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Studies in which harm outweighs benefit but in which the intervention effect is presented mostly as beneficial would be better not published – A comment on the SPRINT trial

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ABSTRACT

Clinical practice in the XXI century is getting more complex and the role of scientific evidence to support clinical decision-making appears to no longer raise any question: most clinicians recognize that it is the combination of good quality scientific data applicable to our patients and the experience of the individual doctor that produces the best quality of care, with consistent and cost-effective results.

In this binomial body of evidence/clinical experience each part has a well-defined role, individually contributing with more or less relative weight to the final decision. One thing is certain: experienced doctors without updated clinical information or updated but inexperienced doctors tend to provide lower quality care, with the ensuing problems.

Scientific data - no matter how good - should be analysed and modulated in order to determine its potential application to our patients (who possibly did not participate in the clinical trials responsible for drug authorization into the market). This is called the external validity of the studies, which is nothing more than the potential for generalization to our patients of the results obtained in clinical trials.

This introduction has to do with the recent publication of the SPRINT trial in the November 26, 2015 issue, of the New England Journal of Medicine[1].

THE SPRINT TRIAL

This was a randomized controlled clinical trial comparing two antihypertensive therapy interventions classified as intensive (systolic blood pressure target [SBP] ≤ 120 mmHg) or standard (SBP target ≤ 140 mmHg).

The study included 9,361 patients, with an age of at least 50 years, with a SBP between 130-180 mmHg and an increased cardiovascular (CV) risk (whose definition included chronic kidney disease and patients with a Framingham score ≥ 15%). Patients with diabetes mellitus or prior stroke were excluded. All major

groups of antihypertensive drugs were used in the study, with priority given to the use of chlorthalidone (as a first-line agent), loop diuretics (for participants with chronic kidney disease) and beta blockers (for individuals with coronary heart disease), combined with lifestyle changes.

The selected outcomes were:

- Primary outcome was a composite outcome defined as the first occurrence of any of the following cardiovascular events: myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes.
- Secondary outcomes included the individual components of the primary composite outcome, death from any cause, and the composite of the primary outcome or death from any cause.
- Pre-specified renal outcomes were also assessed using a different definition for patients with chronic kidney disease (eGFR < 60 ml per minute per 1.73 m^2) at baseline and those without it. The renal outcome in patients with chronic kidney disease was a composite of a reduction in the eGFR of 50% or more or the long-term need for dialysis or renal transplant; in patients without chronic kidney disease, the renal outcome was defined by a reduction in the eGFR of 30% or more to less than 60 ml per minute per 1.73 m^2. Incident albuminuria and the rate of adverse side effects were also pre-specified outcomes.

Clinical and laboratory data were obtained at baseline and then every three months over a median follow-up period of 3.26 years, instead of the pre-planned follow-up period of 5 years, as the monitoring boundary of benefit had been exceeded in the population undergoing intensive treatment. In other words, the study was stopped before the initially defined mean follow-up period had been reached, due to benefit detected in the intensive arm of the aggregate sample.

During a median follow-up period of 3.26 years, the average SBP in the intensive therapy group was 121.5 mmHg, while in the group undergoing standard therapy it was 134.6 mmHg. The average number of drugs required to achieve the target blood pressure value was 2.8 in the first group and 1.8 in the second.

The table (adapted from doi: 10.7326 / ACP-JC-2016-164-4-015) shows the statistically significant observed event rates and the RRR, NNT, RRI and NNH (definitions in the Table) calculated for the follow-up period.

The authors concluded that in patients with systolic blood pressure greater than 140 mm Hg and increased cardiovascular risk, intensive vs. standard blood pressure control reduced the number of cardiovascular events and overall mortality, but at the expense of a significant increase in side effects.

Table

Rate of events of intensive vs. standard therapy (follow-up of 3.26 years)

Outcomes	Intensive therapy	Standard therapy	RRR	NNT
Primary outcome	5.2%	6.8%	24% (11 to 35)	61 (42 to 138)
CV mortality	0.8%	1.4%	43% (15 to 62)	167 (116 to 480)
Heart failure	1.3%	2.1%	38% (16 to 55)	127 (87 to 301)
Global mortality	3.3%	4.5%	27% (10 to 39)	84 (57 to 227)
			RRI	**NNH**
GFR reduction (patients without kidney disease)	3.8%	1.1%	244% (142 a 399)	38 (23 a 64)
Hypotension	2.4%	1.4%	67% (23 to 126)	107 (67 to 253)
Syncope	2.3%	1.7%	34% (1 to 78)	173 (87 to 8199)
Acute kidney injury	4.1%	2.5%	65% (32 to 107)	62 (43 to 111)
Electrolyte abnormalities	3.1%	2.3%	35% (5 to 72)	127 (69 to 716)

RRR = relative risk reduction; NNT = number needed treat; RRI = relative risk increase; NNH = number needed to harm.
The values shown in brackets are 95% CI.

COMMENTS

That high blood pressure is a major cardiovascular risk factor is not in doubt. For example, the Global Burden of Disease Study, an epidemiological study sponsored by the World Health Organisation (WHO), identified arterial hypertension as the most important risk factor globally[2]. Moreover, various clinical trials have shown that treatment of hypertensive patients reduces the incidence of cardiovascular events[3].

The target for systolic blood pressure in patients aged 60 years or older without diabetes or chronic kidney disease has been much discussed, with conflicting opinions whether it should be < 140 mmHg or < 150 mmHg[4]. This issue is far from resolved, with an ongoing discussion among experts.

Regardless of the agreed target - which is by no means unanimous - the most important thing is not, in our view, blindly "correct" the blood pressure value, but to strike a balance between the benefit and the harm associated with any anti-hypertensive intervention.

In terms of benefit, it is well known that, based on epidemiological data, there is no lower boundary for blood pressure value (no matter how low) at which the benefit disappears. In other words, when we reduce the SBP from 160 to 150 mmHg, we reduce the risk. If we continue to lower the SBP, we continue to reduce the risk, even when blood pressure reaches a value below the normal level of 120 mmHg[5]. It is around this value we have to take into account the problem of iatrogenesis (harm). Furthermore, the J-curve phenomenon is a well-known factor that tells us that from a certain SBP level down the risk not only does not decrease but can even go up[6].

A fundamental law of therapy tells us that the higher the baseline risk of the patient, the more effective our intervention is. So, in high-risk individuals the adverse effects rate is - within certain limits - acceptable, as benefit clearly outweighs harm, and thus the final balance is in favour of the patient. On the other hand, when the baseline risk is low, then the expected benefit is also small and iatrogenesis can easily be higher than benefit, thus defining a negative benefit/harm balance.

The SPRINT trial is one of those studies that, by their massive impact, deserve special attention.

What the US researchers sought to determine was whether to target a lower systolic blood pressure value (around 120 mmHg on average) would prove more beneficial than a higher target value (140 mmHg) in an at high risk sample of elderly patients.

The first question to ask is why this study was done. Why should anyone try to reach a lower average SBP in patients at the sixth decade of life (or older), with a most likely modest benefit and an also likely high iatrogenic risk? A commercial interest should not be present here, as the SPRINT trial was funded by an American public institution not linked to the pharmaceutical industry... It is our opinion that the study was done due to the systematic search for pharmacologic interventions to modulate minimal risks, which is a practice long adopted in the US.

In the study, patients had to take an extra drug to achieve an SBP value of < 120 mmHg that was added to the 2 antihypertensive drugs, which on average they were already taking. This step had, however, very modest results, since less than half of the intensive treatment group of patients achieved a systolic blood pressure below the target (a very common phenomenon in everyday practice, which we as clinicians know well). Furthermore, the greatest benefit was observed in patients with an age of at least 75 years, a population requiring a more complex prescription scheme, increased use of combination therapies, a more aggressive detection process of iatrogenesis and a greater number of medical follow-up appointments.

When we look at the results of the SPRINT trial, what we find is that the benefit observed in most of the selected outcomes (as measured by numbers needed to treat during the study period to prevent a cardiovascular event) was in most cases lower than the harm (measured by the numbers needed to harm during the study period to cause iatrogenic events). For example, in the study, investigators had to treat 127 patients to prevent a heart failure episode while they had to treat just 38 patients to induce a decrease in renal function, and, thus, the intervention has a negative benefit/harm balance and its use in individual patients should be carefully assessed.

It is also important to take into account the known amplification effect of benefit when the studies are stopped before the planned period of follow-up, a phenomenon certainly present in this study[7].

In short, it is our opinion that the results of the SPRINT study are globally useless if not harmful to elderly hypertensive patients and should be ignored by the medical community that treats them. And that, in this fragile population, it should be recommended a wiser approach that takes into account the quality of life at the final years of their life.

Disclosure of Potential Conflicts of Interest: None declared.

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