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# To whom recommend intensive treatment for hypertension?

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Arterial hypertension is the main identifiable cardiovascular risk factor, and although the benefit of blood pressure reduction is universally acknowledged, the scientific community has long been divided over the therapeutic blood pressure targets to be reached, also considering the estimated overall cardiovascular risk and the presence of individual risk factors and associated comorbidities. During the last few years, numerous clinical studies and meta-analyses, in particular, the SPRINT study, have been published, demonstrating the advantages of an intensive antihypertensive treatment, over a target blood pressure value (<140/90 mmHg), in the reduction of major cardiovascular events, myocardial infarction, stroke, heart failure, and all-causes cardiovascular mortality. Stemming from these results the major International Guidelines revisited the therapeutic objectives, recommending blood pressure value <130/80 mmHg for the vast majority of hypertensive patients until the age of 65 and suggesting a reduction of the target also in the elderly. Numerous studies and meta-analyses demonstrated that the reduction of the risk of coronary or cerebral events, and of all-causes cardiovascular mortality, is independent from the baseline value of blood pressure and the individual estimated risk. It has been also demonstrated that an early institution of antihypertensive treatment is associated with a faster realization of the recommended targets, and consequent significant benefits in terms of reduction of the incidence of myocardial infarction, heart failure, and major cardiovascular events, particularly when blood pressure control is achieved during the first 6 months of treatment, and even better during first 3 months. Other studies outlined that combination therapy with two or more drugs, mainly in a single pill configuration, are superior in reaching the recommended therapeutic targets. This is the reason why this strategy is strongly supported by the European Society of Cardiology/European Society of Hypertension (ESC/ESH) 2018 Guidelines, specifically the use of renin–angiotensin–aldosterone system inhibitors [angiotensin-converting enzyme (ACE) inhibitors and Sartans], in combination with calcium antagonist and/or thiazide diuretics, with the option to add antagonist of mineralcorticoid receptors, when an adequate blood pressure control has not been reached, or other classes of drugs, such as beta-blockers, when specific clinical indications are present, first and foremost ischaemic cardiomyopathy or heart failure. The newly proposed therapeutic goals are particularly important in high-risk patients, such as patients with previous cardiovascular events, diabetes mellitus, renal insufficiency, and patients older than 65 years of age.

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## Introduction

Despite the fact that in recent years considerable and scientific progress has been made in identifying the pathophysiological processes responsible for arterial hypertension; in diagnosis and treatment, arterial hypertension still represents the main and most widespread modifiable cardiovascular risk factor, with a prevalence estimated at 30–45% in the adult population (1.13 billion people worldwide, 150 million in Europe alone), destined to increase further in parallel with the progressive increase in the population over the age of 60 based on periodic demographic surveys.[1] The increase in systolic blood pressure values above 140 mmHg is responsible for over 9 million deaths each year, about 5 million acute coronary syndromes and more than 2 million ischaemic and haemorrhagic strokes. Numerous studies have also shown a constant linear correlation between blood pressure values >115/75 mmHg and the number of both coronary and cerebrovascular atherothrombotic events.[1]

Although a subject can be defined as hypertensive if his blood pressure levels exceed 140/90 mmHg and despite having been considered sufficient blood pressure values just below this threshold, numerous studies have shown that most of the cardiovascular events in actually occur in patients so far considered to be well controlled by antihypertensive or even non-hypertensive therapy[2] and above all the systolic pressure range between 130 and 140 mmHg deserves a thorough evaluation, also in light of the resounding reclassification of arterial hypertension proposed by the American guidelines only a few months ago.[3]

In view of these results, especially in recent years the scientific debate has become increasingly heated regarding the optimal blood pressure values to be achieved with lifestyle changes and drug therapy. The theoretical phenomenon of a J curve has in fact for a long time constituted, and continues to constitute, a cause for concern in the medical and scientific community, in addition to that attributable to the possible adverse effects of antihypertensive drugs, correlated to the hypothesis that arterial pressure 115/75 mmHg are not able to guarantee an adequate tissue perfusion, in particular in the coronary artery, cerebral and renal districts, especially in subjects with a concomitant atherosclerotic disease, diabetes mellitus, and dysfunction of the microcirculation.

However, starting from the 2003 meta-analysis of the Blood Pressure Lowering Treatment Trialists' Collaboration,[4] in the following years various studies have investigated the benefits of achieving more ambitious blood pressure targets with more intensive therapeutic strategies.

In 2014, Thomopoulos *et al.*[5] showed that a more intensive reduction in blood pressure is able to reduce the incidence of stroke by 22%, coronary heart disease by 14%, stroke and coronary artery disease by 16%, but in the absence of significant results with regard to heart failure cardiac and cardiovascular and all-causes mortality.

A clear dividing moment in the management and treatment of arterial hypertension is represented by 2015, the year of publication by the SPRINT study (Systolic Blood Pressure Intervention Trial), which enrolled more than 9000 hypertensive patients with high cardiovascular risk, comparing cardiovascular outcomes in the group subjected to an intensive treatment, with a systolic blood pressure target <120 mmHg, with those found in subjects receiving standard therapy with the aim of reaching values <140 mmHg.[6] The primary composite endpoint was myocardial infarction, other acute coronary syndromes, stroke, cardiac decompensation, and death from cardiovascular causes. After 1 year of treatment, mean systolic blood pressure values of 121.4 and 136.2 mmHg were observed in the groups subjected to intensive and standard treatment, respectively. After a follow-up of 3.26 years, the incidence recorded in the primary endpoint was decidedly lower in patients treated more aggressively (1.65% vs. 2.19% per year, hazard ratio 0.75), with a 27% reduction in the number of deaths for cardiovascular causes.[5] Although the SPRINT study has received some methodological criticisms, including that of having excluded diabetic patients or those with a history of stroke and having used a new technique for measuring clinical arterial pressure, with an automatic oscillometric instrument and the patient at rest and alone in the doctor's study, it was the first randomized trial to convincingly demonstrate the benefits of an intensive reduction of systolic blood pressure below previously established levels and to revolutionize the therapeutic indications of the main international guidelines.[7,8]

These results have been further confirmed by some meta-analyses that have taken place in recent years and that have included the SPRINT study.

Ettehad *et al.*[9] analysed the results of 123 studies that included more than 600 000 patients, showing that a decrease of 10 mmHg in systolic blood pressure values corresponded to a 20% reduction in the incidence of major cardiovascular events, of 17% in the risk of coronary heart disease, 27% of stroke, 28% of heart failure, 13% of death from all causes, regardless of the initial values of systolic blood pressure (even <130 mmHg) and estimated cardiovascular risk. If it is indeed intuitive how the absolute reduction of cardiovascular outcomes is proportional to the underlying cardiovascular risk, it should also be emphasized that the residual risk is higher in patients with high or very high risk and, therefore, the benefits of an intensive treatment of blood pressure are also obtained in subjects at low or moderate risk, so as to avoid the subsequent development and of hypertension-mediated organ damage.

A further meta-analysis, which included 44 989 patients, confirmed that the achievement of blood pressure values below 135/80 mmHg is related to a reduction in the incidence of major cardiovascular events (14%), myocardial infarction (13%), stroke (22%), albuminuaria (10%), but without statistically significant results in the risk of chronic renal failure, cardiovascular mortality, and all causes. The relative risk reduction is proportional to the decrease obtained in the arterial pressure values. As for the possible adverse events, resulting from a more intensive pharmacological treatment, if it is true that the cases of hypotension, even severe, falls, electrolyte imbalance, and acute renal failure were higher in patients with lower blood pressure, it is also true that the difference between the various groups did not reach statistical significance.[10]

**Table 1** Therapeutic targets of clinical systolic and diastolic blood pressure according to the ESC/ESH 2018 guidelines (modified from Williams *et al.*[1])

| Age group (years) | Therapeutic range for clinical SAP (mmHg) | | | | | Therapeutic range for clinical DAP (mmHg) |
|---|---|---|---|---|---|---|
| | Ipertensione arteriosa | + Malattia coronarica | + ictus/TIA | + Diabete | + IRC | |
| 18-65 | ≤130If toleratedNo < 120 | ≤130If toleratedNo < 120 | ≤130If toleratedNo < 120 | ≤130If toleratedNo < 120 | ≤140If toleratedNo < 130 | 70-79 Independent form age, co-morbidity, and previous cardiovascular events |
| 65-79 | 130-139If tolerated | 130-139If tolerated | 130-139If tolerated | 130-139If tolerated | 130-139If tolerated | |
| ≥80 | 130-139If tolerated | 130-139If tolerated | 130-139If tolerated | 130-139If tolerated | 130-139If tolerated | |

By virtue of these numerous and increasingly convincing observations, both the new guidelines of the American College of Cardiology/American Heart Association (ACC/AHA), published in 2017,[2] and those of the European Society of Cardiology/European Society of Hypertension (ESC/ESH),[1] just published, reviewed the therapeutic goal of blood pressure 140/90 mmHg, identifying the new goal of 130/80 mmHg for all hypertensive patients aged between 18 and 65 years (recommendation in Class IA), or lower if well-tolerated. In this context, it should be noted that in both cases we refer to values of clinical arterial pressure, as the use of ambulatory and home blood pressure monitoring, despite being useful tools for the doctor to obtain a better diagnostic framework, for the moment they have very precise and limited indications, among which above all masked and white coat hypertension.

The guidelines also emphasize that the 130/80 mmHg target should also be applied to defined categories of patients with high cardiovascular risk, such as those suffering from ischaemic heart disease, cerebrovascular disease, diabetes, and heart failure with reduced or preserved ejection fraction. Particular attention is also given to elderly patients, i.e. those over 65 years of age, highlighting how, especially if in good clinical conditions and in the absence of motor and cognitive deficits, they must obtain systolic pressure values between 140 and 130 mmHg, not being able to be more satisfied than the previous, and too bland objective, between 150 and 140 mmHg; the recommendation also extends to patients over 80 years of age, as long as they are not fragile and in the absence of adverse effects related to therapy (*Table 1*).

As for the coexistence of diabetes mellitus, it is known that the patients affected are to be placed in the category with high or very high risk of fatal cardiovascular events in case of organ damage, in most cases higher than 10%, percentage that must be multiplied by a factor of three if non-fatal events are also included. For this reason, the guidelines of the ACC/AHA[2] recommend starting an antihypertensive therapy already for pressure values ≥130/80 mmHg in these subjects[2]; European guidelines,[1] on the other hand, do not currently express stringent recommendations on the need to start treatment in subjects with arterial pressure values in the normal-high range (systolic 130–139 mmHg, diastolic 80–89 mmHg), while defining appropriate antihypertensive therapy with a single drug in very high-risk patients.

Although the ACCORD study (Action to Control Cardiovascular Risk in Diabetes),[11] which compared cardiovascular events (myocardial infarction and non-fatal stroke and cardiovascular disease mortality) in 4733 intensively treated diabetic patients (systolic blood pressure <120 mmHg) o standard (<140 mmHg), did not reach statistical significance, numerous other trials and meta-analyses have confirmed the benefits of reducing therapeutic targets.

A meta-analysis of 73 913 subjects reported a 39% reduction in the number of ischaemic and haemorrhagic strokes in those reaching systolic blood pressure values <130 mmHg. Two other meta-analyses showed a significant reduction in the risk of myocardial infarction, stroke, albuminuria, retinopathy progression, and major cardiovascular events in diabetic patients with a mean arterial pressure of 133/76 mmHg compared to the group with mean values of 140/81 mmHg.[12] Although the SPRINT study excluded diabetic patients, a sub-study showed comparable benefits of intensive treatment in subjects with carbohydrate and normoglycaemic intolerance.[6]

Regarding diastolic blood pressure, the ADVANCE study showed a significant reduction in cardiovascular events for values <75 mmHg.[13]

Particular attention should be paid to patients with a history of coronary events, as these represent 40% of all cardiovascular events in hypertensive patients from the age of 30 and, vice versa, high blood pressure is responsible for over 25% of acute coronary syndromes.

A recent analysis of 22 672 hypertensive patients with stable coronary artery disease within the CLARIFY registry showed a significantly increased cardiovascular risk in those who continued to have blood pressure values >140/80 mmHg despite therapy.[14]

In this category of patients, an argument similar to diabetes can be made regarding the need to start an antihypertensive therapy for blood pressure in the normal-high range and to reach a target <130/80 mmHg.

An analysis of 274 patients with ischaemic heart disease who underwent intravascular ultrasonography as part of a

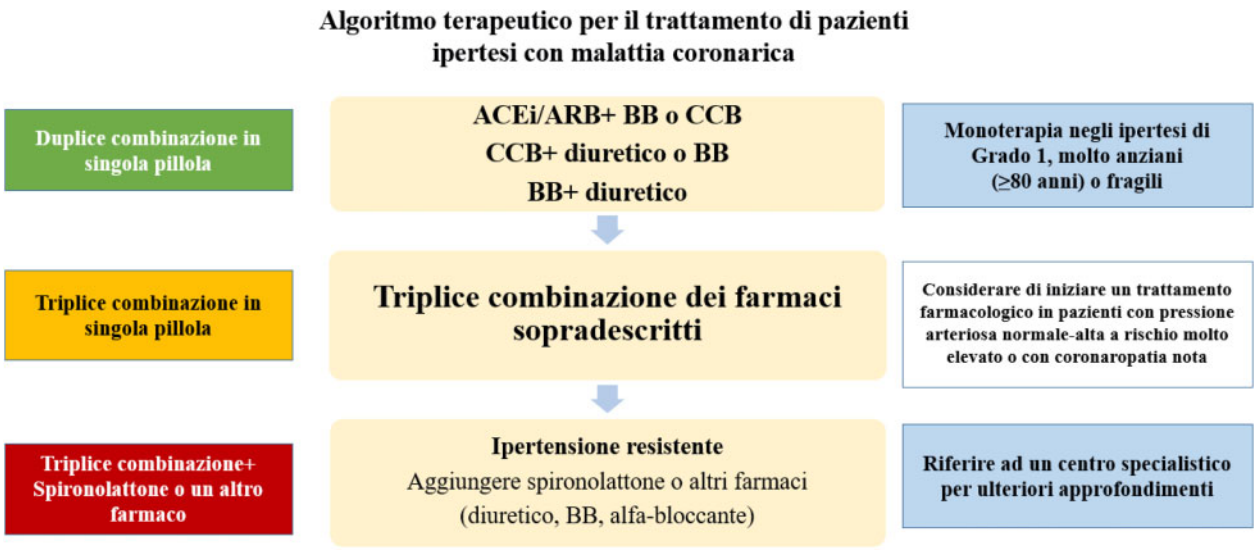


**Figure 1** Therapeutic algorithm for the treatment of hypertensive patients with coronary artery disease (modified from Williams *et al.*[1]). ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers (sartans); BB, beta-blockers; CCB, calcium antagonists

sub-study of the CAMELOT trial (Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis) demonstrated an average reduction of 4.6 $mm^3$ in the volume of coronary plaque in subjects that reached arterial pressure values <120/80 mmHg, in the absence instead of significant changes for values <140/90 mmHg, supporting the need to reduce therapeutic targets at least below 130/80 mmHg, as previously underlined.[15]

However, the debate remains on a possible harmful effect of blood pressure values <120/70 mmHg in these patients, in consideration of the altered limits of self-regulation of the coronary flow within an already damaged circulation and of the much feared J effect. For this reason, the ESC/ESH 2018 guidelines recommend targets between 130 and 120 mmHg for systolic blood pressure and between 80 and 70 mmHg for diastolic blood pressure.[1] *Figure 1* summarizes the therapeutic algorithm proposed by the European guidelines for the treatment of hypertensive patients with known coronary artery disease.

With regard to patients with previous strokes or transient ischaemic attacks, numerous studies, including the most recent Secondary Prevention of Small Subcortical Strokes (SPS),[16] have shown the reduction of cardiovascular events, especially of recurrent cerebrovascular events, related to a decrease in systolic blood pressure values <130 mmHg.

In view of the high cardiovascular risk caused by the presence of overt organ damage, such as that represented by peripheral vascular disease, left systolic or diastolic ventricular dysfunction, thoracic or abdominal aortic aneurysm, European and American guidelines agree in recommending targets <130/80 mmHg even in patients with these diseases.

On the other hand, there are several recommendations regarding patients suffering from chronic renal failure. As a high cardiovascular risk category, the ACC/AHA guidelines recommend pharmacological treatment already for systolic blood pressure values >130 mmHg.[2] The ESC/ESH 2018 guidelines, on the contrary, suggest a less aggressive strategy, considering the fragility and comorbidities often associated and the greater risk of hydro-electrolyte imbalances and progression of renal failure, recommending the achievement of systolic pressure values between 140 and 130 mmHg.[1] *Figure 2* summarizes the therapeutic algorithm proposed by the European guidelines for the treatment of hypertensive patients with known coronary artery disease.

A separate chapter is represented by the treatment of arterial blood pressure in elderly patients, in consideration of the results of the trials published in the last 5 years and in particular of the SPRINT, which has enrolled patients even older than 75 years of which it was recently published an analysis by subgroup (SPRINT SENIOR). The latter demonstrated a significant reduction in fatal and non-fatal cardiovascular events and in all-cause mortality in elderly patients, not necessarily in optimal general conditions, treated intensively, in the absence of a significant increase in adverse events.[17]

Data from SPRINT SENIOR[17] were included in a meta-analysis of 10 857 patients,[18] which also investigated the results of the JATOS trial (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients)[19] in patients of over the age of 65, of the VALISH trial (Valsartan in Elderly Isolated Systolic Hypertension)[20] and a study conducted by Wei *et al.*[21] in patients over 70 years. A more intensive antihypertensive therapy showed a 29% reduction in major cardiovascular events, 33% of cardiovascular mortality, and 37% of heart failure, statistically significant, and a reduction of 21 and 20%, respectively, in the incidence of myocardial infarction and stroke, although below statistical significance. For each 1 mmHg difference between the standard and intensive therapy groups in the mean systolic pressure values reached, a 3% reduction in the incidence of cardiovascular events was shown.[18]

The HYVET trial (Hypertension in the Very Elderly Trial) confirmed the reduction of the risk of death, fatal stroke,

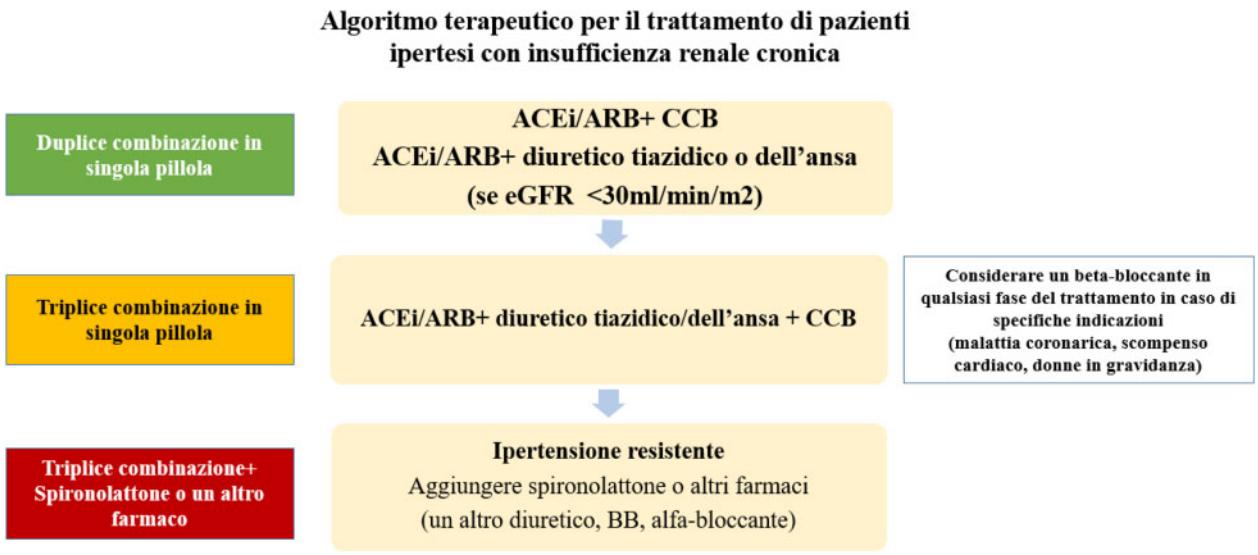


**Figure 2** Therapeutic algorithm for the treatment of hypertensive patients with chronic renal failure (modified from Williams *et al.*[1]). ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers (sartans); CCB, calcium antagonists; eGFR, estimated glomerular filtrate.

and heart failure in patients older than 80 years who did not interrupt antihypertensive therapy for reasons closely related to old age.[22]

In consideration of these numerous evidences, while the ESC guidelines of 2013[23] recommended to start an antihypertensive treatment only for systolic pressure values above 160 mmHg, with a target between 140 and 150 mmHg, the guidelines recently published recommend a pharmacological strategy even for values >140 mmHg, with a target between 130 and 140 mmHg for all patients over the age of 65, as long as it is well-tolerated and in the absence of adverse events, judging the previous recommendations to be too conservative.[1]

In consideration of the growing recommendations concerning the reduction of blood pressure targets and the increasing number of evidences that an early treatment of blood pressure reduces the development and progression of hypertension-mediated organ damage, the current international guidelines indicate to start a pharmacological treatment also in patients suffering from Grade 1 arterial hypertension with a cardiovascular risk starting from mild to moderate. Numerous studies and meta-analyses have indeed shown how the reduction of the relative risk of coronary and cerebrovascular events, of cardiovascular mortality and of all causes is independent of the baseline values of arterial pressure and the estimated individual risk[24] It has also been shown that the early initiation of an antihypertensive treatment is associated with a faster achievement of the recommended targets, with significant benefits in terms of reduction of myocardial infarction, heart failure and major cardiovascular events, especially if adequate blood pressure control is achieved within 6 months and even more within 3 months.[24]

It has been shown in numerous studies that combination therapies with two or more drugs, especially in a single pill, are superior in achieving the recommended therapeutic targets. For this reason, this strategy is strongly recommended by the ESC/ESH 2018 guidelines, and in particular the use of inhibitors of the renin-angiotensin-aldosterone system (ACE inhibitors and sartans) in association with calcium antagonists and/or thiazide diuretics, with the possibility of adding receptor antagonists for mineralocorticoids, in case of failure to achieve adequate blood pressure control, or other classes of drugs, such as beta-blockers, in the case of precise clinical indications, first of all ischaemic heart disease and heart failure.[1]

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