The “SPRINT results” need careful interpretation, and a Korean observational study is far from validate them in the real world

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Abstract
The SPRINT randomized controlled trial has compared two thresholds of antihypertensive therapy in patients at high cardiovascular risk without diabetes, with unsettling results. The group with systolic blood pressure target <120 mmHg reduced significantly both the total cardiovascular events and the all-cause mortality compared with the group with standard SBP <140 mmHg, threshold recommended by the International Guidelines.

The authors of a large Korean cohort study of unselected participants from the “real world” claim to have confirmed the SPRINT results. They followed three large subgroups of residents with hypertension, free of CV disease at baseline and with different BP control, pretending that the subgroup with SBP <120 mmHg had better clinical results.

We performed an analysis of several serious errors in the interpretation of the SPRINT and the Korean studies, and conclude that they have mislead many commentators, unaware of several pitfalls. These can ultimately cause clinical damage and lead to an increase of costs difficult to bear for the Health Systems.

Background
The SPRINT [1] randomized controlled trial (RCT) has compared two thresholds of antihypertensive therapy in patients at high cardiovascular (CV) risk without diabetes, with generic drugs and unsettling results. The group with systolic blood pressure (SBP) target <120 mmHg (mean reached 121.5) reduced significantly both the total CV events and the all-cause mortality compared with the group with standard SBP <140 mmHg (mean achieved about 135 mmHg), threshold recommended by both the 2013 European Guideline and the Guideline of the Eighth Joint National Committee (JNC 8) USA 2014.

The authors of a cohort study on the insured Korean population [2], which benefits of universal medical visits in the mandatory national single-payer program NHIS, claim to have confirmed the SPRINT results. They followed from 2007 to the end of 2013 a cohort of 67,965 unselected participants from the “real world”, mean age 52, with three large subgroups of residents with hypertension, free of CV disease at baseline and with different BP control. Indeed, the subgroup with SBP <120 mmHg showed greater CV protection; the subgroup with SBP from 120 to <140 (corresponding to the current international BP guidelines) showed an intermediate CV protection, while the subgroup with SBP ≥140 mmHg, defined “out of control”, had the worst CV results.

The authors seem oriented to apply the SPRINT BP thresholds in the “real world.”

Objective
This commentary aims to show that these two studies are currently misinterpreted, and that the uncritical application of their conclusions can cause an excess of mortality and public and private expenditure for antihypertensive drugs. These two outcomes can instead be reduced aiming to appropriate BP thresholds and choosing the most cost-effective generic drugs.

Methods
We performed an analysis of several serious errors in the interpretation of the SPRINT randomized trial [3] and of the Korean cohort study [2].

Results
The large RCT SPRINT, funded by the American Public Health, aimed to determine the most appropriate target of SBP for high CV risk patients (almost all on antihypertensive therapy and with a SBP ≥130), selected by two main exclusion criteria that follow.

• Diabetes, since the RCT ACCORD [3] in diabetic patients did not show overall benefits in the intensively treated group, with SBP reduced under 120, compared to the standard group, with average SBP of about 134 mmHg unless a significant but modest reduction of stroke with target <120 mmHg, which was however largely counterbalanced by an excess of serious adverse events and, in tendency, by a slight increase in total mortality. This tendency towards an increased risk of
all-cause mortality with further treatment (1.05, 95% CI 0.95 to 1.16) is confirmed by a large meta-analysis of 49 RCTs [4]. This occurred if baseline SBP was less than 140 mmHg.

- Stroke, since the previous RCT SPS3 [5] in patients with recent lacunar stroke showed a trend to benefit in reducing SBP to <130 compared to a target of 130-149 mmHg.

Another exclusion regarded patients with hypertension highly resistant to the treatment in place.

In SPRINT 9,360 patients of average age 68 years, SBP average 139 mmHg and 20.1% probability of having a CV event in 10 years (by the Framingham calculator) were randomized to two SBP target: stringent (average value reached 121.5 mmHg) or standard (average reached about 135). The composite primary outcome was: heart attack/acute coronary syndrome, stroke, heart failure or death for CV causes.

The RCT was stopped after 3 years and 3 months, because the intensive treatment significantly reduced the primary outcome (hazard ratio 0.75; 95% CI 0.64-0.89) and all-cause mortality (hazard ratio 0.73; 95% CI 0.60-0.90), with a number needed to treat (NNT) of 61 patients to reduce one CV event and 90 to avoid one death. The benefits were greater in patients over 75 years old.

The participants assumed an average of 1.8 medications each with standard therapy, and 2.8 (1 more medication) with the intensive treatment. Specific adverse events were more common with the intensive treatment (Table 1).

In SPRINT a prespecified subgroup was constituted by 2,636 subjects ≥75 years [6] (average age 80). After a median follow up of slightly more than three years, the average SBP was 123 mmHg in the group with intensive treatment and 135 in the standard one, with DBP of 62 and 67 mmHg respectively. The primary composite outcome occurred less in the first group: 7.7% vs 11.2%, with a NNT of 27 to prevent one CV event. Total mortality was also lower: 5.5% vs 8.1%, with a NNT of 41 treated to avoid one death. Surprisingly, significant differences of similar magnitude were also observed in people with poor fitness and frailty indicators (but SPRINT enrolled individuals resistant to the treatment in place).

The interruption could give a great overestimation, without which the effect may pass from "moderate" to "modest" or even vanish. Thus, it is questionable having truncated the planned follow-up, in a RCT whose results could change SBP targets for hundreds of millions of people every year, from now on. Thinking to this, the ethical theme of wanting to immediately communicate the possible benefits is very weak, more so because the lack of credibility of SPRINT low target is now restraining its adoption.

So in high-risk patients should we point to a SBP of less than 120 mmHg?

| Serious adverse event | Intensive | Standard | RR     |
|----------------------|-----------|----------|--------|
| hypotension          | 2.4%      | 1.4%     | 1.67*  |
| syncope              | 2.3%      | 1.7%     | 1.33*  |
| electrolyte abnormalities | 3.1%  | 2.3%     | 1.35*  |
| damage or acute renal failure | 4.1%   | 2.5%     | 1.66*  |
| Elderly              |           |          |        |
| hypotension          | 2.4%      | 1.4%     | 1.71   |
| syncope              | 3.0%      | 2.4%     | 1.23   |
| electrolyte abnormalities | 4.0%  | 2.7%     | 1.51   |
| damage or acute renal failure | 5.5%   | 4.0%     | 1.41   |

* In these cases the differences have reached significance.

International Guidelines, which by 2013 had accepted unified target <140/90 for all adults, with higher limits in the elderly/very elderly. Nonetheless, aiming to the drastic targets of SPRINT with drug therapies is risky and not supported by the sum of evidence, for the eight reasons listed below.

1) First of all, it was not given enough attention to the unusual method of measurement of the BP in the SPRINT trial: an average of three measurements with an automatic device, in a quiet room without any doctor, nurse or other person, after 5 minutes of rest sitting.

Measurements on 353 hypertensive patients performed in similar conditions to those described in SPRINT [8], were immediately repeated by experienced doctors using the auscultation method of the current clinical practice. It was demonstrated that the average BP values were 15/8 mmHg higher. If the SBP detected in SPRINT were increased of 15 mmHg, in order to relate it to the current practice, it would mean that in SPRINT there were better results with SBP values equivalent to about 136.5 mmHg (intensive group) compared to 150 mmHg (standard group). Explained in this way, the SPRINT results would not be so amazing, but only a confirmation of what is already well known.

2) The RCTs stopped early “for benefit” may exaggerate the positive effects reported. An important systematic review [9] showed that, with less than 200 events, the overestimation of the benefit may be substantial. In fact, comparing completed RCTs versus stopped-for-benefits ones, the risk of overestimation decreases with the increase of the number of events: with less than 200 events, there is a very large overestimation (RR 0.37; 95% CI 0.31-0.44); from 200 to 500 events a large overestimation (RR 0.65; 95% CI 0.56-0.77); and finally with more than 500 events a moderate overestimation (RR 0.88; 95% CI 0.80-0.96). In SPRINT total deaths were only 180: in theory the benefit observed in the intensive group of treatment could completely disappear by completing the follow up, planned for a maximum of 6 years. Even with the 250 events of the primary composite outcome, the interruption could give a great overestimation, without which the effect may pass from "moderate" to "modest" or even vanish. Thus, it was questionable having truncated the planned follow-up, in a RCT whose results could change SBP targets for hundreds of millions of people every year, from now on. Thinking to this, the ethical theme of wanting to immediately communicate the possible benefits is very weak, more so because the lack of credibility of SPRINT low target is now restraining its adoption.

3) SPRINT must be located in the context of all the evidence derived from the RCTs comparing thresholds of more or less aggressive BP. A systematic review [10] which added SPRINT to the RCTs already considered in a previous Cochrane review, including also two newer RCTs, for a total of 11 RCTs and 38,584 participants, shows that the most aggressive target does not reduce the all-cause mortality (RR 0.95; 95% CI 0.86 to 1.05). In addition the mortality data in SPRINT diverge from those of the other RCTs: sensitivity analyses excluding SPRINT shows that, in the 10 remaining RCTs (29,223 individuals), all-cause mortality showed rather a tendency to increase (RR 1.03) [10].

4) The benefits, impressive in absolute terms, are less impressive in absolute terms, also because in SPRINT not so many events occurred. The primary outcome has passed from 2.19% per year in the group with standard targets to 1.65% per year in the group with stringent targets. It was necessary to treat for 3 years and 3 months 61 people to avoid one event in 1 of them. In other words, 60 were treated without CV benefits (some with excess adverse events). Focusing on all-cause mortality, it...
was necessary to treat 90 people for 3.26 years to prevent 1 death, while there is no evidence that the other 89 have had their life prolonged.

5) The absolute increase in serious adverse events attributed to the treatment (Table 1) is not so mild as it may appear, especially for the increase in renal damage or acute renal failure. But there was also an increase of the total number of SAEs (defined as "fatal events or endangering the lives and resulting in significant or persistent disability, or which require/prolong hospitalization"). By subtracting from these total SAEs the number of deaths, more frequent with standard targets, the total number of serious but non-fatal events is significantly higher in the intensive group (RR 1.07, 95% CI 1.02 to 1.14), with a number needed to harm (NNH) of 42 [10].

Adverse effects have not increased loss at follow up in SPRINT patients, carefully followed in a RCT, but in clinical practice and with long follow up the increase in adverse effects may reduce the adherence and persistence.

6) Another element of caution should derive from the fact that SPRINT is not double blind, but it was conducted in open. This can introduce bias, typically performance bias (when administering interventions) and detection bias (in assessing the outcomes in favor of lower-target group).

7) The precautions are worth even more because SPRINT could heavily change target for seniors, with catastrophic results, as shown by well-conducted observational studies, such as an U.S. historical cohort with about 650,000 seniors with chronic kidney disease (CKD) [11], or a cohort of 79,376 octogenarians [12], or an Italian prospective cohort with 1,587 very elderly in Milan [13]. Or, in addition, in CHD patients: a SBP <120 was associated with worse outcomes than a SBP of 120-139 mmHg [14].

The risks of causing death with aggressive therapies seem important with frail elderly [15], even if SPRINT tackled the problem by creating a dilemma, since the frail subgroups in this RCT had similar results to the other participants [6].

8) More than 90% of SPRINT participants were already on antihypertensive therapy, many of them with two drugs (therefore it is likely they had had grade 1 or 2 hypertension for a long time). The group with standard therapy reached the 1st year its average SBP of only 3 mmHg, lowering it to 136 mmHg. As we are talking about average values, it is probable that some patients already stable at about 130 mmHg of SBP, randomized in the standard group, had their current antihypertensive drug removed, with possible unfavorable consequences.

Furthermore, since almost all patients were on hypertension therapy, the results cannot be used as an indication to start with antihypertensive medications in elderly hypertensive with physiological SBP between 130 and 140 [16]. Even more after the great RCT HOPE-3 [17], successfully completed after 5.6 years of follow up and not stopped as SPRINT. The HOPE-3 started with antihypertensive drugs (candesartan + hydrochlorothiazide/HCTZ) in patients at intermediate CV risk, average age 66 years and SBP 138 mmHg, without CV disease. This gave benefits only to participants at the highest tertile of SBP (average 154 mmHg). Instead, the lower two tertiles, with medium SBP average 154 mmHg, it is probable that some patients already stable at about 130 mmHg of SBP, randomized in the standard group, had their current antihypertensive drug removed, with possible unfavorable consequences.

Which antihypertensive medications?

SPRINT has not only tried to identify the optimum pressure target in high CV risk patients, but it has provided also very efficient strategies to achieve them. In fact it used all patent-expired drugs. The most used, 55% of patients in the intensive group, was low-dose chlorthalidone, which would be a first evidence-based choice (see also Italian systematic reviews [18], which show the relative advantages of chlorthalidone and indapamide, compared to the more used HCTZ. The advantages of chlorthalidone upon HCTZ are also evident in a network meta-analysis of direct comparisons [19]). Unfortunately smear campaigns for commercial interests, since chlorthalidone is very cheap, still obstacle its prescription, starting from specialists, even though from 2011 the famous NICE Guidelines [20] of the United Kingdom clearly affirmed that other thiazides diuretics should be replaced by the two thiazide-like diuretics chlorthalidone and indapamide.

At the 2nd place by frequency of use in SPRINT there was amlopidine (almost 53% of patients in the intensive group), a calcium-antagonist very effective on stroke and mortality in RCTs meta-analysis. In some cases it was used along with chlorthalidone, to obtain stronger hypotensive effects.

At the 3rd place there were β-blockers (41%, including metoprolol and atenolol, often associated with chlorthalidone).

At the 4th and 5th there were angiotensin receptor blockers (39.7%, losartan and azilsartan) and ACE-inhibitors (37%).

Unfortunately, the media and the large majority of medical journals have ignored that SPRINT has used only inexpensive generic drugs, and primarily the very effective but even cheaper chlorthalidone.

Ko et al. [2] concluded that a stricter BP control in hypertension, following the SPRINT [1] criteria, is associated with a decreased risk of major CV events (MACE) in an unselected population. In the hypertensive adults ≥20 years covered by Korean NHIS, after a 6.6 years mean follow-up, those above the SPRINT criteria but below the JNC-8 goals (in particular, SBP <140 mmHg) showed a greater risk of MACE (multivariable-adjusted HR 1.17; 95% CI 0.94-1.45), and, always in tendency, a greater risk of CV death, myocardial infarction, stroke versus those below the SPRINT BP goals.

This conclusion, and the abstract, which generally reflects what the media portray, are astonishing. Indeed the all-cause mortality, which is the obvious most valued outcome for the majority of patients (if correctly informed), moved to the opposite direction, with a significant HR 0.83 (0.72-0.95) in those above the SPRINT but below the JNC-8 goals.

In tendency even those above the JNC-8 goals had a lower all-cause mortality (0.98; 0.84-1.15). Provided that this is an observational study, the contradictory results between CV events and all-cause mortality might be due to confounding, but the dissociation between these two outcomes is not such an unusual event with antihypertensive drugs.

It is noteworthy that almost all the RCTs on antihypertensive drugs conducted in very elderly have increased in tendency the all-cause mortality [21], though reducing stroke. HYVET [22,23], with low-dose indapamide, followed by a low-to-moderate dose ACE-inhibitor as needed, was the first RCT which had reduced the former and the latter.

Nobody doubts the benefits of lower BP on stroke and ischemic heart disease mortality. The doubts concern how low should we go in lowering BP with drugs, and whether, for very low BP levels, there could be a dissociation between some CV outcomes and all-cause mortality. This is the case of Ko’s et al. study [2], and also of other studies. For example the largest on-treatment cohort analysis [24], a Swedish national sample 187,106 participants with type 2 DM - a group at high

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risk for CVD, with a mean 5-years’ follow-up, showed that patients with the lowest baseline SBP (110–119 mmHg), on the one hand had significantly lower risks than the reference group (130–139 mm Hg) for nonfatal and total acute myocardial infarction, nonfatal and total CVD, and nonfatal coronary heart disease. On the other hand, the lowest BP group did have, however, an elevated risk for heart failure and all-cause mortality. In addition, this group had the highest levels of mortality due to infection; nervous, respiratory, and gastrointestinal diseases; and external causes.

We think that this is a very important message to take home. Would a patient prefer to avoid dying/suffering from a non-fatal myocardial infarction, a non-fatal stroke or a non-fatal CVD but incrementing his risk of (premature) mortality, or would he choose to die later? For the majority of patients this is a rhetorical question, but this is the natural conclusion that emerges from the cited researches.

In another systematic review [25] the optimal BP target is not consistent with SPRINT target. In fact the most intensive blood pressure-lowering treatment group, with better outcomes, had mean BP levels of 133/76 mmHg, compared with 140/81 mm Hg in the less intensive treatment group. 133 is 11,5 mmHg higher than the mean BP levels of 121,5 mmHg declared by the SPRINT authors.

The real world cohort-study here analyzed [2], with 67,965 unselected participants, mean age 52 and 1,982 deaths, far to give support to the SPRINT criteria, seems rather to in-validate them, and raises questions about some insufficiently highlighted SPRINT limits, already reported in the text above.

Discussion

The scientific community is sharing part of the criticism to SPRINT, while, with respect to other issues raised by this trial, there is a heated debate.

As regards to the Korean study [2], the main objection that we have moved is that the authors emphasize only the CV protection provided by more stringent target of SBP, but definitely forget (even denying it) the far more worrying aspect of a specular and significant increase in all-cause mortality. Although the auditors of the Journal of American College of Cardiologists seemed to agree with this our critical remark, our letter has not been published, despite neither the Editorialists [26] nor other published letter have noticed it.

Conclusions

The SPRINT trial results have mislead many commentators, unaware of its serious pitfalls, and of the substantial incomparability of its BP value-reading with those carried out by the physicians in the current clinical practice.

The serious misinterpretation of a Korean study [2], claiming to give support to the SPRINT criteria in the real world, is likely to aggravate the confusion about SBP optimal-and-safe targets.

The erroneous interpretation of studies on SBP thresholds can cause clinical damage and lead to an increase of costs difficult to bear.

Conflict of interest

None

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