Editorial

Hypertension Management and Prevention: The Devil is Ever in the Details of Targets

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Since the 1990s the development of the chemical treatment of human disorders, based on principles of human physiology, and clinical pharmaco-kinetics and -dynamics, has culminated in coherent sets of drug treatments that work reliably in most of the chronic non-communicable diseases affecting people worldwide. In the past 10-12 years the progressive refinement of antihypertensive drug treatment via well powered randomised clinical trials (RCTs) and meta-analyses thereof, has provided physicians with a core of blood pressure (BP) management knowledge which they can adapt easily across gender, ethnic groups, age bands, and coexisting disorders.

Even if the complex disorder-tailored management knowledge is not agglomerated into practice guidelines, the overall logic and workflow are simple enough to apply in urban communities without the use of a smartphone app. For instance, moderate hypertension, consisting of a sustained average blood pressure of 160/100 to 179/109 mmHg, usually responds within 2 months to a combination of angiotensin-converting enzyme inhibitor (AceI) and calcium ion-channel antagonist (calcium blocker, [CB]). However, some patients in the upper zone of this BP range might need a third drug, such as a ß1-selective ß-blocker or ß-blocker/α_1 blocker, a thiazide or thiazide-like diuretic, or an α_1-blocker—depending on their coexisting disease(s).

Upon such refinements depend the recommendations in practice guidelines, including the clinical practice guideline (CPG) for hypertension of the Ministry of Health, Singapore, which will soon appear after a prolonged gestation—the last guideline was published in 2005. The advices in the upcoming guideline were carefully weighed in the light of rigorously selected RCTs. Practitioners might regard the CPG as a comprehensive resource of sound and reliable advice for bespoke treatment for a particular patient, and indeed that is its basic purpose. Naturally, only time will tell to what extent the CPG succeeds in this broad objective.

It is always wise to reflect on the evolutionary nature of the RCT information from which CPG advices are derived. What is not broadly understood is that the vast majority of reviewed RCTs completed between 1986 and 2016 relied on several different instruments for BP measurement, the accuracy of which ultimately depended on unrecorded or non-implemented calibration with the gold-standard of directly measured intra-arterial blood pressure. The mercury column manometer (manual and analogue) and the aneroid manometer (semi-automatic and analogue) have been largely superseded by non-invasive arterial pressure technology, e.g. oscillometric wave algorithms yield numbers derived from pulse-wave forms.[1] From the latter design emerged the miniature "automated" oscillometric devices widely used in Singapore hospitals, polyclinics and many family medical centres. Strictly speaking, the latter are semi-automatic, but it is a matter of time before manometry becomes fully automated. The components retained from the earlier devices are only the pump and the inflatable cuff.

Why is BP measuring technology important? It matters because the physics of pulsatile and approximately laminar blood flow within human arteries is constant, but the BP values might not be measured linearly by all the current devices across the pressure range of, for instance, 115/75 to 220/120 mmHg (± 1 standard deviation [SD], covering 68.3% of a population), never mind an extreme range such as 80/50 to 280/160 mmHg (± 3 SD, or 99.7%). Secondly, assuming perfect size fitting of cuff-to-upper arm and well trained handlers, the mercury manometer needs calibration infrequently, and is better for accuracy of the systolic and diastolic BP, whereas digital oscillometric manometers produce BP values that are affected by heart rate, pulse pressure, arterial stiffness (the inverse of compliance), and atrial fibrillation.[2] Stiffer arteries in older persons blur the change in capacitance or in piezo-resistance, which constitutes the voltage signal translated by a microprocessor, via a simple algorithm, into numbers (viz. digits) of mmHg. Oscillometric BP estimation in older persons therefore tends to yield less accurate values of mean arterial pressure (= 2/3 diastolic BP + 1/3 systolic BP).

A blizzard of antihypertensive treatment trials has shown beyond reasonable clinical and statistical doubt that real and measurable cardiovascular (CVS) preventive benefit

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follows, within months in some persons, the reduction by single-digits of mmHg in the blood pressure below arbitrary but agreed thresholds. As the demographic load in many affluent countries expands for persons aged ≥70 years, any errors in measured BP clearly will affect many more people at very high CVS-event risk.

But, for measuring heart rate and the average BP simultaneously in many persons, digital meters—if calibrated often and applied consistently—are far ahead in speed and convenience.[1] Portable digital "monitors" applied on the upper arm are thus an epidemiologist's dream machine. It is no surprise that 24-hour ambulatory (brachial) BP monitoring has replaced mercury column manometry as the reference standard for determining an individual's BP status, i.e. for diagnosis and classification.

Crucially, however, the instantaneous BP varies hugely according to the individual's anxiety level, the extent of adrenergic nervous system activation (or recent exercise), ambient noise level, and the presence of other persons during the BP measurement. It goes without saying that the latter factor can greatly raise the measured BP, analogous to a nocebo effect[3]—the converse of the placebo effect. And yet this BP upsurge is widely ignored in both wards and clinics, and sometimes incompletely accounted for in RCTs.

Of the dozens of RCTs in the past 30 years, only the SPRINT and SPRINT-75 studies[4,5] were conducted using automated devices that measured the BP while the patient was sufficiently rested, and alone, in a quiet room. Moreover, none of the study patients had high pulse pressure. Experienced physicians know that about 1 in 5 persons will regularly show isolated clinic hypertension (e.g. 210/115 mmHg measured by an aide using an automatic oscillometric device), which settles towards 130+ mmHg systolic pressure, within about 10 minutes when the patient is alone. Yet most of the past 30 years' RCTs were conducted with manual non-automated, non-oscillometric manometers in the presence of one or more clinic or research staff. Careful studies have shown that the BP values recorded in non-rested persons under non-standardised, non-ideal, clinic conditions usually overestimate the actual systolic BP by about 10 or 12 mmHg.[6,7]

Admittedly such a difference is not critical for showing treatment-related changes in physiology so long as (i) BP changes due to drug treatment or other (e.g. device-related) interventions are not compared across different techniques of BP measurement, (ii) within-subject changes in the BP are consistently tracked across time (in cohort studies), and (iii) the lowest zone of BP is not linked to a paradoxical rise in CVS-event risk (the familiar J curve or J-shaped relation).

Debate continues on whether it matters that a clinician targets the patients' BP values at 120/80 mmHg (measured by a mercury manometer, for example), whereas the SPRINT target BP was measured by an automated oscillometric device.[4] Will the patient's mercury-manometric systolic pressure of 120 mmHg in the clinic actually represent an oscillometric BP of about 110 mmHg, which could be physiologically harmful to that patient in terms of arterial perfusion of the heart, brain and kidneys?

Due to physiological variation, an individual's home-at-rest systolic BP varies such that about 30 serial values can narrow the SD to 4 mmHg.[8] To decrease 95.5%, that is 2 SDs, of these averaged values below 130 mmHg would entail a true systolic BP of about 122 mmHg. By extension, to decrease 2 SDs of averaged values below 120 mmHg (the intensive treatment target) would require a true systolic of about 111 mmHg. The latter pressure, measured by mercury manometry, translates into a systolic pressure of about 100 mmHg by digital oscillometry. A physician faced with this requirement might well intensify the antihypertensive treatment—potentially causing postural hypotension, or physiological harm in terms of arterial perfusion of the heart, brain and kidneys, or both.

Natural caution in this area suggests that a new consensus might occur on systolic BP targets such as 130 mmHg rather than 120 mmHg.[9] However, a recent meta-analysis of 49 RCTs involving nearly 74,000 diabetic persons suggested that a systolic target of 139 mmHg or lower is linked to a rise in CVS death, "with no observed benefit".[10] This result is counterintuitive, as we would expect the largest clinical benefit in CVS-event prevention to occur in higher-risk patients,[11] as many earlier meta-analyses had shown.

Nonetheless, clinicians and bio-scientists will note that the SPRINT and SPRINT-75 studies of people at high CVS-event risk were funded and conducted by the National Institutes of Health USA, as opposed to the vast majority of pharmaceutical-company funded treatment trials, whose results produced the outcome interpretations within most or all practice guidelines to 2016. The publication of the two SPRINTs was a blast of fresh air. As usual, though, the fresh air contained some deficiencies: unlike the bulk of antihypertensive RCTs, they failed to decrease mortality from myocardial infarction, all CVS events, and from heart failure. Despite its early ending, SPRINT's outcomes might apply to about 7.6% of American adults, and 1 in 5 patients were aged 75 years or more.[5] Will the SPRINTs infer a scientific need to build up a pragmatic database of treatment outcomes using the strict evidential and methodological criteria applied?

It appears likely that some large-scale RCTs exceeding 4-5 year time-frames will be conducted to the exacting standards pioneered by SPRINT in subpopulations such as elderly people, and those with diabetes, chronic kidney disease, recent stroke, and any combination thereof. The effective numbers needed to benefit or to harm should be

fairly small in the multimorbid group. While the results of an early-wave meta-analysis of the latter kind supported the SPRINTs in terms of CVS-event reduction and the progression of albuminuria, between-group CVS mortality and all-cause deaths did not decrease with intensive BP reduction towards 118/75 mmHg.[12] Therefore, we await a comprehensive review in due time.

There is one bright spark on this horizon, viz. the bioscientific dynamos in China[13-16] might yet produce the evidential goods which should underpin the finetuning of the therapeutic BP targets and border posts that physicians heed to design minimum effective treatments for the best (net) benefits. One such in-progress RCT is the Chinese high normal blood pressure study (CHINOM) (Zhang Yuqing, personal communication at the 13th Asian Pacific Congress of Hypertension, Singapore, 6-8 October 2017). It promises to provide information on the biological value of multipronged pressure reduction in the approximate +1 SD of any human population, that is the Gaussian "hump" zone consisting of persons with BP of systolic 125-139 mmHg and diastolic 75-89 mmHg. The data from CHINOM could provide insights on pragmatic treatment targets in "relatively healthy" adults with borderline hypertension. Much will depend on the accuracy and consistency of that fundamental issue: pressure measurement.

REFERENCES

1. Wan Y, Heneghan C, Stevens R, McManus RJ, Ward A, Perera R, et al. Determining which automatic digital blood pressure device performs adequately: a systematic review. J Hum Hypertens 2010;24:431-8.
2. Selmyte-Besuspare A, Barysiene J, Petrikonyte D, Aidietis A, Marinskis G, Laucevicius A. Auscultatory versus oscillometric blood pressure measurement in patients with atrial fibrillation and arterial hypertension. BMC Cardiovas Disord 2017;17:87.
3. Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet 2016;389:2473-81.
4. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. New Engl J Med 2015;373:2103-16.
5. Williamson JD, Supiano MA, Applegate WB, Berlowitz D, Campbell RC, Chertow GM, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized trial. JAMA 2016;315:2673-82.
6. Kjeldsen SE, Jund-Johansen P, Nilsson PM, Mancia G. Unattended blood pressure measurements in the Systolic Blood Pressure Intervention Trial: implications for entry and achieved blood pressure values compared with other trials. Hypertens 2016;67:808-12.
7. Bell KJ, Hayen A, Macaskill P, Craig JC, Neal BC, Fox KM, et al. Monitoring initial response to angiotensin-converting enzyme inhibitor-based regimens: an individual patient data meta-analysis from randomized, placebo-controlled trials. Hypertens 2010;56:533-9.
8. McManus RJ, Glasziou P, Hayen A, Mant J, Padfield P, Potter J, et al. Blood pressure self-monitoring: questions and answers from a national conference. BMJ 2008;337:a2732.
9. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957-67.
10. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016;352:1-10.
11. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.
12. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet 2016;387:435-43.
13. Zanchetti A, Liu L, Mancia G, Parati G, Grassi G, Stramba-Badiale M, et al; ESH-CHL-SHOT trial investigators. Continuation of the ESH-CHL-SHOT trial after publication of the SPRINT: rationale for further study on blood pressure targets of antihypertensive treatment after stroke. J Hypertens 2016;34:393-6.
14. Zanchetti A1, Liu L, Mancia G, Parati G, Grassi G, Stramba-Badiale M, et al; ESH-CHL-SHOT trial investigators. Blood pressure and LDL-cholesterol targets for prevention of recurrent strokes and cognitive decline in the hypertensive patient: design of the European Society of Hypertension-Chinese Hypertension League Stroke in Hypertension Optimal Treatment randomized trial. J Hypertens 2014;32:1888-97.
15. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A; FEVER Study Group. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens 2005;23:2157-72.
16. Zhang Y, Zhang X, Liu L, Wang Y, Tang X, Zanchetti A; FEVER Study Group. Higher cardiovascular risk and impaired benefit of antihypertensive treatment in hypertensive patients requiring additional drugs on top of randomized therapy: is adding drugs always beneficial? J Hypertens 2012;30:2202-12.