South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Cardiovascular conditions

Summary review

Date: July 2018

Blood pressure targets

Background

Diseases of lifestyle are a growing problem in South Africa, and a recognised focus of the Department of Health. Several international studies have demonstrated clear cost-effectiveness of various BP lowering strategies driven by high population prevalence and long time to accrue additional benefit in primary prevention approaches. The recent SPRINT trial demonstrated both CVS endpoint and mortality advantages of tight control in older patients, which led to a recent US recommendation for a lower overall treatment threshold.

Evidence

A number of systematic reviews have been performed related to this topic. They vary in the exact question addressed and whether or not they include data from SPRINT, but as a group they provide useful insights, although not necessarily definitive answers.

When comparing information from these sources it is worth remembering that individual trials and reviews do not have entirely consistent definitions of endpoints, and vary in selected duration of treatment and follow-up. Definitions of what constitute primary prevention (versus treatment in the presence of comorbidities) also vary. Some reviews focused on initial treatment thresholds whereas others looked at achieved target levels.

One of the earliest post-SPRINT reviews was that by Ettehad et al[1]. In this review of 123 studies with 613 815 participants, the key finding was for every 10 mmHg systolic BP reduction achieved the MACE relative risk was 0·80, (95% CI 0.77 to 0.83), that for CHD was 0·83, (95% CI 0.78 to 0.88), stroke was 0.73, (95% CI 0.68 to 0.77), and for heart failure was 0.72, (95% CI 0.67 to 0.78). There was also a significant mortality benefit (0.87, 95% CI 0.84 to 0.91). Specifically, this benefit was also seen in the stratum with baseline BP of < 130 mmHg, and this information has been used as evidence to support a tighter treatment threshold.

In this generally well-conducted systematic review several issues warrant attention. Firstly, although Higgins (2003) arbitrarily defined heterogeneity as low if I^2 was around 25% or less and moderate

[1] Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-967

around 50% and the authors acknowledge this, the figures for outcomes, ranging from 25% to 41% warrant acknowledgement. Of more concern for this review, for each endpoint the effects sizes (Fig 4 from the article, reproduced below) when stratified by level of initial BP cluster quite consistently, even with the impression of a trend (greater benefit from treating higher BP, although the authors state that benefit did not differ significantly by this variable). Concerningly, however, for BP < 130 mmHg, there is almost an outlier effect with consistently larger benefit in this group, but with wide confidence intervals reflecting the small absolute number of events in this group – e.g. in the mortality endpoint group, only 4.1% (410/9998) of events in the control arm occurred in the group with BP < 130 mmHg. The conclusions around this group are hence considerably less robust, and probably mostly driven by SPRINT. A final point is that the method of standardisation used in the review may have affected study weights and increased the size of treatment effects[2].

A detailed review of SPRINT will not be provided, but key issues were the elderly population, the choice of method for measuring BP (likely to generate values between 10 and 20 mmHg lower than with older methods[3]) and the issue that the trial was stopped early, which some authors argue may have led to an overestimation of effect size. It should also be noted that the participants had non severe hypertension and despite intensive monitoring and the use of an average of 2.8 anti- hypertensive medications less than 50% 0f patients in the intensive treatment arm achieved a systolic BP <120 mmHg.

A more recent review was published in 2018[4] using slightly different methodologies.

In this review, (74 trials, 306 273 participants) overall benefits across the different outcomes was satisfyingly consistent with the previous article. In this review, the only group where starting BP of <140 mmHg was associated with any statistically significant benefit was for heart failure (RR 0.88, 95% CI 0.78 to 0.98).

[2] Brunström M, Carlberg B. Standardization according to blood pressure lowering in meta-analyses of antihypertensive trials: comparison of three methodological approaches. *J Hypertens*. doi:10.1097/HJH.0000000000001574

[3] Filipovský J, Seidlerová J, Kratochvíl Z,K arnosová P, Hronová M, Mayer O Jr. Automated compared to manual office blood pressure and to home blood pressure in hypertensive patients. *Blood Press*. 2016;25(4):228-234.

[4] Brunstrom M, Carlberg B. Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels A Systematic Review and Meta-analysis *JAMA Intern Med*. 2018;178(1):28-36. doi:10.1001/jamainternmed.2017.6015

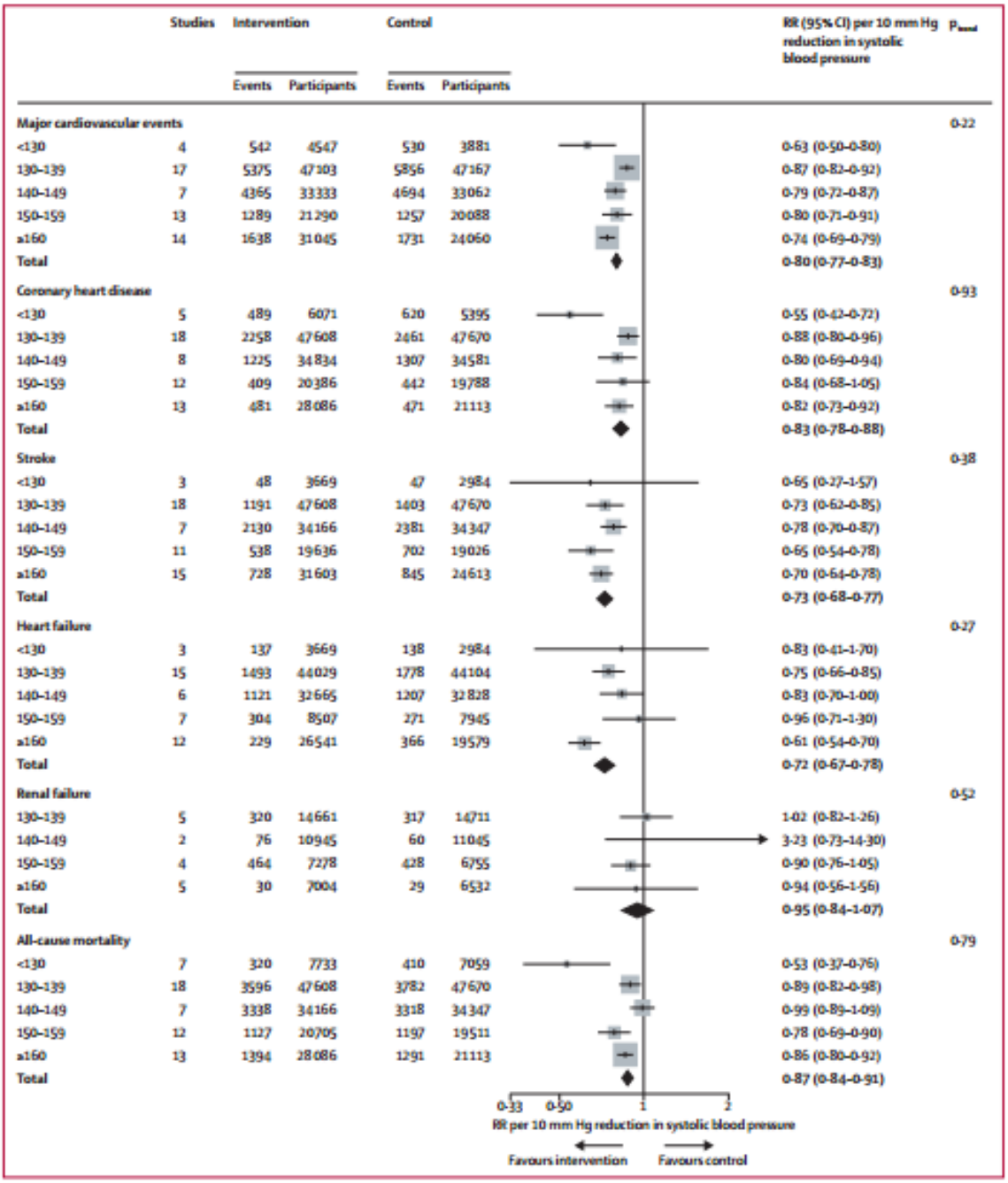
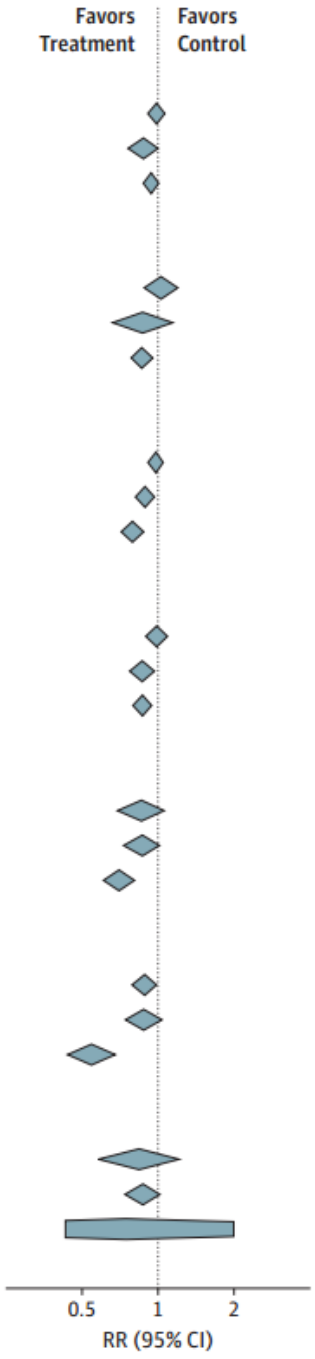


Figure 4: **Standardised effects of a 10 mm Hg reduction in systolic blood pressure stratified by blood pressure**
Blood pressure strata are baseline blood pressure values, not achieved blood pressure after treatment. RR=relative risk.

Figure 1. Effect of Treatment to Lower Blood Pressure (BP) at Different BP Levels in Primary Prevention

Baseline SBP, mm Hg	No. of Events/ Participants/Trials	RR (95% CI)	Heterogene I^2 Value, %
All-cause mortality			
<140	4897/68 816/16	0.98 (0.90-1.06)	11.6
140-159	2731/41 049/15	0.87 (0.75-1.00)	43.2
≥160	4361/79 900/18	0.93 (0.87-1.00)	17.0
SBP interaction, *P* = .18			
Cardiovascular mortality			
<140	2633/66 480/12	1.03 (0.87-1.20)	43.4
140-159	1465/42 587/15	0.86 (0.65-1.14)	57.9
≥160	2290/78 789/17	0.85 (0.77-0.95)	18.0
SBP interaction, *P* = .02			
Major cardiovascular events			
<140	7354/67 928/13	0.97 (0.90-1.04)	30.6
140-159	3951/43 489/16	0.88 (0.80-0.96)	31.0
≥160	4627/77 733/16	0.78 (0.70-0.87)	53.8
SBP interaction, *P* = .004			
Coronary heart disease			
<140	1618/62 617/11	0.98 (0.88-1.09)	0.0
140-159	1369/42 543/14	0.86 (0.76-0.96)	0.0
≥160	2018/78 617/17	0.86 (0.78-0.94)	0.0
SBP interaction, *P* = .13			
Stroke			
<140	1775/62 751/11	0.85 (0.68-1.06)	54.1
140-159	1429/41 641/13	0.86 (0.72-1.01)	21.4
≥160	1929/79 900/18	0.69 (0.60-0.80)	47.3
SBP interaction, *P* = .16			
Heart failure			
<140	2261/60 879/9	0.88 (0.78-0.98)	29.8
140-159	1113/35 254/10	0.87 (0.73-1.04)	5.3
≥160	520/23 395/10	0.53 (0.42-0.67)	17.6
SBP interaction, *P* = .005			
End-stage renal disease			
<140	488/24 512/5	0.84 (0.57-1.24)	42.5
140-159	870/32 984/7	0.88 (0.74-1.04)	0.0
≥160	32/5566/2	0.73 (0.01-6.45)	0.0
SBP interaction, *P* = .32			



An earlier systematic review[5] showed broadly similar results although it was published before SPRINT. For the intensive therapy group (mean BP 133/76 mmHg), MACE were reduced (RRR 14%, 95% CI 4 to 22), as was myocardial infarction (RRR 13%, 95% CI 0 to24), and stroke (RRR 22%, 95% CI 10 to 32) but without benefit on CCF (RRR 15%, 95% CI –11 to 34), or total mortality (RRR 9%, 95% CI –3 to 19).

[5] Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016;387(10017):435-443.

A network meta-analysis of randomized trials (17 RCTs, 55163 patients with 204103 patient-years of follow-up) including SPRINT found a benefit of lower systolic BP targets for reducing stroke and myocardial infarction. There was no significant difference in mortality, cardiovascular mortality or heart failure in the < 120mmHg target group when compared to the higher target groups.[6]

The Network Meta-Analysis did not only look at the benefits of lower BP targets but importantly also considered the potential harm and severe adverse events which were highest for BP target <120mmHg. Cluster plot included below.

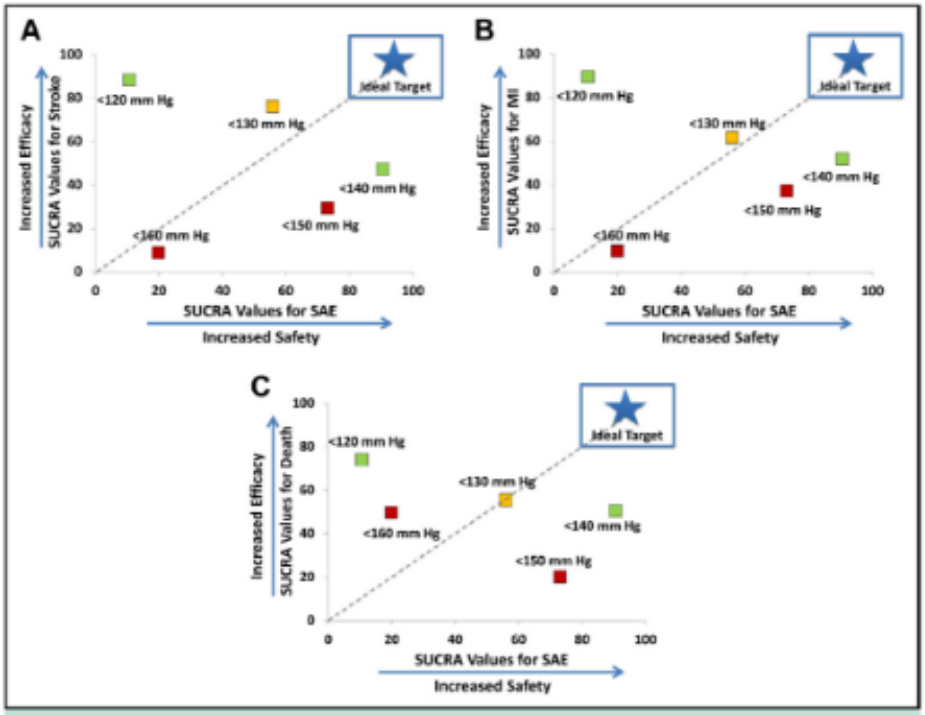


Figure 4 (A) Cluster plot for stroke vs serious adverse effects. (B) Cluster plot for myocardial infarction vs serious adverse effects (SAE). (C) Cluster plot for death vs serious adverse effects. The higher the surface under the cumulative ranking curve values of a systolic pressure target, the greater is the efficacy or safety. "Star" indicates the ideal systolic pressure target that maximizes outcomes efficacy and safety endpoints. MI = myocardial infarction; SUCRA = surface under the cumulative ranking curve.

Summary

The results of systematic reviews of more intensive lowering of BP are discordant, with differences explained by variations in methodology. In the review showing apparent clear benefit, there were criticisms of the mechanism of standardisation, and the results in the subgroup analysis of those with BP < 120mmHg showed results with wide confidence intervals due to small absolute numbers of events.

In addition, the relative benefits in this group were discordantly large, and possibly influenced by SPRINT. In SPRINT the automated BP measuring process may have generated lower readings allowing

[6] Bangalore S, Toklu B, Gianos E, *et al*. Optimal Systolic Blood Pressure Target After SPRINT: Insights from a Network Meta-Analysis of Randomized Trials. Am J Med. 2017;130(6):707-719.

for an alternative explanation of the findings in that the better outcomes may have been due to the presence of a third antihypertensive rather than necessarily the BP target.

Any possible benefits need to be balanced with potential harm particularly in a setting where it may not be possible to closely monitor or treat severe adverse events. Of particular concern is that among the participants who did not have chronic kidney disease at baseline, a decrease in the eGFR of 30% or more to a value of less than 60 ml per minute per 1.73 m^2 occurred more frequently in the intensive-treatment group than in the standard-treatment group (1.21% per year vs. 0.35% per year).[7]

Although not part of the scientific summary it is important that prior to a change in policy, assessment of the compliance to the current policy and the availability of appropriate resources to introduce a new policy must be considered to ensure that safe implementation is feasible. While it is likely that a tailored approach allowing for more intensive control of BP in high risk individuals may accrue additional benefits, from a public sector perspective it can be argued that higher yield interventions (e.g. lifestyle modifications in younger patients, as recommended in the US guideline) coupled with an intense focus on optimizing control in patients already identified as hypertensive (local evidence mirrors international experience of less than 50% control in this group) may be more appropriate until the evidence has settled more clearly in favour of the tighter target.

[7] SPRINT Research Group; Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103-2116.