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# Treatment of Hypertension: Which Goal for Which Patient?

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**Abstract**

Hypertension remains the most important risk factor for cardiovascular disease. If antihypertensive drugs choice is well guided today, blood pressure (BP) target still a subject of controversies. Residual risk is matter of debate and the lower- the better dogma is come back again regarding to data reported from recent trials. The J curve, reason for European Society of Hypertension Guidelines reappraisal in 2009, is criticized by recent data. The one goal (<140/90 mmHg) fit 90 mmg 90 mmHg) fit all should be adapted as a personalized goal guided by evidence generated by randomized controlled trials. Target controversy is back because of the results of ACCORD and SPRINT trials challenging the common systolic BP target less 140 mmHg to less than 120 mmHg. The first was performed in diabetic patients and the second in patients at high cardiovascular risk; elderly aged of 75 years and above, or patients with chronic kidney disease, or with pre-existing subclinical or clinical cardiovascular disease or a Framingham 10-year cardiovascular disease risk score of 15 % or above, however non diabetic. If the first trial was negative, SPRINT reports a huge reduction of the composite primary outcome, which included myocardial infarction, other acute coronary syndromes, stroke, heart failure or death from cardiovascular causes by 25 %, and the risk of death from all causes by 27 %, when target systolic BP is lower than 120 mmHg compared to lower than 140 mmHg. However, BP was measured by automated office BP technique which correlates more with home BP measurement than auscultatory office BP measurement. Also, only significant less heart failure in the intensive arm was driving the difference in mortality favoring the intensive arm in SPRINT. The greater use of diuretics may have

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demasked latent heart failure in hypertensive patients with rather high cardiovascular risk.

More convincing data suggest that BP should be diagnosed early and treatment should be started at BP level of 140 mmHg and above, based on an office BP measurement, confirmed by an out-of-office BP measurement. Target systolic BP should be less than 140 mmHg if BP is measured by classic auscultatory method, less than 120 mmHg in high risk patients if BP is measured by automated office BP measurement. These targets are relevant in elderly patients if no orthostatic hypotension occurred, patients with non proteinuric chronic kidney disease (eGFR $<$ 60 ml/mn/1.73 $m^2$) and patients with cardiovascular disease or a Framingham score more than 15 %. However attention should be taken on diastolic BP if lower than 70 mmHg because of an increasing risk of ischemic heart event and on renal function since acute renal failure is more frequently reported at these low targets.

In diabetic patients, SBP target should be less than 140 mmHg according to ACCORD trial. However, for patients with protein-creatinine ratio $>$500 mg/g (albumin-creatinine ratio $>$ 300 mg/g), with or without diabetes, lower SBP target should be proposed for renal protection aiming SBP $<$ 130 mmHg as recommended by KDIGO guidelines.

In patients at low or intermediate risk, without cardiovascular disease, SBP should start to be treated when SBP is above 140 mmHg, and when treated, target BP should be less than 140 mmHg as reported by HOPE-3 trial.

**Keywords**

Hypertension in the diabetics • Hypertension in the elderly • Blood pressure goals • Hypertension and cardiovascular prevention • Hypertension and microvascular complications • SPRINT trial • ACCORD trial • Ambulatory blood pressure measurement

## 1 Introduction

Cardiovascular diseases are a worldwide leading cause of mortality and morbidity, even in most developing countries, as Tunisia, where cardiovascular mortality is the leader, accounting for about 29 % causes of deaths (Hajem and Hsairi 2013). Hypertension remains the most important risk factor. According to the recently published global, regional and national comparative risk assessment of 79 behavioral, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, (GBD 2013 Risk Factors Collaborators 2015), high systolic blood pressure (BP) accounted for 6.9 million deaths in 1990 and 10.4 million deaths in 2013 with a 49.1 % progression and 208.1 million DALYs (disability-adjusted life-years) in 2013. This data contrast with the emergence of many treatment choices for hypertension in the last three decades, reflecting the magnitude of this clinical problem and highlighting that the treatment of hypertension remains difficult.

If BP was measured since eighteenth century by Stephen Hales (Lewis 1994), we have to wait for the contribution of the Framingham Heart Study to recognize that high BP is an eminent cardiovascular risk factor (Kannel et al. 1961). The Veterans Administration Cooperative Study on Antihypertensive Agents was the first study

demonstrating in 1967 the benefit of BP reduction ([no authors listed] 1967). It included men with diastolic BP (DBP) of 115–129 mmHg. The treatment, including hydrochlorothiazide, reserpine and hydralazine hydrochloride, caused a remarkable average BP reduction of systolic/diastolic (SBP/DBP) by 43/30 mmHg in the active treatment arm. This reduction resulted in a reduction of cardiovascular events after only 11 months follow-up, with 21 fatal or morbid events in placebo arm as opposed to one event in the active treatment arm. The study was therefore stopped prematurely. The second larger Veterans Administration Cooperative Study conducted in patients with milder hypertension (HTN) confirmed the effect of BP control on stroke and congestive heart failure occurrence ([no authors listed] 1970). From then on, several questions were raised: what is the definition of HTN? at which level of BP should one start to treat? and down to which level should BP be reduced to obtain the highest protective effect?

## 2 Definition of Hypertension

The best definition of HTN at a personnel point of view was given by G. Rose (1980); indeed, hypertension is the level of arterial BP at which the benefits of intervention exceed those of inaction. However, it is difficult to translate this definition to the daily practice, there is a need for a numerical definition. Earlier in 1980s and early 1990s the definition of HTN was BP > 160/95 mmHg, up to 1993 where the definition of HTN was reduced to a level equal or above 140/90 mmHg. This definition still adopted nowadays by all guidelines.

The definition of HTN relates an attributable risk to a BP level. In most populations and age groups, there is a linearly relationship between systolic blood pressure (SBP) and risk of cardiovascular mortality, cardiovascular events and strokes. Among patients younger than 65 years, there is a progressive increase in the risk of stroke and coronary artery disease with a parallel increase in SBP. Increasing risk is, however, not equivalent for DBP. For the population of 65 years old and above, the risk continues to increase with the increase of SBP, however, a reversal occurs with the DBP where the risk of cardiovascular events increases with the rise of DBP but also with the fall of it, showing a J curve (Neaton and Wentworth 1992).

The Multiple Risk Factor Intervention Trial (MRFIT) assessed the combined influence of BP, serum cholesterol level, and cigarette smoking on death from coronary heart disease (CHD) for 316,099 men screened in whom 6327 deaths from CHD have been identified after an average follow-up of 12 years. Strong graded relationships between SBP above 110 mmHg, and DBP above 70 mmHg and mortality due to CHD were evident. SBP was a stronger predictor than DBP; however, the greater risk was attributed to the highest SBP (≥160 mmHg) and the lowest DBP (<70 mmHg) highlighting the pulse pressure as a powerful actor in this coronary artery disease related death risk (Neaton and Wentworth 1992). The definition of HTN based on DBP in the 1960s was therefore not justified. However all current guidelines define HTN without focusing on the non linearity of the risk attributed to DBP with a fixed SBP level.

In Joint National Committee 7 guidelines (Chobanian et al. 2003) and ESH 2007 guidelines (ESH-ESC Task Force on the Management of Arterial Hypertension 2007) was introduced the terms of Pre-Hypertension (BP 120–139/80–89 mmHg) and High-normal BP (BP 130–139/85–90 mmHg) respectively. In fact, a stepwise increase in cardiovascular event rates was noted in persons with higher baseline blood-pressure categories.

The Framingham Heart Study investigated 6859 subjects, 35–64 years of age, free from cardiovascular disease and HTN (Vasan et al. 2001). As compared with optimal BP (<120/80 mmHg), high-normal BP (130–139/85–89 mmHg) was associated with a risk-factor–adjusted hazard ratio for cardiovascular disease of 2.5 (95 % CI, 1.6–4.1) in women and 1.6 (95 % CI, 1.1–2.2) in men. However, the 10-year cumulative incidence of cardiovascular disease was lower in younger individuals; 4 %

for women and 8 % for men; than in older subjects (those from 65 to 90 years old), the incidence was 18 % for women and 25 % for men.

These data should make HTN definition change to 130/85 mmHg or even lower, however; there is a need for data showing that reduction of BP from 130 to less than 120 mmHg for SBP will induce a reduction of cardiovascular events. Also, the definition of HTN takes in account the economic challenge of BP reduction from 140/90 to 130/85 mmHg; even if controlling BP with medication is unquestionably one of the most cost-effective methods of reducing premature cardiovascular morbidity and mortality (Elliott 2003). This evidence has many limits since BP reduction by treatment should reduce the risk of development of renal, cerebral and cardiovascular diseases to validate starting treatment at the level of which risk is increased.

## 3 Impact of Blood Pressure Control

An increasing number of trials have provided evidence that antihypertensive therapy to attain BP control provides a relative cardiovascular protection. The best evidence was shown by trials reporting BP reduction with antihypertensive treatment compared to placebo or no antihypertensive treatment. The last on date was HYVET trial including 3845 patients aged 80 or older who were randomized to active treatments or placebo without antihypertensive medications (Beckett et al. 2008).

According to the intention-to-treat analysis and as compared to the baseline value 173.0/90.8 mmHg, SBP/DBP values obtained while the patient was seated had fallen by a mean of 14.5 ± 18.5/6.8 ± 10.5 mmHg in the placebo group and by 29.5 ± 15.4/12.9 ± 9.5 mmHg in the active-treatment group at 2 years. This reduction of SBP/DBP by active treatment was associated with a 30 % reduction in the rate of fatal or nonfatal stroke (p: 0.06), a 39 % reduction in the rate of death from stroke (p: 0.05), a 21 % reduction in the rate of death from any cause (p: 0.02), a 23 % reduction in the rate of death from cardiovascular causes (p: 0.06), and a 64 % reduction in the rate of heart failure ($p < 0.001$).

A meta-analysis including 11 randomized controlled trials and 67,475 individuals compared antihypertensive therapy with placebo and aimed to investigate whether the benefits of BP-lowering drugs are proportional to baseline cardiovascular risk. Patients were risk stratified according to their estimated 5-year risk of having a major cardiovascular event. Lowering BP provides similar relative protection at all levels of baseline cardiovascular risk, but progressively greater absolute risk reductions were obtained when baseline risk increases, yielding to a possible benefit for more intense BP reduction in high risk patients (Blood Pressure Lowering Treatment Trialists' Collaboration 2014).

More recently, Thomopoulos et al. (2014) reported a meta-analysis on the effects at different baseline and achieved blood pressure levels on cardiovascular disease. Results of this meta-analysis favor BP-lowering treatment even in grade 1 hypertension at low-to-moderate risk, and lowering SBP/DBP to less than 140/90 mmHg. Achieving less than 130/80 mmHg appears safe, but only adds further significant reduction in stroke and all-cause death. Is it important to achieve earlier BP target on the occurrence of cardiovascular outcomes?. A response strand was generated by the VALUE Trial. This study (Julius et al. 2004) compared the effect on cardiovascular morbidity and mortality of a calcium channel blocker based strategy versus an angiotensin II receptor blocker based strategy in a high cardiovascular risk population. An unexpected equivalence between the two strategies was reported. The result was explained, in part, by a significantly better earlier BP control achieved in the amlodipine group. In fact, after the first month of treatment, SBP is on average 4 mmHg lower, DBP by 2.1 mmHg lower ($p < 0.0001$). A respective difference of 2 and 1.6 mmHg persists after the sixth month until the end of the study ($p < 0.001$).

It is so clearly proved that control of BP results in saving lives and reducing cardiovascular death and events. The debate becomes down to which level BP should be dropped?

## 4 Is the Lower the Better? – The Dogma of J Curve

Observational studies show a direct linear relationship between SBP/DBP values as low as 115–110 and 75–70 mmH respectively, and cardiovascular events, without evidence within this range of a J curve phenomenon. The Prospective Studies Collaboration (Lewington et al. 2002) performed a meta-analysis including one million adults from 61 prospective trials. Authors reported that within each decade of age at death, the proportional difference in the risk of vascular death associated with a given absolute difference in usual BP is about the same down to at least 115 mmHg usual SBP and 75 mmHg usual DBP, below which there is little evidence.

At ages 40–69 years, each difference of 20 mm Hg usual SBP is associated with more than a twofold difference in the stroke death rate, and with twofold differences in the death rates from ischemic heart disease and from other vascular causes.

So, evidence that achieving lower BP targets by treatment may enhance protection in hypertensive patients at higher risk, yielded ESH/ESC task force (for the management of arterial hypertension- 2007guidelines) to suggest that target BP should be at least <130/80 mmHg in diabetics and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria) (ESH-ESC Task Force on the Management of Arterial Hypertension 2007).

The evidence available on the BP targets of antihypertensive treatment has been reviewed by Zanchetti et al. (2009). In uncomplicated hypertensive patients, SBP reduced to less than 140 mmHg with active treatment was associated with a difference in outcome. This evidence supports the recommendation of guidelines to reduce SBP to less than 140 mmHg in the general population of patients with grade 1 or 2 hypertension and low or moderate total cardiovascular risk. However, for the elderly hypertensive patients, these authors reported no trial evidence in support of the guidelines recommendation to adopt the less than 140 mmHg SBP target in this population suggesting a target SBP of less than 150 mmHg.

When considering diabetic patients, lower BP goal less than 130/80 mmHg is also not supported by incontrovertible trial evidence. Even if HOT (Hansson et al. 1998) and Syst-Eur (Tuomilehto et al. 1999) trials, reported a greater absolute reduction of cardiovascular outcomes for a small BP difference in diabetic but not in nondiabetic hypertensive patients, these data were not confirmed by ACCORD trial (ACCORD Study Group 2010). This landmark trial in diabetic population tested a strict BP control (SBP less than 120 mmHg) compared to a standard target (SBP less than 140 mmHg) on the primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes). The only benefit reported was significant fewer strokes, but counterbalanced by a significant high level of serious adverse events as hypotension and fall of eGFR to less than 30 ml/mn/1.73 $m^2$.

STENO-2 trial showed a significant reduction of microvascular complications 8 years and all cardiovascular events 13 years after study start with an intense treatment strategy including a BP < 130/80 mmHg versus less strict strategy with a standard BP goal of 130–139 mmHg in type 2 diabetic patients with microalbuminuria (Gaede et al. 2003, 2008). However, the positive results attributed to the intense strategy cannot be directly attributed to a strict BP target, since the two groups were not comparable elsewhere. This study however, highlights the importance of a combined optimal strategy to reduce cardiovascular and microvascular events in type 2 diabetes.

Out of cardiovascular prevention, there are solid data regarding the benefits of a SBP target less than 130 mmHg when considering diabetic

patients with proteinuria aiming to reduce renal events (end stage renal disease). The meta analysis of Bakris et al. (2000) considering type 2 diabetic patients with proteinuria reported less estimated glomerular filtration rate loss (eGFR) when BP is under 130/85 than at 140/90 mmHg. In type 2 diabetic patients without proteinuria, however, no evidence was reported by ACCORD trial (ACCORD study Group 2010).

The Kidney Disease Improving Global Outcome KDIGO clinical practice guideline for the management of BP in chronic kidney disease outlined the strict target of BP < 130/80 mmHg only in patients with abnormal albumin excretion rate, meaning those with microalbuminuria or A2 category as defined by urine albumin-creatinine ratio more than 30 mg/g or A3 category (severely increased) as defined by urine albumin-creatinine ratio above 300 mg/g or Protein-creatinine ratio above 500 mg/g, with or without diabetes (Kidney Disease: Improving GlobalOutcomes (KDIGO) Blood Pressure Work Group 2012). However, since microalbuminuria is also a marker of vascular damage, defining target BP based on the presence of microalbuminuria should consider the presence of subclinical coronary heart disease (Jarraya et al. 2013).

In diabetic patients with coronary heart disease, as for those without diabetes, no evidence have been reported for a better cardiovascular outcome with a tight control of BP (<130 mmHg) versus usual control (130–139 mmHg). However, patients with uncontrolled HTN develop more cardiovascular events. In the 6400 type 2 diabetes patients with coronary artery disease of the INVEST trial, patients who achieved SBP of 130–140 mmHg had better outcome than those with value >140 mmHg. However, there is no additional benefit observed in the group achieving target SBP <130 mmHg (Cooper-DeHoff et al. 2010).

Moreover, this INVEST trial reported evidence of J curve, not for stroke, but for coronary events with a nadir DBP of 70 mmHg, compromising coronary blood flow at diastolic phase, in patients with already narrowing coronary arteries by atheroma reducing blood flow (Messerli et al. 2006).

The irbesartan Diabetic Nephropathy Trial (IDNT) included diabetic patients with proteinuric diabetic nephroipathy. The primary end point included doubling of serum creatinine, development of end stage renal disease or death. It was significantly reduced by an ARB, irbesartan than a calcium channel blocker, amlodipine, although BP was similarly reduced (Lewis et al. 2001). Investigating independent and additive impact of BP control on renal outcomes in the IDNT trial, Pohl et al reported a linear relationship between SBP and development of renal endpoint (end stage renal disease or doubling of serum creatinine), without a nadir down to less than 121 mmHg. However, for the same patients, reduction of SBP was associated with an increase in the relative risk of death when SBP <121 mmHg, showing a J curve (Pohl et al. 2005).

In general, the benefits of increasingly intensive therapy must be weighed against the potentially increased incidence of serious side effects associated with such a regimen, as the acute reduction of eGFR reported in ACCORD trial with a significantly more hypotension in the intensive BP lowering arm. (ACCORD Study Group et al. 2010).

As far as goals of treatment are concerned, the 2009 ESH guidelines update document recommends that SBP pressure should be lowered below 140 mmHg (and DBP below 90 mmHg) in all hypertensive patients, irrespective of their grade of risk (Mancia et al. 2009). On the basis of the results of clinical studies, it is advisable to lower BP to values within the range 130–139 mmHg for systolic and 80–85 mmHg for diastolic as recommended by the French Society of Hypertention (SFHTA) in their 2013 guidelines on hypertension (Blacher et al. 2013). Thus, it appears by this reappraisal, that the concept of lower BP goals, to be pursued in diabetics or very high risk patients, is no longer recommended because there is no evidence from trials of a greater benefit, nor can the procedure be regarded as easily achievable in current clinical practice.

The update document of guideline underlines the so-called "J-curve phenomenon" related to an increase rather than a reduction in the incidence of coronary events when BP values are below

120–125 for systolic and 70–75 for diastolic. It suggests not to lower blood pressure values too much, particularly in patients with a history of a previous coronary event. This recommendation was confirmed and adopted in the 2013 ESH/ESC guidelines (Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology 2013).

## 5 SPRINT Guided Goal of BP on Treatment: The Lower the Better Finally Approved?

After the failing of ACCORD (ACCORD Study Group 2010) to validate low BP target for diabetic patients, the Systolic Blood Pressure Intervention Trial (SPRINT) aimed to challenge the SBP target less than 120 mmHg versus usual SBP target less than 140 mmHg in patients with a high cardiovascular risk (SPRINT Research Group et al. 2015). This study excludes diabetic patients already tested in ACCORD trial, patients with polycystic kidney disease investigated in the HALT Progression of Polycystic Kidney Disease Study (Schrier et al. 2014), patients with excessive proteinuria >1 g/24 h already investigated in MDRD trial and REIN trial (Peterson et al. 1995; Ruggenenti et al. 2005) and patients who already developed a stroke investigated in the Secondary Prevention of Small Sub-cortical Strokes 5PS3 trial (The SPS3 Study Group 2013) and also tested in the ESH-CHL-SHOT trial (Zanchetti et al. 2016).

SPRINT (SPRINT Research Group et al. 2015) is the largest study that tested how maintaining SBP at a lower level than currently recommended will impact mortality, cardiovascular and kidney diseases. It enrolled 9361 participants aged 50 years and older in about 100 medical centers and clinical practices throughout the USA and Puerto Rico from 2009 to 2013.

The study population included 2636 elderly aged of 75 years and above, 2646 patients with chronic kidney disease as defined by an eGFR rate < 60 ml/min/1.73 $m^2$ and 1877 patients with pre-existing subclinical or clinical cardiovascular disease or a Framingham 10-year cardiovascular disease risk score of 15 % or above. This study included also about 35 % female 29.9 % black and 10.5 % Hispanic.

The study participants were randomly allocated into two groups. The standard treatment group received an average of 1.8 BP medications to achieve a target of less than 140 mmHg; the intensive treatment group received an average of 2.8 BP medications to achieve a target of less than 120 mmHg.

SPRINT results were awaited for 2018, but the significant preliminary results were announced on September 11, 2015 (National Heart, Lung, and Blood Institute 2015). The intensive intervention, that achieves a target SBP of 120 mmHg, reduced the rate of the composite primary outcome, which included myocardial infarction, other acute coronary syndromes, stroke, heart failure or death from cardiovascular causes by 25 %, and the risk of death from all causes by 27 %, compared to the target SBP of less than 140 mmHg.

Results were largely mediated and commented by medical journals (Kjeldsen et al. 2016a; Taler 2016; Cohen and Townsend 2016; Nilsson 2016) but also media such as *New York Times* (2015) that headed "lower blood pressure guidelines could be lifesaving".

These results were supported by the conclusions of two meta-analyses. The first pooled data from SPRINT and ACCORD trials and showed that the primary endpoint still in favor of BP reduction <120/80 mmHg (Perkovic and Rodgers 2015). The meta-analysis by Xie et al. (2016) included randomized controlled trials with at least 6 months' follow-up that randomly assigned participants to more intensive versus less intensive BP-lowering treatment, with different BP targets or different BP changes from baseline. It showed that after randomization, patients in the more intensive BP-lowering treatment group had mean BP levels of 133/76 mm Hg, compared with 140/81 mm Hg in the less intensive treatment group. Intensive BP lowering treatment achieved relative risk reductions for

major cardiovascular events (14 % [95 % CI 4–22]), myocardial infarction (13 % [0–24]), stroke (22 % [10–32]), albuminuria (10 % [3–16]), and retinopathy progression (19 % [0–34]), but without effects on heart failure (15 % [−11 to 34]), cardiovascular death (9 % [−11 to 26]), total mortality (9 % [−3 to 19]), or end-stage kidney disease (10 % [−6 to 23]). Severe hypotension was more frequent in the more intensive treatment regimen (RR 2.68 [1.21–5.89], p = 0.015), but the absolute excess was small (0.3 % *vs* 0.1 % per person-year for the duration of follow-up).

Furthermore, recent analyses of BP targets in two large outcome trials, VALUE (Kjeldsen et al. 2016b) and ONTARGET (Verdecchia et al. 2015), have refuted the concept of increase of cardiovascular events when BP is lower than we usually accept during treatment of HTN. However, the major benefit is achieved with BP control less than 140/90 mmHg, while there is only some limited additional stroke protection with consistent BP control less than 130/80 mmHg (Mancia et al. 2016).

The SPRINT trial failed to show significant reduction in stroke, acute coronary syndrome or myocardial infarction that composed the primary outcome, unlike heart failure which was significantly reduced by 43 % (p 0.002). Less heart failure in the intensive arm was driving the difference in mortality favoring the intensive arm in SPRINT. Patients included in intensive arm were up-titrated in BP medication and received one more antihypertensive drug frequently a diuretic. A thiazide-type diuretic was prescribed for 54.9 versus 33.3 % and aldosterone antagonists for 8.7 versus 4 % patients, respectively in the intense and the usual arm. The greater use of diuretics may have demasked latent heart failure in hypertensive patients with rather high cardiovascular risk (Thoma et al. 2016).

The earlier stop of SPRINT trial than originally planned by the director of the National Heart, Lung and Blood Institute (NHLBI) based on the recommendation of the Data Safety Monitoring Board, makes interpretation of secondary outcomes results difficult since underpowered for that.

However, the way of BP measurement should be considered when interpreting SPRINT results. In fact, BPs in SPRINT were measured with patients seated in a quiet room without talking and taken as an average of three measurements with an automated device that was preset to wait 5 min before measurements without the observer being present. This technique called automated office BP measurement is known to reduce the "white coat" effect. It correlates tightly with the average daytime BP measured by ambulatory blood pressure monitoring, and up to 20 mmHg lower than conventional auscultatory SBP measured at the office (Myers et al. 2012).

Positive results reported by SPRINT should also be balanced by the harmful of this strategy. The number needed to harm in the trial is important, 100 for hypotension, 167 for syncope, 125 for electrolyte abnormalities and 62 for acute kidney injury (respectively +1 %, +0.6, +0.8 % and +1.6 absolute risk increase). Just a reminder of the number needed to treat to reach the primary outcome is 61 and the absolute risk reduction is −1.6 % (Thoma et al. 2016).

SPRINT included patients with SBP starting from 130 mmHg. That seems to validate crucial definition of high BP since the normal high BP or pre-hypertension are terms introduced in guidelines but does not already justify starting antihypertensive treatment. As reported at the baseline characteristics of the study participants, only 9.2 and 9.6 % respectively from intensive and standard treatment groups were not using antihypertensive agents. That means others patients are currently using antihypertensive treatments and their BP are controlled at 130 mmHg and above. So we can't validate to start treating patients at high risk from the latter cut off. In the same rationale, the Heart Outcomes Prevention Evaluation (HOPE)-3 Trial randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo (Lonn et al. 2016). The mean BP of the participants at baseline was 138.1/81.9 mmHg; the decrease in BP was 6.0/3.0 mmHg greater in the active-

treatment group than in the placebo group. This study doesn't report any benefice on composite primary (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) nor secondary outcomes (resuscitated cardiac arrest, heart failure, and revascularization) after a median follow-up of 5.6 years. However, with the sub-group analysis, patients with upper third of SBP > 143.5 mmHg who were in the active-treatment group had significantly lower rates of the first and second primary outcomes than those in the placebo group. The pre-hypertension should not be treated, even if the cardiovascular risk is higher than at normal BP.

## 6 In Summary, Which BP Goal for Which Patient?

BP should be diagnosed early and treatment should be started at BP level of 140 mmHg and above, based on an office BP measurement, confirmed by an out-of-office BP measurement. Target SBP should be less than 140 mmHg if BP is measured by classic auscultatory method, less than 120 mmHg in high risk patients if BP is measured by automated office BP measurement. These targets are relevant in elderly patients if no orthostatic hypotension occurred, patients with non proteinuric chronic kidney disease (eGFR < 60 ml/mn/1.73 $m^2$) and patients with cardiovascular disease or a Framingham score more than 15 %. However attention should be taken on DBP if lower than 70 mmHg because of an increasing risk of ischemic heart event and on renal function since acute renal failure is more frequently reported at these low targets.

In diabetic patients, SBP target should be less than 140 mmHg according to ACCORD trial. However, for patients with albumin-creatinine ratio > 300mg/g or Protein-creatinine ratio > 500mg/g, with or without diabetes, lower SBP target should be proposed for renal protection aiming SBP < 130 mmHg as recommended by KDIGO guidelines.

In patients at low or intermediate risk, without cardiovascular disease, SBP should start to be treated when SBP is above 140 mmHg, and when treated, target BP should be less than 140 mmHg as reported by HOPE-3 trial.

Finally, superiority of ambulatory over office BP measurement in predicting mortality and cardiovascular events should be promoted when treating hypertension (Dolan et al. 2005; Sega et al. 2005). Validated target BP are SBP less than 135 mmHg for home BP measurement and 130, 135 and 120 mmHg for respectively 24 h, daytime and nighttime period (Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology 2013).

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