PERSPECTIVE

First, a seat; then, an upgrade

Abilash Sathyanarayanan [1]✉

The Sir Stanley Peart Essay Competition is an annual event run by the British and Irish Hypertension Society to encourage Early Career Researchers to continue the ethos of Sir Stanley Peart. Sir Stanley Peart was a clinician and clinical researcher who made a major contribution to our understanding of blood pressure regulation. He was the first to demonstrate the release of noradrenaline in response to sympathetic nerve stimulation. He was also the first to purify, and determine the structure of, angiotensin and he later isolated the enzyme, renin, and carried out many important investigations of the factors controlling its release in the body. This year, the essay topic was "Do we need new classes of antihypertensive drugs?". In his prize-winning essay, "First, a seat; then, an upgrade", Dr Sathyanarayanan argues that we do not need new classes of antihypertensive drugs, instead we should focus our attention on addressing the factors that lead to high blood pressure in the first place and use our existing drug classes more effectively.

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INTRODUCTION

Do we want new classes of antihypertensive agents (AHTs)? Of course we do! There is no doubt that we do. The markets certainly seem to agree. The treatment resistant hypertension market was worth 13 billion dollars in 2021 and it is steadily expanding [1]. There are already multiple novel classes of AHTs vying for the dispatchment into the treatment algorithm [2]. In fact, we have always wanted new/improved classes of AHTs, even back in the nineties [3] and this pursuit is sure to be interminable and insatiable. However, that is not the question under examination in this essay. This one discusses - 'Do we *need* new classes of AHTs?' and I argue that we do not.

I seek to provide contributions to this discussion voicing the more Luddite leaning circles within the hypertension fraternity (with good reason). I initially make arguments drawn from empirical data and subsequently focus on ethical quandaries.

PULLING THE PLUG

The lifetime risk of hypertension exceeds 80% [4]. Hypertension is currently present in about one third of the global population [5]. However, hypertension is not a natural feature of aging [6], and studies in populations without acculturation into modern lifestyles show minimal or no increases in blood pressure (BP) with increasing age [7, 8].

The juxtaposition of these facts brings into question what we are attempting to do in trying to fix the global hypertension epidemic. Do we need new classes of medications to increase the pressure on the lid, or should we attempt to turn off the cooker?

I agree that this reductionist view of the problem may seem partially antediluvian, impracticable (and importantly commercially unprofitable) – but I present this view to simply provide an antithetical pushback to the prevailing ideas of what constitutes advancement in hypertension research.

CAPTAIN, NEW SAIL NEEDED? PORT IN SIGHT!

The underlying tenet of hypertension management (like many chronic medical conditions), is the aggregation of mild to moderate treatment effects of various drugs to reach the goal BP [9]. The average number of medications to reach goal BP in hypertension trials is only 2.6 drugs [10].

However, we have six major classes of first line AHTs [11], and in addition five other classes - mineralocorticoid receptor antagonists (MRAs) (with even more agents in development) [12], alpha-blockers [13], central sympatholytic agents, direct vasodilators [14], and imidazoline receptor agonists [15].

The prevalence of 'apparent' resistant and refractory hypertension is only about 10–20% and less than 1% respectively, in clinical practice [16, 17]. This minority is despite very low AHT adherence rates (at best 50%) [18] and a high prevalence of pseudo-resistant hypertension in this population (about one-third of patients, due to non-adherence and other factors) [19].

Therefore, most patients with inadequately controlled hypertension would be able to achieve their goal BP with the existing drug classes - if administered and consumed appropriately.

CAN I JOIN THE CLUB?

More than 70% of patients with hypertension are overweight or obese, and obesity accounts for 65–75% of the risk of hypertension [20, 21].

Semaglutide and Tirzepatide lead to mean weight loss of 15.2% [22] and 25.3% [23] from baseline, respectively, when used for obesity. In addition, there are multiple other obesity treatment agents in phase 3 trials [24].

Even if these agents never demonstrate any weight independent effects on the BP, they are likely to occupy an important position in the overall cardiovascular risk management in a large proportion of patients with hypertension, lead to significant

[1]Nottingham University Hospitals, Derby Rd, Lenton, Nottingham NG7 2UH, UK. ✉email: drabisat@gmail.com

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reductions in BP due to weight loss, and have 'AHT sparing' effects. This has already been demonstrated in trials [25, 26].

Therefore, once these agents enter routine use, they are likely to lead to a reduction in the average number of medications to reach goal BP or even allow complete withdrawal of all AHTs.

DOES SWAPPING COUNT?

Randomised trial data show reduction in cardiovascular events and mortality when a salt substitute (with 25% potassium chloride by mass) was used in the place of regular salt [27]. Metanalyses also show significant reductions BP with this approach [28]. The World Health Organisation and the US Food and Drug Administration endorse this intervention as a population-based strategy [29]. This approach needs a governmental policy for implementation in high income countries as most of the sodium in the diet comes from 'hidden salt' added to processed food [30].

There is evidence that such a population-based strategy works [31], with an effect size on the BP that is comparable to many AHTs [32, 33].

LESS SPARKLE, MORE SUBSTANCE

While we discuss siphoning more of the finite research funding into the development of new classes of AHTs, I deliberately re-emphasise some widely known and uncomfortable facts about human life on earth.

Half the world's population has no access to essential health care [34], a quarter live in impoverished conditions, 9.2% (719 million people) live on less than $2.15 per day (extreme poverty line) [35], and robust primary healthcare is severely underfunded or does not exist at all in many low- and middle-income countries (LMIC) [36].

A hundred more babies die before their first birthday (per 1000 live births) [37] and children with cancer are four times more likely to die from it [38] in low resource settings in comparison to the developed countries.

To make matters worse, there is increasing hypertension prevalence in LMIC and more than 80% of the people with hypertension (>1 billion people) live in LMIC [5]. Only a third are aware of their diagnosis, and less than 10% achieve BP control [39].

Although it is not strictly one or the other, when considering funding research into new drug targets for hypertension, it is important to also study how to first deliver AHTs that have already been in use for decades.

IT MIGHT HAVE BEEN

The BP is an example of a remarkably good surrogate outcome measure in clinical trials [40]. It is non-invasive, low cost, low risk, and can be measured in a variety of settings [41]. We have decades of epidemiological data that are applicable to many ethnicities [42]. It is statistically efficient due to the near normal distribution in the population and due to it being a continuous outcome measure – reducing sample size needs drastically to detect a clinically meaningful difference, compared to a dichotomous outcome [43, 44]. Using ambulatory BP further allows sample size reduction by minimising variance [45].

Despite the existence of this robust outcome measure, we are not seeing the expected 'explosion' of clinical trials answering questions that are pertinent to LMIC in hypertension research. For example, despite having 220 million people with hypertension in India [46], a culturally acceptable version of the DASH diet has never been tested via a trial in people of Indian ethnicity. This is despite the presence of data to suggest possible heterogeneity of the treatment effect with the DASH diet in ethnic subgroups [47–49]. Please note that the original DASH trial needed less than 500 participants and the intervention phase lasted only 8 weeks [50].

Lack of low cost validated BP measurement devices is another example [39]. None of what I am suggesting is revolutionary, but therein lies its strength – there is precedence to this approach, and the lack of such studies is ethically indefensible.

ONE-TIME FEE, NO RECURRING CHARGES

Orchidectomy is sometimes used as a lower cost option for androgen deprivation therapy in prostate cancer treatment instead of medical options which can be prohibitively expensive during prolonged therapy [51, 52]. Such cost considerations for androgen deprivation therapy apply even in the USA [53]. Other examples include – surgical techniques for contraception [54], fundoplication for reflux disease [55], surgical procedures for epilepsy [56], and early cholecystectomy for cholecystitis [57, 58].

The research into device/procedure-based therapy for hypertension until now has predominantly concentrated only on patients with resistant hypertension [59], and this needs to be widened to other patient groups.

As more techniques become available and non-proprietary methods are developed in the future, such non-pharmacological approaches to hypertension may be more enduring and deliverable on a large scale. Such procedures have shown to be successful in addressing healthcare access issues in low resource settings and can be cost-effective [60, 61].

OLD DRUG, NEW TRICKS

The prevalence of primary aldosteronism (PA) in the hypertensive population exceeds 20%, and in the resistant hypertension subgroup is more than 50% [62, 63]. Despite this high pre-test probability, only 1–3% of patients get screened for PA, even in developed countries [64, 65].

Even when PA is diagnosed, further work up is resource intensive, invasive, and is not available to most patients with hypertension globally [66, 67]. It is unlikely that this situation with PA management is going to change soon given that we have gaps in even the initial recognition hypertension globally, which need to be addressed first [39, 68].

A conservative calculation (20% prevalence) shows that amongst the 1.28 billion patients globally with hypertension [69], 200 million patients have PA. Only about 20% of them live in developed countries [5]. The 'gold standard' management pathway for PA needs to be urgently adapted for local systems based on resource availability.

Although there are data to suggest that aldosterone may have 'BP independent' effects, we do not have robust randomised trial data comparing important 'hard outcomes' between medical management and surgical treatment of PA [70]. Furthermore, adrenalectomy is only recommended in lateralising PA, and for bilateral adrenal disease (the most common finding in PA) MRAs remain the mainstay of treatment [71].

Currently, guidelines recommend MRAs only as the fourth line medication in the management of hypertension [72, 73]. A pragmatic approach to this issue would be to include MRAs earlier in the hypertension treatment pathway (e.g., alongside a first line agent) [68]. This approach needs to be studied with randomised trials and it may play an important role in hypertension management in LMIC. This is likely to be better than what we currently offer many of these patients with PA– no screening and no treatment.

New renin and aldosterone assays with shorter turnaround times (about 10 minutes) [74, 75] have already been developed. A 'cheap point of care test' in the future may help risk stratify patients during initial presentation for early consideration of MRAs. In this important area - new drugs are good, but new tests are better.

FIRST, A SEAT; THEN, AN UPGRADE

In conclusion, the largest absolute benefits in reducing adverse cardiovascular outcomes from hypertension that are yet to be realised clearly lie in furthering implementation studies, optimising current treatment modalities, and in health policy research - and not in drug class expansion. The current real-world data on the state of hypertension treatment provide persuasive inferences to support the above.

All human lives on earth are equal irrespective of each person's per capita GDP (Gross Domestic Product). All human suffering and death, and the emotions around them are equal, irrespective of your ethnicity or the country of birth. Expansion of AHT coverage and reducing sodium intake could potentially save about 80 million lives globally over the next two to three decades [76].

Not pursuing the right approach will allow the contrary.

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COMPETING INTERESTS

Professor Phil Chowienczyk has an interest in Centron Diagnostics, a company that has produced technology for blood pressure measurement. Professor Ian B Wilkinson has received research grants from AstraZeneca, GSK and scientific advisory board consultation fees for Viatris, Astra Zeneca and Roche. Dr Abilash Sathyanarayanan, Dr Sarah Partridge and Professor Peter Sever have no competing interests to declare for this manuscript.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Abilash Sathyanarayanan.