SPRINT: the race for optimal blood pressure control

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Received 24 October 2015; accepted 24 October 2015; online publish-ahead-of-print 11 December 2015

The discovery of blood pressure

When Steven Hales, for the first time, measured blood pressure in an awake horse in 1733,1 he was not aware of the fact that this haemodynamic parameter varies substantially in any organism depending on the situation and with a daily rhythm. Even less was he aware of the fact that some individuals may have elevated blood pressure and that this may be bad for their health. Indeed, until the beginning of the 20th century most physicians felt that elevated blood pressure would be a response to a requirement of the organs in hypertensive patients.

Nevertheless, when Franklin D. Roosevelt, the 32nd president of the USA, came into office, blood pressure was meticulously measured and documented (Figure 1),2 but its importance hardly recognized. Roosevelt’s personal physician Admiral Ross T. McIntire obviously was completely surprised when his patient suddenly experienced a cerebral haemorrhage in 1945 and subsequently died. In his statement to the press he said ‘it came out of blue sky’.3

Today, thanks to the Framingham study4 and many other large epidemiological projects, it is obvious to us that blood pressure was indeed the underlying cause of the fatal event of the president and for myocardial infarction and stroke in millions of hypertensive patients. In any case, in Roosevelt’s time it would have made no difference as no effective treatment was available except Kempner’s rice diet5 which hardly any patient could maintain over prolonged periods of time and neither did the president.

The advent of blood pressure lowering

After the war, more and more drugs that were able to lower blood pressure became available, among them mercurial diuretics, then reserpine and guanethidine.6 Of note, in the 1950s, as early antihypertensive drugs were not very effective and/or associated with severe side effects, surgeons started to perform sympathectomies in patients with uncontrolled hypertension.7 Indeed, and this is of interest for the current debate on renal nerve ablation,8 they were able to show that mortality was reduced particularly and most impressively in patients with severe hypertension and end-organ damage. However, because of the side effects and complications of the operation, it was quickly abandoned as a therapeutic regimen in hypertensive patients.

In the 1970s, the Veterans Administration Trial, for the first time, showed that indeed blood pressure lowering was protecting against stroke, myocardial infarction, and death.9–10 Ever since, blood pressure lowering became a major activity of most physicians in their daily practice. With the advent of additional and more effective drugs with an excellent safety profile — drugs such as betablockers,11 calcium antagonists, ACE-inhibitors,12 and angiotensin-receptor antagonists — blood pressure control became possible in the overwhelming majority of the patients. Indeed, today only a minority of patients is considered to be treatment resistant.13

Target blood pressure

The target blood pressure, however, remained a matter of discussion. Indeed, initially 160/95 mmHg was considered sufficient, then guidelines changed the target values to 140/90 mmHg14 and just recently the US JNC-8 guidelines15 changed the target value again for elderly patients to 150 mmHg in the systolic range.

As blood pressure has a strictly linear relation to myocardial infarction, stroke, and death,16 it would appear that—as in lipid management—the lower the better should be the rule. Obviously, there is a limit in lowering blood pressure because of ensuing hypotension associated with dizziness and eventually falls and syncope. Nevertheless, ideal blood pressure has been defined by many guidelines and in consensus papers as being in the range of 120/80 mmHg.

As a result, trials have been designed to test the hypothesis whether 120/80 mmHg would be more protective against future cardiovascular complications than 140/90 mmHg, but all of them so far failed. For instance, the results of the Action to Control Cardiovascular Risk in Type 2 Diabetes (ACCORD) trial17 showed no benefit of an intensive blood pressure reduction in patients with diabetes mellitus (Figure 2) and the HOT study showed an optimal protection against combined major cardiovascular endpoints in the
range 80–85 mmHg for diastolic blood pressure and in the range 130–140 mmHg for systolic blood pressure\textsuperscript{17,18} Thus, it comes as great surprise that the recently stopped SPRINT trial now clearly demonstrates that lower is indeed better and that patients reaching 120/80 mmHg have less cardiovascular major adverse cardiovascular events than those with blood pressures of 140/90 mmHg.

*Figure 1* Franklin D. Roosevelt, the 32nd president of the USA, shortly before his fatal cerebral haemorrhage (left) and his blood pressure during his presidency until his death (right; from Ref. 2).

*Figure 2* Cardiovascular event rate in the ACCORD trial (from Ref. 17).
The SPRINT trial

This landmark trial sponsored by the National Institute of Health in Bethesda studied more than 9300 patients aged 50 years or older with high blood pressure in about 100 centres across the USA and Puerto Rico. However, although the study population was diverse and included women, different racial and ethnic minorities as well as the elderly, SPRINT - in contrast to ACCORD - did not include patients with diabetes, prior stroke, or polycystic kidney disease. Between 2010 and 2013, the SPRINT investigators randomized study participants into two groups that differed according to targeted levels of blood pressure. The standard group received on average two blood pressure medications to achieve a target of \(<140\) mmHg systolic while the intensive treatment group received medications to achieve a target of \(<120\) mmHg systolic and received an average of three drugs. The primary endpoints were the rates of cardiovascular events such as myocardial infarction, heart failure, stroke, and death. Excitingly, these events were reduced by almost a third and the risk of death by almost a quarter (Figure 3).

What are the reasons that SPRINT was positive, while ACCORD was neutral? First of all, it is statistical power: While ACCORD enrolled 4'377 patients, SPRINT recruited more than twice as many, i.e. 9'361 hypertensives. Also, SPRINT did not include diabetics, while ACCORD was focusing on this patient group. Finally, the achieved blood pressure reduction was also slightly higher in SPRINT compared to ACCORD (17 vs. 14 mmHg systolic).

Figure 3 Results of the SPRINT trial: Primary Outcome and Death from Any Cause. Shown are the cumulative hazards for the primary outcome (a composite of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) (Panel A) and for death from any cause (Panel B). The inset in each panel shows the same data on an enlarged y axis. CI denotes confidence interval.
How generalizable are the results of SPRINT? Obviously, they do not apply to diabetics, patients with polycystic kidney disease or severe renal failure. Of note, the effects of intensive blood pressure lowering was homogenous throughout all 6 prespecified subgroups, i.e. age, gender, race, previous cardiovascular disease, previous chronic kidney disease and baseline systolic blood pressure. Whether diabetics should be excluded is questionable; indeed, the combined results of both ACCORD and SPRINT suggest consistency of both data sets (Figure 4).21 However, what to do with patients under 50 or those over 50 with no other risk factors remains unanswered. Finally, the sweet spot of target blood pressure within the J-curve may differ in different patients, a fact that still calls for a physician with experience in managing patients with high blood pressure.

What is the prize of such an impressive benefit? As expected, hypotension and syncope was more common in the intensive group as was hyponatraemia and hypokalemia (possibly due to the more frequent use and/or higher dosages of diuretics) as was a decline in glomerular filtration rate (possibly due to the more frequent use and/or higher dosages of inhibitors of the renin angiotensin system).22 Thus, these variables have to be monitored more carefully, if a target blood pressure of 120 mmHg is envisaged.

### Clinical implications

What do these results mean for us? Obviously, we should adapt our current practice, if we want to serve our patients. Lower blood pressure target levels means more drugs, as also documented by the SPRINT trial, but also better combinations as well as the optimal use of non-pharmacological interventions such as weight loss, exercise, and dietary measures.

As a result of such ambitious target levels, the number of uncontrolled hypertensives will inevitably rise. This, on the other hand, is an opportunity for interventional measures to lower blood pressure such as renal nerve ablation,23 baroreceptor stimulation,24 and central arteriovenous anastomosis.25

Overall, SPRINT opens the door for an even better management of blood pressure to the benefit of our patients. It is our duty now to implement appropriate measures to reach this goal.

### Acknowledgement

There are no conflicts involved with this Editors page nor was this publication supported by any industry or grant agency.

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