

## Bending the blood pressure curve down: are we succeeding?



Until just a few decades ago, raised blood pressure was regarded as a benign and natural process of ageing that did not warrant treatment. In the 1966 edition of his textbook *Diseases of the Heart*,<sup>1</sup> the cardiologist Charles Friedberg noted that treatment of individuals with a blood pressure lower than 200/100 mm Hg was not indicated. Since then, the accumulation of a large body of evidence on raised blood pressure has fundamentally changed clinical practice and health policy worldwide. Large-scale epidemiological studies<sup>2</sup> have proven beyond doubt that long-term exposure to raised blood pressure is associated with a substantially increased risk of cardiovascular disease, with no apparent benign range at any age. An analysis<sup>3</sup> of population-based studies has quantified the absolute burden of blood pressure-associated death and disability, showing that raised blood pressure has been the leading risk factor for cardiovascular death in every region of the world for the past 30 years. Furthermore, a range of effective and cost-effective interventions for modifying blood pressure-associated risks have been identified.<sup>4,5</sup> Not only have these findings changed clinical practice and public health but they have also become the foundations of global policies; for example, WHO's Global Action Plan for the prevention of non-communicable diseases 2013–20 specifies a 25% reduction or containment of the prevalence of raised blood pressure as one of its nine voluntary targets.<sup>6</sup>

To what extent have these tremendous achievements been effective in reducing the burden of raised blood pressure so far? The most comprehensive and updated answer to this question comes from a report by the NCD Risk Factor Collaboration published in *The Lancet*.<sup>7</sup> In their study, the authors use population-based surveys involving 19.1 million adults to estimate temporal trends in mean systolic and diastolic blood pressure and the prevalence of raised blood pressure (defined as blood pressure  $\geq 140$  mm Hg systolic or  $\geq 90$  mm Hg diastolic) from 1975 to 2015 in 200 countries. The collaboration found that across all countries, age-standardised mean blood pressure has been largely stagnant in men and decreased only by about 2.5 mm Hg in women, with the change in women occurring before 2000 and no apparent change since.

Although at first glance these static trends seem disappointing, a closer look at the disaggregated results and the comparisons of trends among regions

and countries reveals several insights that will help to refocus our efforts. One key insight is that substantial and continuous reductions in mean blood pressure and prevalence of raised blood pressure are achievable, as evident from the decreasing trends in the high-performing, mainly high-income, regions and countries. However, the opposing trends in several other, mainly low-income and middle-income countries, suggest that these countries are unlikely to achieve substantial reductions in mean age-standardised population-level blood pressure if no additional measures are taken. In fact, the report reminds us that even with containment of age-standardised blood pressure, the absolute number of people affected by raised blood pressure is likely to continue to grow in low-income and middle-income countries, mainly because of ageing and population growth, which are only partly counteracted by other trends.

But what are the key drivers of age-standardised blood pressure reductions? Can we learn from the success in high-performing countries to bend the blood pressure curve down in less successful regions and to accelerate reductions in better performing regions? The few available long-term national surveys that started in the 1950s showed that the reduction in mean blood pressure preceded the availability of specific interventions targeting it.<sup>8,9</sup> This fact suggests that a substantial proportion of the change is likely due to population-wide interventions. Such interventions include some now well established factors such as dietary and lifestyle changes, but also some less well measured factors such as early-life nutrition, or emerging exposures such as indoor temperature, air pollution, and noise. In the past three decades, improved medical care and widened use of anti-hypertensive treatments of proven effectiveness have made further contributions to blood pressure reductions.<sup>8,10</sup> However, these treatments remain heavily underused in both rich and poor countries,<sup>2</sup> calling for alternative models of health-care delivery that are less dependent on health-care professionals and instead make evidence more directly accessible to end-consumers.<sup>11,12</sup>

Effective control of raised blood pressure requires collaborative, multisectoral, national efforts to improve implementation of available evidence. The failure to tackle this issue more decisively will come at a high cost, particularly to disadvantaged individuals and societies.



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The clear view of recent achievements, as provided by the NCD Risk Factor Collaboration, should help us to collectively steer the action plan more effectively and equitably towards decreasing blood pressure globally.

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I declare no competing interests.

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- 1 Friedberg CK. Diseases of the heart. Philadelphia, PA: W B Saunders Company, 1966.
- 2 Rahimi K, Emdin CA, MacMahon S. The epidemiology of blood pressure and its worldwide management. *Circ Res* 2015; **116**: 925–36.
- 3 Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. *Lancet Diabetes Endocrinol* 2014; **2**: 634–47.
- 4 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* 2015; **387**: 957–67.
- 5 Murray CJL, Lauer JA, Hutubessy RCW, et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 2003; **361**: 717–25.
- 6 WHO. Global action plan for the prevention and control of NCDs 2013–2020. Geneva: World Health Organization, 2015.
- 7 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2016; published online Nov 15. [http://dx.doi.org/10.1016/S0140-6736\(16\)31919-5](http://dx.doi.org/10.1016/S0140-6736(16)31919-5).
- 8 Ezzati M, Obermeyer Z, Tzoulaki I, Mayosi BM, Elliott P, Leon DA. Contributions of risk factors and medical care to cardiovascular mortality trends. *Nat Rev Cardiol* 2015; **12**: 508–30.
- 9 Goff DC, Howard G, Russell GB, et al. Birth cohort evidence of population influences on blood pressure in the United States, 1887–1994. *Ann Epidemiol* 2001; **11**: 271–79.
- 10 Ikeda N, Gakidou E, Hasegawa T, Murray CJL. Understanding the decline of mean systolic blood pressure in Japan: an analysis of pooled data from the National Nutrition Survey, 1986–2002. *Bull World Health Organ* 2008; **86**: 978–88.
- 11 Rahimi K, Macmahon S. Blood pressure management in the 21st century: maximizing gains and minimizing waste. *Circulation* 2013; **128**: 2283–85.
- 12 Sundström J, Arima H, Woodward M, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014; **384**: 591–98.

## The end of almost 10 years of negative RCTs in advanced hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is associated with poor prognosis, with around 12% survival at 5 years.<sup>1</sup> Most patients are diagnosed at advanced stages, with tumour portal thrombosis, metastasis, or both (Barcelona Clinic Liver Classification [BCLC] stage C).<sup>2</sup> In 2007–08, after several negative phase 3 randomised controlled trials, in the SHARP trial,<sup>3</sup> sorafenib was shown to increase overall survival (median 10.7 months [95% CI 9.4–13.3], hazard ratio [HR] 0.69 [0.55–0.87]) compared with placebo (7.9 months [6.8–9.1]) in patients with advanced HCC.

For the first time, strong evidence confirmed that advanced HCC could be sensitive to a systemic drug, and this positive signal offered a glimpse of hope in the field. However, the almost 10 years that followed were arduous for physicians, who made strong efforts to include patients in several clinical trials worldwide, but with disappointing negative results. Phase 3 clinical trials of first-line therapies against sorafenib did not improve survival because of toxicity (sunitinib) or absence of efficacy (brivanib, erlotinib, etc) as did all phase 3 trials on second-line therapies that compared new biological agents (everolimus, brivanib, ramucirumab, etc) with placebo.<sup>4</sup> Moreover, clinical

trials testing sorafenib or brivanib in combination with chemoembolisation in intermediate HCC (BCLC stage B), or in an adjuvant setting after curative treatments, were also negative.<sup>5,6</sup>

Regorafenib is an oral multiple-kinase inhibitor targeting RAF, KIT, RET, and PDGFR, as well as VEGFR1 and TIE2; it has already been approved for the treatment of metastatic colorectal cancer and gastrointestinal stromal tumours. In *The Lancet*, Jordi Bruix and colleagues<sup>7</sup> report results of the international, phase 3, randomised controlled RESORCE trial that assessed regorafenib compared with placebo in advanced HCC in 573 patients who had progressed under sorafenib. Regorafenib increased overall survival, with a median survival of 10.6 months (95% CI 9.1–12.1) compared with 7.8 months (6.3–8.8) for the placebo (HR 0.63 [95% CI 0.50–0.79]; one-sided p<0.0001).<sup>7</sup> The adverse events of regorafenib were almost the same as those of sorafenib (hand-foot skin reaction, diarrhoea, hypertension, etc) and must be carefully monitored (ie, 53% for the hand-foot skin reaction in the RESORCE trial and 21% in the SHARP trial). Dermatological adverse events on sorafenib have been associated with better