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EDITORIAL

Combatting the Global Crisis of Cardiovascular Disease☆

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Cardiovascular diseases (CVD) are the biggest killers worldwide, currently responsible for approximately 18 million deaths per year, 70% of which occur in low- and middle-income countries (LMIC) [1]. CVD are the largest cause of disability adjusted life year (DALY) loss – a measure that takes into account premature death and disability. This DALY loss includes seven million premature deaths annually, 80% of which currently occur in LMICs [2]. Proportionately, more CVD deaths in LMICs occur among people in economically productive age groups. Globally, the economic loss (due to both direct health care costs and loss of productivity) from non-communicable diseases between 2010 and 2030 is expected to be almost US$50 trillion, about half of which relates to CVD [3]. This is directly growing socio-economic inequalities both within and between countries, with catastrophic expenditure due to cardiovascular events becoming an increasingly common reason for households being pushed back into poverty [4].

There are a number of fundamental society-level drivers of this changing disease burden, but a key proximate cause of the CVD epidemic is non-optimal blood pressure (BP). Globally, it is has been estimated that approximately 20% of all deaths are attributable to non-optimal BP and, most alarmingly, this problem is worsening as population distributions of BP in LMICs become increasingly adverse [5]. For this reason, the Global Burden of Disease Study now identifies high BP as the leading risk factor for disease and disability globally, replacing other factors such as childhood undernutrition or unsafe water. This is true across the world except for the most disadvantaged billion who live in the least developed nations [6].

So, How Do We Tackle BP-Related Disease?

There is widespread familiarity with two major paradigms of disease prevention – public health approaches that attempt to shift the entire population distribution of a risk factor in a favourable direction, and clinical approaches that focus on the treatment of individuals with risk factor levels above a certain threshold. These two approaches are, of course, not mutually exclusive. Population-based approaches such as reducing dietary sodium, increasing physical activity and decreasing unhealthy alcohol use are critical to achieving large, sustainable population-level benefits. From the perspective of individual patient approaches, despite huge advances over recent decades in the availability of highly effective and safe drugs for BP treatment, large gaps in implementation and scale-up persist [7]. This provides an opportunity to challenge traditional paradigms and develop innovative solutions both in terms of clinical care and health systems' responses. From the perspective of LMICs, innovation is particularly important and provides an opportunity to "leap-frog" traditional approaches which are unlikely to address the CVD crisis.

The dominant clinical approach to hypertension management over the last half-century has been to start treatment with monotherapy, and increase dosage in a step-wise fashion before adding additional treatments. However, only about one-half of people in high-income countries and one-quarter of those in LMICs who are started on BP

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lowering treatment achieve a BP level of less than 140/90 mmHg [7]. There is good evidence that a major contributor to this treatment gap is therapeutic inertia – a very real but complex sociological phenomenon resulting in absence of or delays in necessary treatment escalation [8]. While there is substantial ongoing research on behavioural strategies to overcome therapeutic inertia, with limited success, attempting to bypass this problem through innovative use of existing drugs provides a ''leap-frogging'' opportunity.

One such strategy was evaluated in the recent TRIUMPH study [9], conducted in Sri Lanka – a middle-income country with rapidly increasing prevalence rates of hypertension and CVD. In this study, 700 patients with newly-diagnosed hypertension, or who were uncontrolled on monotherapy, were randomised to usual care or the use of a fixed-dose combination pill containing three classes of BP lowering drug each at half-standard dose (''Triple Pill''). The rationale for this approach is evidence that for all major classes of BP lowering drug, a half-standard dose achieves most of the BP lowering effect, and a combination of drugs acting through different mechanisms is likely to provide synergistic effects [10]. Conversely, with the exception of angiotensin-converting enzyme (ACE)-inhibitors, adverse effects are much more dose-dependent, with fewest problems observed using half-standard doses [10]. TRIUMPH was a highly pragmatic trial, where all other treatments (including changes to BP lowering drugs) in both arms were left to the discretion of the treating doctor. At 6 months follow-up, 70% of those randomised to the Triple Pill strategy achieved target BP levels, compared with 55% in the usual care group. The mean difference in systolic BP between randomised groups was almost 10 mmHg. The effects of the intervention were similar regardless of whether this was initial treatment or the patient had previously been on monotherapy. The findings provide a strong rationale for considering initial or early use of fixed-dose combination therapy for the treatment of mild-to-moderate hypertension.

While such new approaches to clinical care are important, even more innovation is required to address what is perhaps the greatest challenge to hypertension management – that is, a massive global failure to implement any effective strategy at scale. With over 1.3 billion people worldwide estimated to have hypertension, and just over one-third on any form of treatment [7], there is an urgent need to develop effective models of care that ensure that people with high CVD risk are not only identified, but are served by a system that actively facilitates their ongoing access to safe, effective, and affordable care.

What Do We Know about Effective Implementation Strategies For BP Management?

There is strong evidence that strategies of team-based care for hypertension (incorporating task sharing between primary care physicians, nurses, pharmacists and community health workers) are some of the most effective for achieving BP control [11]. Notably, we have seen that BP lowering drugs can be effectively administered by a non-physician team member, such as a nurse or pharmacist [12,13]. This has important positive implications for the control of BP in LMICs, where doctors are in highest demand and shortest supply. Interventional studies have shown that electronic clinical decision support systems, accessed through mobile phones and tablets, can be successfully used by non-physician health workers to aid the identification of high risk CVD patients through community-based screening, and increase the uptake of BP lowering treatment [14,15]. When combined with home-based BP monitoring, and coaching to encourage lifestyle modification and adherence to medicines, the effectiveness of these strategies is further enhanced [11].

While each of these interventions provide great promise within the tight boundaries of a randomised controlled trial, their successful implementation in the real world requires a deeper understanding of the broader health system in which implementation occurs – health systems that are complicated, unpredictable, and constantly reacting (and adapting) to health service needs, scientific developments, and technological innovation. In LMICs, these health system complexities are compounded by scarce resources, and multifaceted challenges related to policy, organisational, financial, workforce, and community level factors. System-level barriers to the successful management of CVD in LMICs are well documented [16–19]. At the health service level, these include availability of essential resources including clinical guidelines and diagnostic equipment, lack of adequately trained health care personnel, poor patient referral links, weak drug supply chains resulting in low availability of essential CVD medicines, and ineffective systems for long-term patient follow-up to aid treatment adherence and re-screening. At the patient level, low awareness of CVD risk factors, financial constraints, and barriers to accessing facility-based services prevent many people from accessing, and adhering to, the care that they need.

To effectively combat the global CVD crisis, innovation is critical to overcoming these fundamental barriers to care in LMICs, where three-quarters of those with hypertension – more than 1 billion people – reside. Traditional approaches to health service delivery, reliant on people presenting to clinics and assuming the necessary preconditions for comprehensive and continuous care, are unlikely to work. Instead, models of CVD care must incorporate strategies that enhance reach to underserved populations. At the heart of this task lies primary health care (PHC) — comprehensive care that is provided in the community, that systematically addresses the broader determinants of health, and that empowers individuals, families and communities to promote and protect their own health and wellbeing [20]. Indeed, strong PHC systems are seen as the cornerstone to achieving universal health coverage [21]. Yet PHC systems in many LMICs are built to provide episodic care with emphasis on acute disease management. Consequently, they are not yet sufficiently adapted to prevent and manage chronic diseases nor to integrate care across diseases.

Encouraging examples from recent interventional studies in the world's most populous LMICs show how technological and service delivery innovations can come together within a PHC framework to address BP-related disease. In the multi-country SimCard trial [15], community health workers, with the aid of a smartphone-based electronic decision support system, provided monthly village-based follow-up visits for more than 1,000 high risk CVD patients in India and China to deliver appropriate of BP-lowering treatment (in this case, monotherapy) and counselling for lifestyle modification (smoking cessation and salt reduction) over a 12-month period. A control arm of similar size received usual care. At 12-month follow-up, patient-reported use of BP-lowering treatment increased by 32% in the intervention group compared to 6.5% in controls. The mean difference in systolic BP between groups was almost 3 mmHg. Notably, BP-lowering was only significant compared to usual care in China, where community health workers were able to dispense treatment at point of care. Other facilitators of success included: provider training; task shifting to non-physician health workers; a supportive team structure; active patient follow up; culturally tailored health education; and, perhaps most importantly, an accessible and stable medication supply.

How Do We Achieve Implementation at Scale?

The answer is that there is no 'one-size-fits-all' approach. Health systems are complex, and the wide diversity of economic, social, cultural and physical environments, both within and between countries, necessitate evidence-based context-specific solutions. However, uniting pockets of clinical, technological and service delivery innovation is our most promising strategy yet for producing the ''leap-frog'' effect necessary to combat the global CVD crisis. Fixed-dose combination therapy, delivered through PHC systems, and within non-traditional models of care, appears to be the clearest path to rapidly curb non-optimal BP in LMICs. But sustainable impact will only be achieved by ensuring that wider health system enablers are in place. Importantly, future implementation research must make concerted efforts to understand the drivers for the success (or failure) of CVD interventions, and identify enabling factors that support context-specific adaptation and larger scale adoption.

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