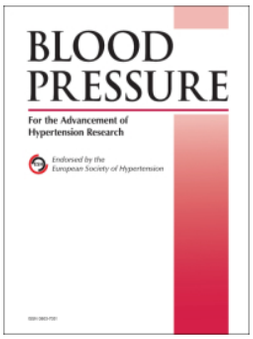

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EDITORIAL

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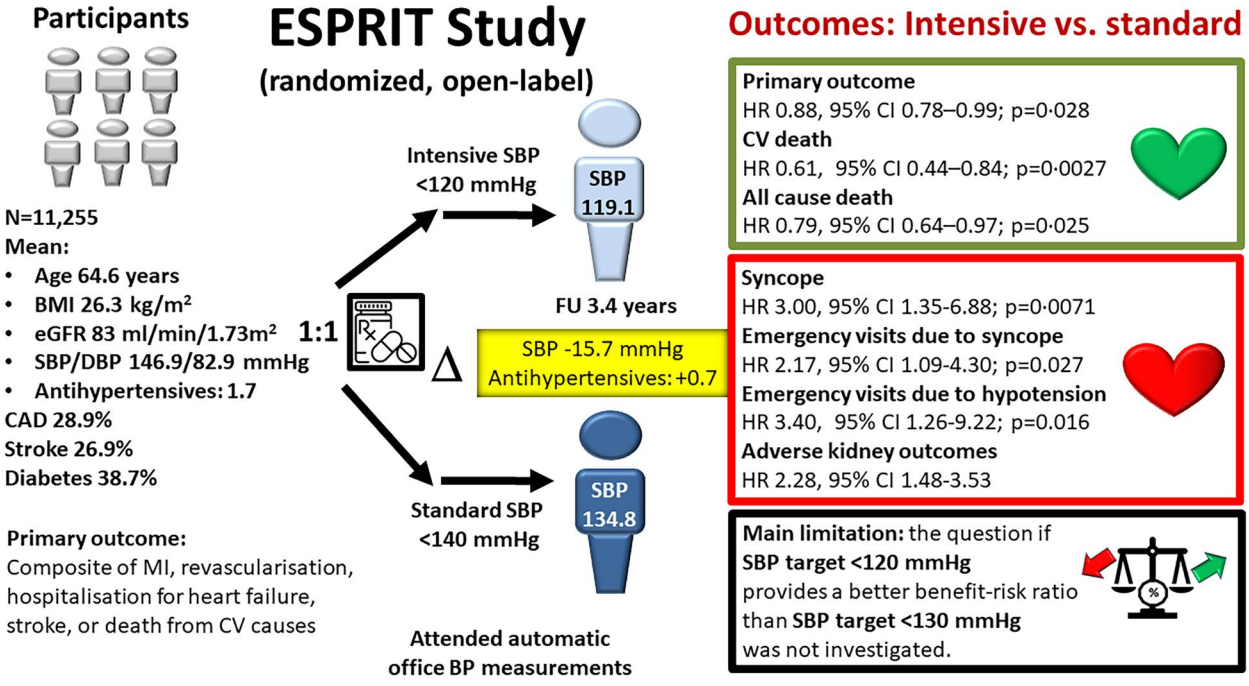
Lowering of systolic blood pressure in hypertensive patients: insights and questions from the ESPRIT study



Context

The optimal target for systolic blood pressure (SBP) and diastolic blood pressure (DBP) that should be achieved by pharmacological treatment in hypertensive patients is a matter of ongoing debate in the management of hypertension and in hypertension guidelines [1–3]. This is also reflected in the 2023 guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH), in which the challenges to identify the evidence for recommending optimal blood pressure (BP) targets for the general hypertensive population have been acknowledged [3]. This is essentially due to the limited consistency of data available from randomised controlled trials (RCT). Indeed, while lowering diastolic pressure to below 80 mmHg is rather consensual among the recommendations, the optimal target for SBP remains controversial. One issue is that the incremental benefit of lowering SBP to below 130 mmHg is not consistently documented in RCTs and their meta-analyses [3,4] and may be even harmful in some special populations, e.g. hypertensive patients with left ventricular hypertrophy (LVH) [5,6] or very old patients ([7]. Therefore, additional studies are still expected that provide stronger evidence in favour of the SBP target with the best benefit-risk ratio, whether less than 140, 130 or 120 mmHg, respectively.

The ESPRIT study

In this respect, the recently reported results of the ESPRIT study (Effects of intensive Systolic blood Pressure lowering treatment in reducing RIsk of vascular evenTs) is important as it sheds new light on this question by virtue of its design [8]. ESPRIT was a multi-center, open-label RCT that compared the efficacy and safety of intensive BP lowering strategy to a SBP target < 120 mm Hg and standard BP lowering strategy to a SBP target < 140 mm Hg [9]. Participants aged at least 50 years with an average baseline SBP between 130 to 180 mm Hg and at high CV risk, defined by

Table 1. Selected baseline characteristics of patients in ESPRIT.

	Intensive treatment ($n=5624$)	Standard treatment ($n=5631$)
Age, years		
• Mean	64.6 (7.1)	64.6 (7.2)
• ≥70	1365 (24.3%)	1384 (24.6%)
Women	2327 (41.4%)	2323 (41.3%)
BMI, kg/m^2	26.3 (3.3)	26.3 (3.3)
Systolic blood pressure, mmHg	146.8 (10.5)	147.0 (10.7)
Diastolic blood pressure, mmHg	82.8 (10.1)	82.9 (10.5)
eGFR, ml/min/1.73m^2		
Mean	83.2 (13.6)	83.5 (13.7)
<60	337 (6.0%)	340 (6.0%)
Comorbidities		
• Diabetes	2180 (38.8%)	2179 (38.7%)
• Coronary heart disease	1632 (29%)	1620 (28.8%)
• Stroke	1520 (27%)	1502 (26.7%)
• Atrial fibrillation	113 (2.0%)	112 (2.0%)
Number of antihypertensive medications		
• 0	149 (2.7%)	149 (2.7%)
• 1	2437 (43.3%)	2451 (43.5%)
• 2	2154 (38.3%)	2111 (37.5%)
• 3	761 (13.5%)	787 (14.0%)
• ≥4	123 (2.2%)	133 (2.4%)
Statin use	2623 (46.6%)	2591 (46.0%)
Aspirin use	2419 (43.0%)	2398 (42.6%)

established CV diseases or 2 major CV risk factors, were enrolled from 116 hospitals or communities in China. The primary outcome was a composite of myocardial infarction, revascularization, hospitalisation for heart failure, stroke, or death from cardiovascular causes, assessed by the intention-to-treat principle. The study (ClinicalTrials.gov, NCT04030234) was funded by the Ministry of Science and Technology of China and Fuwai Hospital in China. Reported secondary outcomes include components of the primary composite outcome, all-cause death, a composite of the primary outcome or all-cause death or kidney outcomes [8]. Important baseline characteristics of the overall 11,255 patients are shown in Table 1. Patients had a mean age of 64.6 years and a body mass index of 26.3 kg/m^2, which is about 2 kg/m^2 (or more) lower than in a hypertension trial including predominantly participants from Western countries [10]. Renal function was well preserved with a mean estimated glomerular filtration rate (eGFR) of 83.4 ml/min/1.73 m^2; only a minority (6.0%) had eGFR values below 60 ml/min/1.73 m^2 (patients with an eGFR <45 ml/min/1.73 m^2 were excluded). Patients with known diabetes (38.7%), a history of coronary heart disease (28.9%) or stroke (26.9%) were also included in the trial. Only a small group of patients was not treated with any antihypertensive drug at baseline (2.7%), while more than half of the patients were treated with at least two antihypertensive drugs. Previous treatment with a statin (46.3%) or Aspirin (42.8%) was also frequent among study participants.

The mean SBP and DBP at baseline were 146.9 and 82.9 mmHg, respectively.

The mean achieved SBP at the end of the study was 134.8 (SD 10.5) mmHg in the standard treatment group (mean number of antihypertensive medications 2.1) and 119.1 (SD 11.1) mmHg in the intensive group (mean number of antihypertensive medications used 2.8) resulting in a SBP difference of 15.7 mmHg (differences in mean number of antihypertensive drugs used 0.7). The mean achieved DBP at the end of the study was 73.7 (SD 10.1) mmHg in the standard and 69.2 (SD 9.1) mmHg in the intensive treatment group resulting in a DBP difference of 4.5 mmHg.

After a mean follow-up of 3.4 years, the primary outcome event occurred in 547 (9·7%) of 5624 participants from the intensive treatment group and 623 of 5631 (11·1%) from the standard treatment group (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.78–0.99; $p=0{\cdot}028$). There was no heterogeneity of effects by diabetes status or a history of stroke. Both death from CV causes and overall death from any cause were significantly reduced as well.

The incidence of serious adverse events including syncope occurred more frequently in the intensive treatment group (24 [0·4%] of 5624) than in the standard treatment group (8 [0·1%] of 5631; HR 3.00, 95% CI 1.35–6.68). The risks for emergency room visits due to hypotension or syncope were significantly increased, 3.4 and 2.2 folds respectively. The risk for adverse kidney outcomes (a composite of end-stage renal disease, sustained eGFR to <10 ml/min/1.73 m^2) was also significantly increased (HR 2.28, 95% CI 1.48-3.53).

Discussion

The ESPRIT Study is an important RCT and we congratulate the investigators of the study and for their successful coping with the challenges induced by the COVID-19 pandemic that affected at least partially the recruitment of patients [9]. The overall outcome result supports a more intensive BP lowering strategy aiming for a SBP target below 120 mmHg. Unlike SPRINT [11], which tested also an intensive versus standard BP lowering strategy and had multiple problems previously discussed [3,12,13], ESPRIT included a reasonable number of patients with diabetes or stroke, and used, very importantly, a consistent protocol for attended automatic office BP measurement in the trial [9]. However, some peculiarities of the study design and results should be mentioned, which call into question the general implementation of this strategy in clinical practice without some reservation. First, the observation that a profound BP lowering strategy in an overall hypertensive population with a mean baseline SBP of 146.9 mmHg resulting in a SBP difference of 15.7 mmHg leads to reduced outcomes is not surprising. One key question and knowledge gap that would have been of great clinical interest is whether a SBP target of <120 mmHg in the intensive group would provide a greater benefit when

compared to a target of <130 mmHg, which is recommended for most patients in the current ESH guidelines [3]. In fact, many patients of the standard treatment group of ESPRIT (means SBP achieved at the end of the trial 134.8 mmHg) were still above this target. Thus, the ESPRIT study results do not exclude the possibility that aiming at an SBP <130 mmHg would have generated similar efficacy outcomes when compared to the intensive SBP < 120 mmHg target. This is important against the background that ESPRIT results raise safety concerns with the SBP target <120 mmHg.

The observation that a large subgroup of patients (53.4% of study population) not receiving statin treatment at baseline showed no benefit is puzzling when compared to previous evidence indicating an additive benefit of statins to BP lowering in patients with elevated BP and no cardiovascular disease [14]. It may possibly represent a chance finding as discussed by the authors.

Another interesting result is the small difference of 0.7 in the mean number of antihypertensive drugs used at the end of the study (2.1 in the standard group versus 2.8 in the intensive group) against the background of a SBP difference of 15.7 mmHg. This may be due to increasing doses of medications used in the study, not reported in the main publication (nor in the Appendix), since dosing of antihypertensive drugs in China might be in general lower [15] as compared to other, e.g. Western countries, [16]. Furthermore, the more frequent use of diuretics in the intensive group (42.5%) as compared to the standard group (15.4%) may explain the lower SBP achieved in the intensive treatment group. Thus, both, the difference in SBP and outcomes observed in ESPRIT maybe at least partially induced by the different use of diuretics supporting their use in combination therapy to achieve lower BP targets. Also, several adverse events were significantly increased in the intensive treatment group including the incidence of syncope, hypotension, and adverse kidney outcomes. They occurred more frequently despite exclusion of patients at risk of developing side effects induced by a profound drop in SBP, including patients with 2+ proteinuria, patients with an eGFR < 45 ml/min/1.73 m2 or patients with an ejection fraction <35%. Episodes of syncope or orthostatic hypotension may have a strong negative impact on medication persistence in many patients.

Conclusions

The ESPRIT study provides important new evidence supporting an intensive BP lowering strategy. Due to limitations of the study-design and several questions prompted by the study results the ESPRIT data are still compatible with the 2023 ESH guidelines recommendation to lower SBP to a target to below 130 mmHg in most hypertensive patients. Whether the lower target SBP provides additional benefit is still an open question, although the ESPRIT data suggest a target below 120 mmHg is superior compared to the 130-140 mmHg range. The debate on 'the lower the better' remains open, also in respect of the safety concerns raised by ESPRIT in the intensive treatment group.

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