in an ischemic myocardium, increasing oxygen consumption and worsening coronary perfusion [58].

An elevated HR may also cause a direct cardiac damage. In different animal species, rapid pacing of either the atria or ventricles led to left ventricular dysfunction [59,60]. Morphologic changes in the left ventricle were characterized by apoptosis and loss of myocytes, increased collagen deposition and fibrosis with resultant increased wall stiffness [59–61].

Because of this body of evidence, some authorities have included elevated HR in their clinical scoring systems such as the Riskard in Italy [62], the Cooper Clinic scoring system in the United States [63] and the Finrisk Score in Finland [64].

Although the data from the literature provide firm support for the importance of HR in predicting the global cardiovascular risk of an individual, some concern still remains due to the fact that no study has yet proved that pharmacological HR reduction in non-cardiac patients can reduce the risk related to tachycardia. Despite this reservation, most members of the panel agreed that HR may be used to build risk classification models in hypertension and proposed that such a recommendation is included in future guidelines. There was some debate about how to incorporate HR into the stratification of the risk. One can use a method that quantifies the risk on a continuous basis, as done in the Riskard [62] and Finrisk [64] studies, or can incorporate it as a yes/no categorical variable as done in the Cooper Clinic scoring system [63]. The latter method implies the identification of a cut-off level for defining high HR, an issue that will be discussed in the next section.

DEFINITION OF TACHYCARDIA AS A CARDIOVASCULAR RISK FACTOR

Despite the abundant evidence about the clinical importance of resting HR, some doubts remain about the clinical utility of this variable because of the difficulty to identify a threshold level between normal and high HR. This problem is common to all risk factors whose relationship with outcome is a continuous one because the partition level between normal and abnormal values has to be defined according to arbitrary criteria. For blood pressure, the 140/90 mmHg level was chosen to define hypertension, but it should be borne in mind that this cut-off was established with arbitrary criteria by a panel of WHO experts and that it roughly corresponded to the lower limit of the highest quintile of the blood pressure distribution in industrialized countries [42].

In textbooks, tachycardia is currently defined as a HR more than 100 bpm [65]. Although this level may be considered useful as a marker of disease, from an epidemiological standpoint a considerable increase in the risk of cardiovascular diseases was present for HRs well below the 100 bpm threshold. An attempt to redefine the normal limits of resting HR was made by adding 2 SD to the mean HR value of a given population [66]. However, using this approach 93–95 bpm cut-off levels were obtained which still do not seem to be clinically useful. In addition, this approach implies the existence of a normal distribution for HR in general or hypertensive populations whereas this is not the case for many populations [67]. Most epidemiological studies found a significant increase in risk for a HR of 75–85 bpm or more either in general or hypertensive populations. In the majority of those studies, individuals were said to have tachycardia if they belonged to the top

quintile of the HR distribution whereas in others the cut-off was chosen arbitrarily on the basis of previously published data. In the studies performed in hypertensive patients, the threshold level used for defining high HR was between 79 and 84 bpm (Table 2). In three studies, it corresponded to the lower level of the top HR quintile [23,26,28] and in four studies it was established according to arbitrary criteria [19,22,25,30]. In the four studies [22,23,26,28] in which the group with tachycardia was compared with the rest of the population (yes/no variable), the increase in risk of all-cause mortality ranged from 20% [95% confidence interval (CI): 15%–25%] in the Valsartan Antihypertensive Long-term Use Evaluation study to 89% (95% CI: 33%–168%) in the Systolic Hypertension in Europe study. In the three studies [19,25,30] in which the group with lowest HR was taken as the reference, the increase in risk associated with tachycardia ranged from 38% (95% CI: 21%–58%) in the Cooper Clinic study to 47% (95% CI: 2%–114%) in the Atherosclerosis Risk in Communities study.

The cut-off level used in the above epidemiologic studies is in agreement with the results obtained in one hypertensive and two general populations with mixture analysis [67]. Mixture analysis is an objective statistical method for identifying within a heterogeneous population two or more subpopulations with normal distribution of the variable under study [68]. According to this method, the cut-off between persons with normal HR and those with tachycardia was between 80 and 85 bpm in the various populations examined [67].

The best approach for defining the upper normal limit of a clinical variable would be to identify the level at which the benefits of treatment outweigh the risks. Unfortunately, no clinical trial has been implemented as yet in hypertension to study the effects of cardiac slowing drugs on morbidity and mortality. The only available data on the effect of HR reduction in humans can be derived from retrospective analyses of patients with myocardial infarction or congestive heart failure [69,70]. Carvedilol has shown beneficial effects in individuals with congestive heart failure but the mortality advantage was clear only in patients with a HR more than 82 bpm [71]. Data obtained with the I/f-channel antagonist ivabradine in patients with congestive heart failure have been inconclusive, though there is some indication that the beneficial effect of this drug can be obtained in patients with HR higher than 70–75 bpm [72–74]. However, it should be noted that ivabradine was almost always given to patients already taking β-blockers and thus the original HR of those patients before β-blockade was likely to be much higher.

Clearly, these results cannot be transferred to patients with hypertension. The panel acknowledges the lack of data and thus cannot suggest an objective cut-off level for the definition of tachycardia in hypertension. However, there was consensus among the members that the traditional 100 bpm value is not appropriate to define the threshold below which HR can be considered normal, because virtually all epidemiologic studies and clinical trials indicated that the risk is elevated for values well below that level. For example, in the aforementioned Cooper Clinic Study [63] having a HR $>$ 80 bpm was associated with a risk of mortality similar to that of having hypertension (blood pressure $\geq$ 140/90 mmHg).

SHOULD TACHYCARDIA BE A TARGET FOR TREATMENT IN HYPERTENSION OR INFLUENCE DRUG CHOICE?

As discussed in the aforementioned sections, HR proved to be a powerful predictor of cardiovascular or all-cause mortality in hypertension, an association as strong as that of other well recognized risk factors for cardiovascular disease. Elevated HR is a common feature in patients with hypertension. In both the Hypertension and Ambulatory Recording VEnetia STudy [75] and the Tensiopulse study [76] about 30% of the hypertensive patients had a resting HR of 80 bpm or more. Thus, there is a large segment of the hypertensive population that could benefit from a treatment able to decrease a high HR. However, the role of β-blockers, particularly of atenolol, as first line therapy for the treatment of hypertension has recently been called into question even in patients with elevated HR [77]. In the Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA) study, the authors found no evidence that the superiority of amlodipine-based therapy over atenolol-based therapy for patients with hypertension uncomplicated by coronary artery disease was attenuated with higher baseline HR [27]. Even more challenging is the recent meta-analysis by Bangalore *et al.* of patients with hypertension from nine large β-blocker trials, which showed that a lower HR achieved from β-blockade compared with other antihypertensives or placebo was associated with an increase in all-cause mortality, cardiovascular mortality, myocardial infarction, stroke and heart failure [78]. However, a careful and critical analysis of those studies may lead to opposite conclusions. The analysis by Bangalore *et al.* was based on aggregate data coming essentially from three large studies, ASCOT, INVEST and LIFE which enrolled over 51 000 of the 68 640 patients included in the nine studies [78]. The results obtained within each of these three studies, based on an individual relationship between posttreatment HR and outcomes are totally in contrast with the aggregate results of the Bangalore *et al.* meta-analysis. In the ASCOT-BPLA study, after 6 weeks of treatment with atenolol-based or amlodipine-based therapy, there was a significant association of HR with future myocardial infarction and fatal coronary outcome [27]. In the INVEST study, in-trial HR calculated as the mean of all measurements after treatment with atenolol or verapamil showed a strong association with the primary composite endpoint [24]. In the LIFE study, persistence or development of a HR 84 bpm or more after treatment with losartan or atenolol was associated with an 89% greater risk of cardiovascular death and a 97% increased risk of all-cause mortality [26]. Thus, if these studies were examined on an individual basis rather than on aggregate data they would show that a low HR achieved after treatment (lower on β-blocker) actually had a favourable effect on cardiovascular outcomes. It should also be pointed out that in these studies HR was measured with different methods (pulse palpation in INVEST, electrocardiogram in LIFE, a semiautomatic device in ASCOT-BPLA).

HR measurement with automatic monitors elicits a smaller alarm reaction than measurement by a doctor or a nurse. Thus, using aggregate data obtained with different methods of measurement in a meta-analysis appears inappropriate. The above considerations suggest that the results of a meta-analysis may be misleading unless they are supported by data drawn from individually based analyses made within each of the studies taken into account.

Admittedly, all members of the panel were frustrated by the reality that no results from randomized clinical trials are available making it difficult to provide treatment recommendations. As mentioned earlier, the effect of pharmacological HR lowering in hypertensive patients has been evaluated only in retrospective analyses in which randomization is lost. Although the results of INVEST and other studies look promising they should be confirmed by interventional randomized clinical trials in hypertensive patients with tachycardia. Two different types of protocol could be used for this purpose:first, two different antihypertensive treatments, one with HR lowering properties and one with neutral effect on HR, could be compared. However, with this approach, a between-treatment difference in blood pressure is likely to occur, and it would be difficult to know whether the between-treatment difference in outcome is due to the difference in blood pressure or in HR. Second, A better alternative would be to use the same antihypertensive treatment in both arms and to randomize one arm to an I/f-channel blocker and one to placebo. Hypertensive patients with fast HR and a high cardiovascular risk profile would be appropriate candidates for this study. Patients who qualify should undergo titration of antihypertensive medication prior to receiving placebo or the I/f inhibitor in order to achieve the target blood pressure (<140 and 90 mmHg). As an alternative one could choose a surrogate endpoint, such as large artery stiffness and/or albuminuria, as the outcome variable. This would allow a much shorter period of follow-up to detect a treatment effect, but would obviously provide a much weaker evidence.

PRACTICAL APPROACH TO THE PATIENT WITH TACHYCARDIA

When facing a hypertensive patient with high HR, the clinician should first investigate if he or she is anaemic or has an underlying chronic clinical condition such as incipient heart failure (Table 3). Once a secondary cause of tachycardia is excluded, the first goal should be to improve an unhealthy lifestyle. Sedentary habits, smoking, excessive alcohol consumption and heavy coffee use increase the sympathetic activity with consequent effects on resting HR. Aerobic exercise is the most investigated and recommended life-style modification for management of early phases of hypertension [79]. Regular endurance exercise causes a reduction of sympathetic activity and an increase of vagal tone with beneficial effects on both blood pressure and HR. Although to decrease blood pressure a low-to-moderate exercise intensity seems to be sufficient, the HR reduction seems to be proportional to the intensity of exercise [80]. The American College of Sports Medicine recommends that moderate-to-vigorous activities should be practiced by most healthy adults [81], but low-intensity exercise may be a safer option for hypertensive patients chiefly for people at high cardiovascular risk. A dietary intervention aiming at weight control and including decreased alcohol and coffee consumption should be implemented.

TABLE 3. Practical approach to the patient with high resting heart rate

For patients who measure their blood pressure at home, reporting of self-measured HR is suggested
The self-measurement protocol should be the same as that recommended by the ESH guidelines for home blood pressure measurement
For patients with high HR in the doctor's office, ambulatory HR may provide additional useful information
Patient's assessment should include a search for a secondary cause of tachycardia
Once a secondary cause is excluded improvement of an unhealthy lifestyle is recommended
Life-style modifications should include a programme of physical activity, smoking cessation, and avoidance of excessive alcohol consumption and heavy coffee use
A dietary intervention aiming at weight control should also be implemented
In symptomatic patients treatment with a cardiac slowing drug (mostly β-1 selective β-blockers) should be considered

ESH, European Society of Hypertension; HR, heart rate.

The panel experts concluded that there is convincing evidence that HR is an important risk factor for cardiovascular disease and that HR measurement should always be included in the overall assessment of the hypertensive patient (Table 4). In most studies of hypertension, HR was considered to be elevated when it was higher than 80–85 bpm. However, the panellists acknowledged that in the absence of convincing data any threshold used to define tachycardia is arbitrary. They also admitted their inability to make practical therapeutic suggestions for the hypertensive patients with high HR. However, it should be kept in mind that absence of evidence does not mean evidence against the importance of tachycardia as a risk factor for cardiovascular disease and that long-term exposure to a potentially important risk factor may impair the patient's prognosis. It appears obvious that in the absence of clinical trials some degree of uncertainty and flexibility with management is expected and the panellists remark that, in hypertensive patients with symptomatic tachycardia there is no evidence that reducing HR by available drugs (mostly β-1 selective β-blockers) would be unsafe. The panellists unanimously made a plea for the implementation of a study that may shed light on this controversial issue. One main aim of this document is to alert researchers and physicians

TABLE 4. Conclusions

High HR is an important risk factor for cardiovascular disease
HR measurement should be included in the overall assessment of the hypertensive patient
HR might be included in future risk charts of international guidelines
In most studies HR was considered to be elevated when it was higher than 80–85 bpm. However, in the absence of objective data any threshold used to define tachycardia remains arbitrary
Lack of evidence makes it difficult to make practical therapeutic suggestions for the hypertensive patient with high HR. However, some degree of flexibility with management is expected and in symptomatic tachycardia HR reduction by available drugs (mostly β-1 selective β-blockers) should be considered
The panellists unanimously made a plea for the implementation of a randomized clinical trial aiming at evaluating the effects of HR reduction in hypertensive patients with high HR

HR, heart rate.

about the importance of measuring HR in hypertensive patients. The present report should be meant as a focal point for robust discussion at national and international conferences in hypertension and for stimulating future investigations.

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Conflicts of interest

There are no conflicts of interest.

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