EDITORIAL

Low-Dose Combination Blood Pressure Pharmacotherapy to Improve Treatment Effectiveness, Safety, and Efficiency

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In this issue of *JAMA*, Webster and colleagues[1] report the results of the Triple Pill vs Usual Care Management for Patients with Mild-to-Moderate Hypertension (TRIUMPH) pragmatic randomized clinical trial that evaluated the efficacy of a low-dose combination pill containing 20 mg of telmisartan, 2.5 mg of amlodipine, and 12.5 mg of chlorthalidone compared with usual care among 700 adults with hypertension in Sri Lanka. The primary outcome was the proportion of patients whose blood pressure (BP) was controlled at 6 months, which was defined as a systolic/diastolic BP of less than 140/90 mm Hg or less than 130/80 mm Hg among patients with diabetes or chronic kidney disease at baseline or newly diagnosed (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2).

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Patients randomized to the triple combination BP-lowering pill were more likely to achieve BP control at 6 months compared with those randomized to usual care (69.5% in the triple combination group vs 55.3% in the usual care group; adjusted relative risk, 1.23 [95% CI, 1.09-1.39], $P < .001$). At 6 months, patients randomized to the triple combination pill demonstrated a lower mean systolic BP (−9.8 mm Hg [95% CI, −7.9 to −11.6 mm Hg]) and diastolic BP (−5.0 mm Hg [95% CI, −3.9 to −6.1 mm Hg]), which were key secondary outcomes ($P < .001$ for both comparisons). The rates of adverse events were 38.4% in the triple combination pill group vs 34.8% in the usual care group. The rates of dizziness, syncope, or presyncope were higher in the intervention group (5.2% vs 2.8% in the usual care group), but the absolute between-group difference in the number of participants affected was small (18 vs 10 participants, respectively).

The triple combination pill therapy has been previously indicated for patients with difficult to control or resistant hypertension, yet the TRIUMPH investigators demonstrated the effects of this therapy among patients with mild to moderate hypertension. A significant proportion of the patients were receiving monotherapy at study initiation. The premise of the TRIUMPH trial was based on research demonstrating the trade-off between differences in BP-lowering efficacy and adverse effects with half doses of antihypertensive medications vs standard doses.[2] Half doses of medications achieve 80% of the BP-lowering effect compared with standard doses, with a log-linear pattern of adverse effects from thiazide-like diuretics, calcium channel blockers, and β-blockers.

Although there was a higher absolute rate of abnormal potassium levels in the triple combination pill group vs usual care (15.6% vs 9.4%, respectively), modeled estimates from TRIUMPH that accounted for baseline serum potassium levels suggest that the effect of the triple combination pill on potassium was small (adjusted difference in serum potassium level, −0.22 mmol/L [95% CI, −0.29 to −0.15 mmol/L]). Furthermore, there appears to be no effect on serum creatinine level (adjusted difference in serum creatinine level, 0.04 mg/dL [95% CI, −0.06 to 0.14 mg/dL]). Even though larger trials are needed to evaluate longer-term safety in more diverse populations, the initial safety signal appears promising.

The relationship between medication dose, BP-lowering effect, and adverse effects has even been extended to quarter doses of medications as reported in a systematic review of 42 trials (n = 20 284 participants).[3] Based on the favorable balance between BP-lowering effects and adverse effects, a recent pilot randomized trial (n = 19 participants) tested the effect of a 4-drug combination of quarter doses of medications (irbesartan, amlodipine, indapamide, and bisoprolol) and demonstrated a reduction in systolic BP by 22.4 mm Hg and a reduction in diastolic BP by 13.1 mm Hg compared with placebo with no difference in adverse effects between groups.[4] Whether these effects can be sustained safely in broader populations remains uncertain.

Clinical practice guidelines recommend lower BP targets,[5] and simpler strategies for achieving these targets are needed. The intervention group in the Systolic Blood Pressure Intervention Trial (SPRINT) was prescribed, on average, 3 drugs to achieve a mean systolic BP of 121.4 mmHg from a mean baseline systolic BP of 139.7 mmHg.[6] The SPRINT intensive treatment algorithm recommended a 2- or 3-drug therapy using a combination of a thiazide-type diuretic, an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker (not both), and a calcium channel blocker with titration or addition of more drugs if the patient had not reached his or her BP target during follow-up.

The SPRINT standard treatment algorithm recommended titration or addition of more drugs without an initial 2- or 3-drug therapy recommendation. The TRIUMPH investigators have thus provided empirical data on a fixed-dose combination strategy to much more easily implement adherence to the SPRINT intensive treatment algorithm, albeit for a shorter duration. Worldwide control of hypertension depends on finding a simpler, safe, long-term therapeutic strategy.

Fixed-dose combination therapy has become essential for hypertension treatment because it is an effective, scalable strategy that improves adherence,[7] and thus BP control. This therapy also can be efficiently incorporated into multilevel in-

terventions through simpler supply chains, fewer pills, and ultimately fewer outpatient visits.

For example, Kaiser Permanente of Northern California demonstrated improved BP control among its beneficiaries from 43.6% to 80.4% between 2001 and 2009 using the 2-drug fixed-dose combination of lisinopril and hydrochlorothiazide as an essential part of its large-scale, multilevel hypertension control program.[8] The rates of the fixed-dose combination therapy of lisinopril and hydrochlorothiazide increased from less than 1% to 27.2% during the same period. It remains unclear how much the fixed-dose combination component contributed to the overall result of the Kaiser program, which also included a patient register, audit and feedback, clinical practice algorithms, and early (2- to 4-week) follow-up with medical assistants.

On the other hand, data from TRIUMPH demonstrate faster time from treatment initiation to BP goal achievement. A larger proportion of patients randomized to the triple combination group achieved goal BP at 6 weeks (67.8% vs 43.6% in the usual care group; adjusted relative risk, 1.53 [95% CI, 1.33-1.76]) and at 12 weeks (72.6% vs 47.4%; adjusted relative risk, 1.51 [95% CI, 1.32-1.72]).

Despite these favorable results, the TRIUMPH study[1] has some limitations. First, the use of usual care as a comparator increases the risk of performance bias because study participants and personnel were not blinded, and the results may overestimate the effect of the intervention. However, the objective measurement of BP used by the investigators likely mitigates the risk of this bias, which the authors highlight based on their methods of printing BP measurements for blinded outcome assessment. On the other hand, BP control rates in the usual care group were higher than typical reports from public health facilities in other middle-income countries; therefore, the true effect may be underestimated.

Second, the primary outcome of BP control was assessed only through 6 months, whereas patients with hypertension will usually be advised to continue BP-lowering pharmacotherapy for longer periods. Third, the study was performed in a single country and evaluation of the efficacy and safety of the intervention is needed in more diverse populations before it can be broadly adopted.

Moreover, as with any new intervention, interpretation of the TRIUMPH results requires contextualization. Other systems-level interventions with significant improvement in BP control rates include the effective use of community health workers,[9] health coaching,[10] provision of health insurance coverage,[11] and self-monitoring of BP with telemonitoring.[12] The Million Hearts initiative of the US Department of Health and Human Services, which is co-led by the US Centers for Disease Control and Prevention and the Centers for Medicare & Medicaid Services, aims to improve BP control using a multilevel approach that includes fixed-dose combination therapy.[13]

Multilevel interventions also need to be scaled and implemented in settings with the greatest burden of hypertension-related cardiovascular diseases, particularly low- and middle-income countries similar to Sri Lanka where the TRIUMPH study was conducted.[14] Data highlighting the epicenters of this global burden provide the rationale for the target populations of Resolve to Save Lives (an initiative of Vital Strategies) 5-year campaign to save 100 million lives through BP control, sodium reduction, and artificial *trans* fat elimination through the World Health Organization's REPLACE action package.[15,16]

Efficiency gains from fixed-dose combination therapy will likely be greater in settings in which barriers are more prevalent than in the United States and these barriers include complex drug supply chain, limited access to medications, and shortage of health care workers to titrate medications. The global scale of elevated BP suggests that an intervention like a fixed-dose combination, which appears to be effective, safe, and efficient, is more likely to be sustained than more complex, labor-intensive approaches.

Blood pressure–lowering medications, although potentially powerful therapies, will be insufficient to help the 3.5 billion adults older than 25 years with an elevated systolic BP (>110 mm Hg).[14] Moving from pharmacological treatment to other policies and regulations like the World Health Organization's "best buys" for noncommunicable disease prevention, which represent primary prevention strategies and include reformulation of food products to contain less sodium, taxation of alcoholic beverages, and price increases on tobacco products, remain central for reducing the burden of hypertension-related conditions.

The TRIUMPH investigators have demonstrated the effects of a promising intervention in a triple half-dose combination therapy, which logically extends findings from prior research to improve BP control among patients with mild to moderate hypertension. This study contributes to the existing literature demonstrating the essential role of fixed-dose combination therapy as a viable strategy for BP control on a global scale.

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Traumatic Brain Injury and Risk of Suicide

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Suicide accounts for 1.4% of deaths globally and ranks as the 17th leading cause of death overall and the second for teenagers and young adults.[1] In the United States, suicide is the 10th leading cause of death overall, and the second leading cause of death among teenagers.[2] In 2016, there were nearly 45 000 suicides in the United States, twice the number of homicides, and the US suicide rate has increased in recent years. Suicide occurs throughout the lifespan, in every country, and across all socioeconomic strata. For each suicide, an estimated 20 to 25 suicide attempts occur.[3] Nonfatal suicide behavior, or parasuicide, is frequently accompanied by serious medical and psychiatric comorbidity and long-term disability. Suicide creates enormous psychosocial and economic burdens on individuals, families, caretakers, and society. Yet stigma, shame, and misunderstanding keep suicide in the shadows.

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The causes of suicide are manifold. The findings reported by Madsen and colleagues[4] in this issue of *JAMA* add to a growing body of evidence pointing to traumatic brain injury (TBI) as an important risk factor for suicide. TBI is particularly common in young adults and the elderly, and severe TBI has long been recognized as a leading cause of death and disability.[5] However, only recently has it been recognized that TBI on the mild end of the injury spectrum can also have persistent and disabling consequences.[6] Mild TBI is far more common than severe TBI, and because primary disabilities after TBI are often cognitive and neuropsychiatric, understanding the relationships between TBI, depression, and impulsivity represents a clinical imperative. The study by Madsen et al[4] provides insights into the underappreciated relationship between TBI and suicide.

Medical interest in acute care of head injuries dates to the ancient Egyptians[7] and has long been a key aspect of military and trauma medicine and neurosurgery. By contrast, appreciation of the chronic effects of these common injuries is a recent phenomenon. This groundswell of interest can be traced to 3 distinct lines of research. The first stems from neuropathological evidence linking repetitive head injuries in contact-sport athletes—especially boxers, but also players of American football, hockey, soccer, rugby, and other contact sports—to chronic traumatic encephalopathy (CTE), a tau protein neurodegenerative disease.[8,9] A second line of research has uncovered evidence of persistent brain pathology in military service members and combat veterans with blast exposure.[10] The third development draws from neuroimaging and neuropsychological studies that show long-lasting brain abnormalities, cognitive deficits, and neuropsychiatric disturbances in patients with mild TBI.[11,12] Although chronic effects of neurotrauma have been known since the early decades of the last century,[8,13] this recent research has thrust TBI and its aftermath into the media spotlight, with increased awareness among the public and increased attention in the medical community.