PERSPECTIVES ON SINGLE PILL COMBINATION TREATMENT AROUND THE WORLD

Introduction

RAVEN VOORA

Division of Nephrology and Hypertension,
University of North Carolina Chapel Hill, North Carolina, USA
ISH Americas Regional Advisory Group (RAG) member

Hypertension is viewed as a major global risk factor for cardiovascular and kidney disease.[1] Prevention and effective and up-to-date management of hypertension are very important to address this major risk factor. In this vein, lifestyle modifications are important along with use of multi-drug regimens. Realizing that more than one medication is oftentimes needed to lower high blood pressure, various hypertension guidelines worldwide recommend single pill combination therapy as an option to simplify medical regimens and promote use of combinations of drugs that are complementary for treatment of hypertension. Recently published data also demonstrates an association between lower rates of adverse outcomes and use of single pill combination therapy.[2]

Raven Voora - raven_voora@med.unc.edu

In this article, members of the Americas Regional Advisory Group (RAG) invited other ISH members from countries around the world to comment on the use of single pill combination therapy in their own respective countries. The goal is to better understand current practices around use of single pill combination therapy and challenges on a global level to managing hypertension and use of guideline recommended therapeutic options. Ultimately, the hope is to increase knowledge of global practices and barriers to providing up-to-date hypertension management. In doing so, we may find that we are more similar than different.

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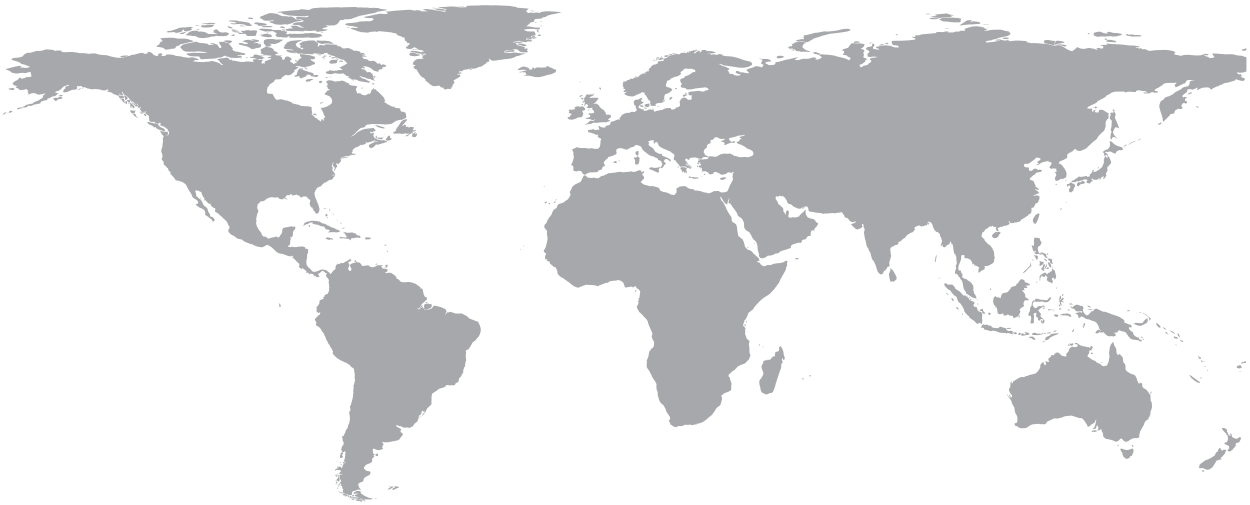

Africa

Erika S. W. Jones

Department of Medicine, Division of Nephrology and Hypertension, Groote Schuur Hospital and University of Cape Town, South Africa.

eswjones@gmail.com

Despite considerable evidence demonstrating the superiority of single pill combination (SPC) antihypertensives, use in sub-Saharan Africa is limited. There is limited literature on the prevalence of SPC use, but in a small study from Nigeria it was reported to be 56.8%.[1] However, this is not representative of African proportions due to the differences in healthcare models. There are numerous reasons for the low uptake of SPC, many of them are related to financial constraints, either at an individual level or a policy maker level.

The costs of managing hypertension and the consequences thereof are nearly insurmountable in low- and middle-income countries. The direct costs for treating hypertension in South Africa (an upper-middle income country but with a low resource environment where patients access government healthcare services) were estimated to be ZAR 10.1bn.[2] These expenses cover the cost of medication as well as the costs for care of hypertension mediated organ damage. In Africa, a large proportion of people self-fund all medical expenses and do not have access to government funded healthcare, including medications. Some pay insurance, but the majority are just unable to afford basic healthcare, never mind ideal healthcare.

Direct costs do not include societal costs, which are close to three times the direct costs.[2] These hidden costs are seldom accounted for. Until we account for all expenses and losses from hypertension, we will continue to overplay the cost of medication at the expense of the individual and the populations we serve. While we do need to account for these expenses, we also need to ensure equitable access to quality affordable antihypertensive SPC medications to limit the rising cardiovascular scourge.

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Americas

Daniel Piskorz

Cardiovascular Research Center at Rosario British Sanatorium, Argentina
ISH Americas Regional Advisory Group member

instcardiología@gmail.com

The International Society of Hypertension initiated activity May Measurement Month showed that only 20% to 30% of Latin American hypertensives are within recommended blood pressure targets. Affordability and accessibility for approved hypertension drugs, patient's lack of treatment adherence and persistence and practitioner's inertia are between the most well-known challenges to improve hypertension control.

The database of the Lombardy Region showed that a two-drug single pill fixed dose combination (SPFDC) strategy as first step in hypertension treatment reduced cardiovascular end points.[1] The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension study (Accomplish) increased the achievement of blood pressure targets from 37% to almost 80% with SPFDC treatment. The Systolic Blood Pressure Intervention Trial (SPRINT) required 2 or more drugs in 60% of patients in the standard arm and almost 85% in the intensive arm to achieve the goals.

The 2,017 Argentina National Registry of Hypertension (Renata-2) showed that 73.4% of hypertensive patients were treated with monotherapy and only 8.3% were treated with SPFDC, despite Argentina Hypertension Guideline recommends in grade 1 and 2 hypertension SPFDC treatment (class of evidence I level of evidence C; class of evidence I level of evidence A, respectively).[2] The CHARTER (**C**ontrol de la **H**ipertensión **ART**erial por **E**specialistas en A**R**gentina [hypertension control by specialists in Argentina]) study included 1,146 patients in 10 hypertension specialist centers in Argentina. The consumption of SPFDC was 42.5%. The fragmentation of the health system in Argentina is the main barrier for the use of SPFDC. Private health funders agree to finance SPFDC, whereas state and unions social services and the retirement institute do not cover the prescription of SPFDC.

The START study by Schmieder R et al in a retrospective claims data supports the notion that SPFDC reduces mortality and cardiovascular events compared to identical drugs as multipills.

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Asia Pacific (APAC)

Wook-Bum Pyun

Department of Internal Medicine,
Ewha Womans University,
Seoul, South Korea

pwb423@ewha.ac.kr

Data from the Korean Fact Sheet 2023 indicates that two out of three patients with hypertension have one or two comorbidities such as diabetes and dyslipidemia. And three out of five patients with hypertension need two or more drugs to control their blood pressure. One or two out of five adults have some problems in swallowing their medication according to reports from the general population.[1] The prevalence of swallowing difficulties will become much higher in the context of aging populations around the world. In particular, elderly patients who have had a stroke, or who take a variety of drugs from various specialised clinics, are more likely to have swallowing diffiicultes.

Asia-Pacific is the region with the highest prevalence of hypertension and cardiovascular morbidities and mortalities and this is ever increasing. And in most Asian hypertension clinics including mine, the initial prescription of single-pill combinations (SPCs) is not the first choice, even though this is the recommendation from national societies of hypertension, but we try to reduce the number of pills using SPCs as early as possible after stabilization of medication.

The big barriers of dose flexibility and pill size are not problematic any more due to various SPC combinations and bio-technical advances.

From reports from Korea and China, the penetration rate of SPCs is increasing this decade with improving adherence and control rates.

The START-Study of Schmieder RE, et al is important and a strong point of reference to increase SPCs by those who still hesitate to prescribe them in their clinics.

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Europe

Claudio Borghi

Chair ISH Europe Regional Advisory Group
Department of Medical and Surgical Sciences, University of Bologna, Italy

claudio.borghi@unibo.it

Persistence to treatment is a crucial issue in relation to patients requiring regular treatment for clinical conditions such as hypertension, dyslipidemia, etc. Poor persistence turns into a shortage in the preventive impact of therapy with a lesser than expected beneficial effect in terms of control of CV risk factors and clinical outcome.

The situation of blood pressure control in European hypertensive patients is far from being satisfactory with a significant difference in the percentage of well controlled patients ranging from 20 to 50% according to a recent report of the NCD working group.[1]

The main reasons for poor controlled hypertension in Europe are the negative attitudes of some patients ("I do not like the drugs"), the insufficient patient-doctor relationships particularly with younger patients with higher potential CV risk,and the poor adherence to treatment, largely based on poor propensity or reluctance to take prescribed drugs, particularly in patients treated with a high number of pills.

Many possible solutions have been provided ranging from professional incentives to some individualized approach to poor persistent patients, but the only one that has provided measurable results is the use of single-pill fixed dose combinations (FDCs).

This strategy has been demonstrated to be very effective in controlling blood pressure and reducing the costs required for the management of hypertension. Unfortunately, some recent Italian data have largely limited our expectations by showing that a large number of patients are still treated with monotherapy with no increase in the prescription of FDC's over time.[2] Now we have new evidence that demonstrate that the administration of a FDC may improve both persistence and outcome in a large population of patients and according to a reliable study design and this would be another brick in the wall against hypertension.

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Middle East and North Africa (MENA)

Rana El-Bikai (Lebanon), Jafar Alsaid (Bahrain/USA) and Abdulla Shehab (UAE)

ISH Middle East and North Africa Regional Advisory Group (MENA RAG) members

Rana El-Bikai – elbikairana@gmail.com

The benefits of Single-Pill Combinations (SPCs) for hypertension have been proven in recent studies to have enhanced treatment adherence and reduce cardiovascular risks and mortality with a better control of blood pressure yet, we are yet to achieve target for a single pill globally.

The MENA region has a vast population living in low and middle-income countries, creating flagrant economic diversity. SPCs could be

considered expensive and thus create an obstacle for physicians to prescribe and patients to adhere to. Collaborative efforts with policymakers and pharmaceutical companies should be implemented to improve pricing schemes and achieve a more balanced cost-effectiveness.

Other barriers include the lack of awareness of benefits of SPCs and availability of standardized management protocols. To help promote the use of SPCs in the region, more widespread education should be made available to train healthcare professionals on the use and benefits of SPCs. Additional data representative of the region in the realms of patient satisfaction, scientific validity, acceptability, access, cultural aspects, and cost-effectiveness, is warranted.

South and Central Asia (SACA)

Prabhakaran Dorairaj

Executive Director, Centre for Chronic Disease Control, New Delhi, India. Member, ISH Council

dprabhakaran@ccdcindia.org

We have learnt a lot regarding hypertension in the last three or four decades. However, hypertension continues to be a disease of three paradoxes. It is:

- Easy to detect but diagnosis rates are dismal.
- Easy to treat but treatment rates are disappointing.
- Several potent drugs are available, but control rates are abysmal. More importantly, hypertension control rates are low at 11% and 20% among rural and urban patients, respectively. We need urgent measures to address this important public health issue.

The second major lesson that we have learnt is that the initiation of treatment should comprise of at least half dose of two drugs in a single pill combination (SPC). This has been emphasized by several guidelines that have been published recently. However, there are several challenges in implementing this on scale in a country like India and in South Asia. First there are no trials from South Asia addressing this issue. To obtain an answer, we are conducting the "Treatment Optimisation for Blood Pressure with Single-Pill Combinations in India (TOPSPIN)" which is a trial to compare the efficacy of three single pill combinations (SPCs) of two anti- hypertensive agents on 24-hour ambulatory systolic blood pressure (ASBP) among individuals with hypertension in India. This is a multi-centre, individual randomized single-blind, parallel-group, three-armed superiority trial.

The results of this study will provide evidence-based information to treat hypertension patients in the South Asian region effectively.

Other issues include addressing supply chain challenges of SPC, patient engagement in a team based care approach, understanding the journey of a patient with hypertension and overall a need for health system redesign to address the burgeoning burden of hypertension in India.